CHAPTER 1

HYDROGEN-BONDING-MEDIATED DIRECTED OSMIUM DIHYDROXYLATION

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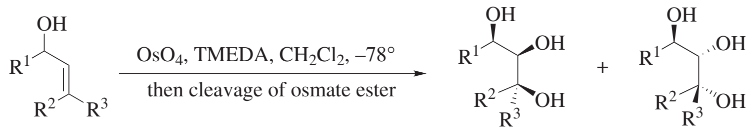
INTRODUCTION

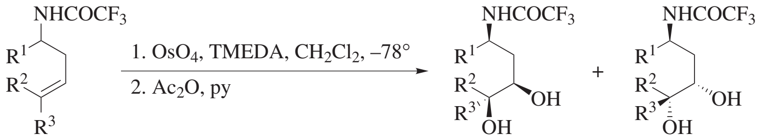
This review focuses on the dihydroxylation of alkenes using osmium tetroxide (OsO_4) that is directed by alcohols and amine derivatives through hydrogen bonding between the substrate and the oxidant.

Discussion focuses on the different types of directing groups that are viable. The outcome from directed dihydroxylation of all the major classes of alkenes, including cyclic and acyclic substrates and varied alkene substitution patterns, is also addressed (Eqs. 1 and 2).[1]



(Eq. 1)

highly *syn* selective



(Eq. 2)

highly *syn* selective

The mechanism section outlines the different reactivity patterns that various ligands can impart onto the osmium oxidant, together with the importance of choosing a solvent that encourages hydrogen bonding. The influence that the directing group has on *syn* selectivity is also discussed, in both the context of its position in space with respect to the alkene, and the relationship between the pKa of the acidic proton and *syn* selectivity.

Criegee first reported the controlled oxidation of alkenes using stoichiometric amounts of OsO_4,[2] and later expanded upon those original observations by noting that pyridine acts as a ligand for osmium and accelerates the dihydroxylation process.[3] Osmium tetroxide has since established itself as the reagent of choice for the *syn*-dihydroxylation of olefins, primarily because of its inertness toward other functional groups and lack of over-oxidation products.[4]

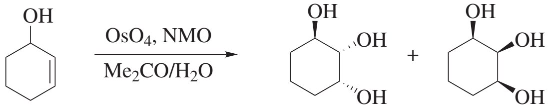
Researchers from the UpJohn company reported a convenient and reliable procedure for dihydroxylation that involved substoichiometric amounts of OsO_4 (typically 5 mol %) and *N*-methymorpholine-*N*-oxide (NMO) as a stoichiometric co-oxidant. This landmark paper defined a procedure that has since enjoyed widespread use.[5]

Observations as to the outcome from the dihydroxylation of chiral substrates were given a basis by Kishi, who reported that *anti* selectivity is generally attained during the oxidation of a wide range of allylic alcohols and protected derivatives thereof.[6,7,8,9] This mode of reactivity, whereby the heteroatom compels oxidation to occur on the opposite face of the alkene (most easily envisaged in cyclic systems) has proven to be very reliable with few exceptions reported. In fact, the high level of *anti* selectivity that is observed in such dihydroxylations has led to a problem: how to overturn this bias and obtain dihydroxylation on the same face as the directing group? Because the facial bias of the substrate (particularly allylic alcohols) is so strong, and often cyclic *cis*-alkenes are involved, it is frequently not possible to use the impressive asymmetric dihydroxylation system developed by Sharpless to control the diastereoselective dihydroxylation of a chiral substrate.[10,11] Therefore, the notion of a heteroatom-directed dihydroxylation becomes an interesting and useful proposition; and as such, the method discussed here forms an excellent counterpart to that described by Kishi.

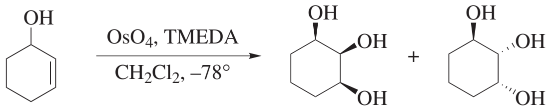
Remarkably, only a few other synthetic methods are known that accomplish the direct addition of a diol unit or a protected diol unit across an alkene while controlling the stereochemical course of the process. In fact, in addition to oxidation with high-valent metal oxo species, only iodine/silver acetate, the Woodward modification of the Prevost reaction,[12] will add two oxygen atoms in a *syn* fashion across an alkene. While this reaction has not enjoyed widespread use in the chemistry community it is discussed in some detail in the "Comparison with Other Methods" section.

MECHANISM AND STEREOCHEMISTRY

The hydrogen bond accepting ability of OsO_4 is enhanced upon complexation by amines. This behavior can be explained simply by the coordination of a Lewis base to the metal center, which leads to increased electron density on the oxo-ligands. Equations 3 and 4 compare the differences of reactivity between the OsO_4–NMO and the OsO_4•TMEDA complexes.



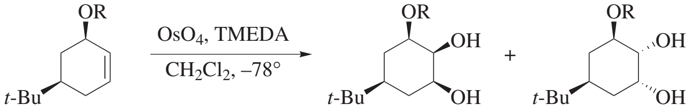
(97%) 5.7:1 (Eq. 3)



(98%) 9:1 (Eq. 4)

Corey showed, through low-temperature X-ray crystallographic analysis, that chiral 1,2-diamines form unique bidentate complexes with OsO_4.[13,14] These findings suggest that an OsO_4•diamine system should benefit from the bidentate nature of the ligand, which would exert an enhanced donor effect on the metal and also on the oxo-ligands. Spectroscopic analysis of the complex, formed at low temperature between OsO_4 and TMEDA (N,N,N',N'-tetramethyl-1,2-ethanediamine), has been carried out. ^{1}H NMR spectra of a 1:1 mixture of OsO_4 and TMEDA reveal the presence of a single, symmetrical compound. Low temperature IR spectroscopy studies indicate a reduction in the Os=O bond order as one traverses the series OsO_4, OsO_4•monodentate amine, OsO_4•chelating-diamine. These findings support the hypothesis that the increase in *syn* selectivity in directed dihydroxylation, following the order OsO_4 < OsO_4•monodentate amine < OsO_4•chelating-diamine, arises from an augmentation in hydrogen bond forming ability.[15]

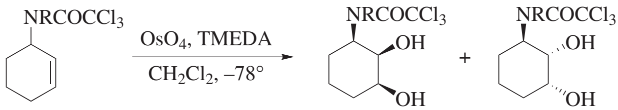
The importance of hydrogen-bonding is further substantiated by the dihydroxylation of methyl ether **1** (R = Me) (Eq. 5) and *N*-methyl trichloroacetamide **2** (R = Me) (Eq. 6).[15] The absence of a hydrogen bond donor in these substrates has a pivotal influence on the stereochemical outcome of the reaction: the *anti* isomer is obtained as the major product in both cases. Also, it is noteworthy that these dihydroxylation reactions are significantly slower than the oxidation of the parent alcohol or trichloroacetamide.



1

R		dr
Me	(65%)	1:25
H	(91%)	24:1

(Eq. 5)



2

R		dr
Me	(78%)	1:10
H	(99%)	>25:1

(Eq. 6)

Further studies established that the OsO_4•TMEDA complex reacts through a hydrogen bond between the substrate and an oxo ligand (see **A**, Fig. 1), rather than a non-ligated amino group of TMEDA (see **B**, Fig. 1).

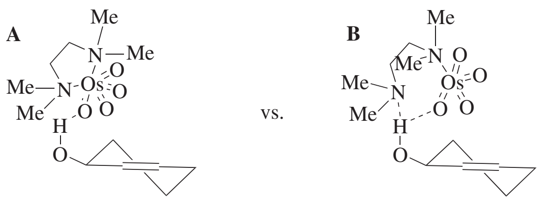
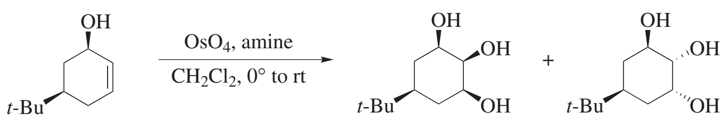


Figure 1. Possible hydrogen-bonding between the substrate and the OsO_4•TMEDA complex.

The results for the dihydroxylation of alcohol **3** in the presence of several bifunctional analogues of TMEDA are shown in Eq. 7. It is noteworthy that all of the amines fail to match the *syn* selectivity observed with TMEDA.[15]



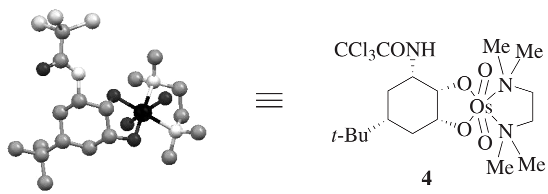
3

Amine	dr
none	1:1.7
Me_3N	1.2:1
$Me_2N(CH_2)_2OMe$	1.1:1
$Me_2N(CH_2)_2OH$	1.1:1
$Me_2NCH_2NMe_2$	1.6:1
$Me_2N(CH_2)_2NMe_2$	4.6:1
$Me_2N(CH_2)_3NMe_2$	2.8:1

(Eq. 7)

High levels of *syn* stereoselectivity are achieved for chelating amines only;[15] if the hypothetical model **B** were correct, it is expected that amines with pendant oxygen functionality should be able to form a hydrogen bond to the substrate and hence direct the dihydroxylation to some degree. Clearly this is not the case, as the level of selectivity in these reactions is comparable to those found using a simple monodentate amine such as Me_3N. These studies provide further evidence for the existence and reaction of a chelated OsO_4•TMEDA complex. Model **A** is, therefore, to be considered the reacting species.[15]

More information on the OsO_4•TMEDA system can be gathered by a closer analysis of the osmate esters produced, which are quite stable and can be easily purified. The X-ray crystal structure of *syn*-osmate ester **4**, obtained from the corresponding alkene and OsO_4•TMEDA, clearly shows the chelating nature of the diamine ligand (Fig. 2).[15]

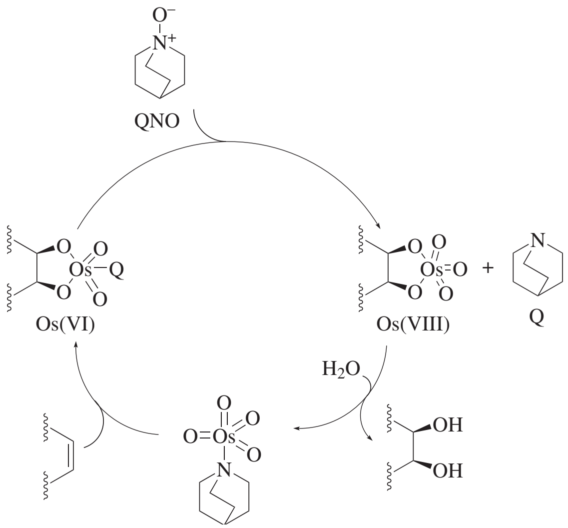


4

Figure 2. X-ray crystal structure of *syn*-osmate ester **4**. Hydrogen atoms have been omitted for clarity.

Another feature of the dihydroxylation reaction using OsO_4 in the presence of amines is the increased reactivity of the reagents towards alkenes. On the basis of literature data, approximate relative rate values for olefin oxidation with OsO_4, OsO_4•quinuclidine, and OsO_4•TMEDA are 1, 100, and 10,000 respectively.[13,16] The use of TMEDA as an additive generates an extraordinarily powerful dihydroxylating system, which is able to react with alkenes even at $-78°$. Under the same conditions, both OsO_4 and OsO_4•quinuclidine are essentially inert. This unique feature of the complex has enabled wide use in different dihydroxylation reactions where standard protocols are found to be ineffective.[17,18]

A disadvantage of the OsO_4•TMEDA system is the requirement for stoichiometric amounts of transition metal due to the inability of the resulting osmate(VI) ester to undergo either direct hydrolysis or in situ oxidation to a more easily hydrolyzed Os(VIII) species. By switching to monodentate amines such as quinuclidine, introduced as its *N*-oxide (QNO), the reactivity and hydrogen-bonding ability of the osmium complex decrease but the dihydroxylation reaction can be carried out with a substoichiometric amount of metal.[19] As the reaction progresses and QNO is reduced, OsO_4 can bind to the released quinuclidine and oxidize the alkene preferentially in a *syn* fashion. The resulting osmate ester is then able to undergo fast oxidation with more QNO, and subsequent hydrolysis (there is no need for the addition of water, as QNO is normally used as a monohydrate) releases the product and regenerates the catalytic species, as shown in Scheme 1.



Scheme 1

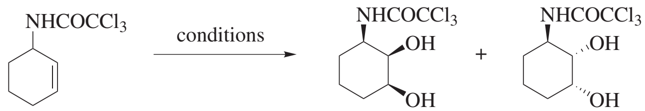
SCOPE AND LIMITATIONS

Although the osmium(VIII) dihydroxylation reaction can be influenced by a number of factors (electronic effects, steric effects, etc.), this chapter focuses on reactions wherein hydrogen-bonding effects are important. The presence of a directing group (usually an amide or alcohol) in either the allylic or homoallylic position combined with a complex of osmium tetroxide with an amine (generally OsO_4•TMEDA) can allow *syn* stereoselectivity and site selectively in the oxidation of a double bond.

Success of the hydrogen-bonding-mediated directed dihydroxylation depends upon a few essential elements. The level of stereoselectivity attained can be widely variable depending upon the geometry, substitution pattern, and position of the alkene relative to the directing group, and other steric or stereoelectronic factors.

Nature of the Amine

The weaker directing effect of the OsO_4•quinuclidine complex results in moderate levels of diastereoselectivity with allylic alcohols. Better results are obtained when trichloroacetamides are used as the directing element. Good levels of *syn* selectivity can be attained with trichloroacetamides due to the enhanced hydrogen bond forming ability of these acidic species, which allows a stronger interaction between the osmium complex and the substrate (Eq. 8).[15,19,20] Protocols that are catalytic in OsO_4[19] are less selective than the stoichiometric method[15,20] but do provide significant levels of *syn* selectivity, with the QNO system being slightly superior to the Me_3NO (TMO) system.



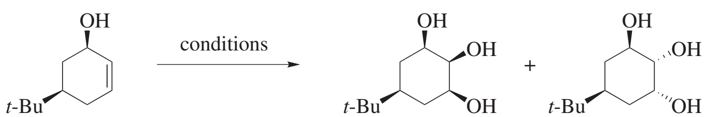
(Eq. 8)

Conditions		dr
OsO_4, TMEDA, CH_2Cl_2, –78° to rt	(99%)	>25:1
OsO_4 (5 mol %), $QNO{\bullet}H_2O$ (1.3 equiv), CH_2Cl_2, rt	(86%)	4.3:1
OsO_4 (cat), Me_3NO, CH_2Cl_2	(93%)	3:1
OsO_4 (cat), NMO, Me_2CO/H_2O, rt	(98%)	1:3.2

The use of a monodentate amine also represents a distinct advantage when the dihydroxylation of hindered allylic trichloroacetamides is required. Because of the smaller size of the $OsO_4{\bullet}$quinuclidine complex compared to the $OsO_4{\bullet}$TMEDA system, increased levels of selectivity are obtained in the directed oxidation of sterically demanding substrates.[19] Replacing $QNO{\bullet}H_2O$, which needs to be prepared beforehand, with commercially available $Me_3NO{\bullet}2H_2O$ makes the dihydroxylation process easier to perform while maintaining good levels of *syn* selectivity.[19]

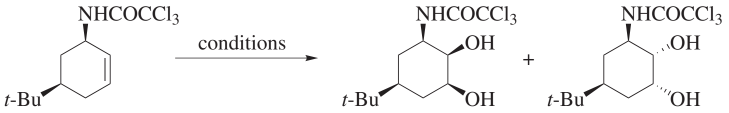
Nature of the Directing Group

The dihydroxylation can be directed if an alcohol or secondary amide group is present within reasonable proximity of the alkene. In general, suitably activated amide derivatives are prone to higher *syn* selectivity than their alcohol counterparts (Eqs. 9 and 10). The enhanced acidity of the trichloroacetamide and trifluoroacetamide relative to that of the corresponding alcohol (pKa values are approximately 11.2, 10.7, and 15 respectively) means that hydrogen-bonding to the $OsO_4{\bullet}$TMEDA reagent is more effective, resulting in a higher *syn* selectivity. Oxidation of amide derivatives bearing less acidic proton donors (Me_3CONHR, *t*-BuOCONHR) afford only moderate *syn* selectivities.[15] The more acidic sulfonamides are not as selective, a result that is probably due to their greater steric bulk. Good levels of *syn* selectivity can be attained with substrates bearing amide directing groups using the hydrogen-bonding conditions catalytic in OsO_4 ($QNO{\bullet}H_2O$, CH_2Cl_2).[19,21]



(Eq. 9)

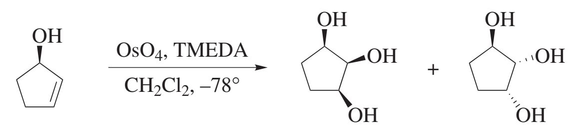
Conditions		dr
OsO_4, TMEDA, CH_2Cl_2, –78° to rt	(91%)	25:1
OsO_4 (5 mol %), $QNO{\bullet}H_2O$ (1.3 equiv), CH_2Cl_2, rt	(—)	1.2:1
OsO_4 (cat), NMO, Me_2CO/H_2O, rt	(91%)	1:4



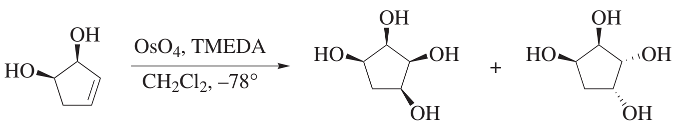
(Eq. 10)

Conditions		dr
OsO_4, TMEDA, CH_2Cl_2, –78° to rt	(96%)	24:1
OsO_4 (cat), Me_3NO, CH_2Cl_2	(81%)	6:1
OsO_4 (5 mol %), QNO•H_2O (1.3 equiv), CH_2Cl_2, rt	(77%)	13:1
OsO_4 (cat), NMO, Me_2CO/H_2O, rt	(86%)	1:1.6

An additional hydroxy group in the vicinity of the allylic hydroxy group can reduce the selectivity of the hydroxylation. Equations 11 and 12 illustrate this effect.[15,21]



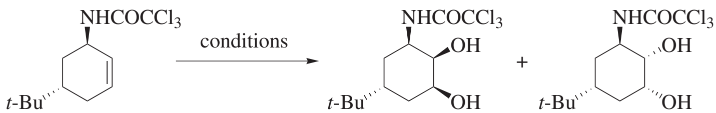
(76%) 7:1 dr (Eq. 11)



(67%) 2:1 dr (Eq. 12)

Steric Effects

Adverse steric effects can, of course, affect the *syn* selectivity dramatically. The bulk of the OsO_4•TMEDA complex hampers its ability to oxidize the hindered faces of alkenes. 1-Amino-2-cyclohexene derivatives and 2-cyclohexenols give the best *syn* selectivity when the donor group is in an equatorial position. When a conformationally locked substrate contains a pseudoaxially disposed directing group, the *syn* selectivity is poor (Eq. 13),[15,20] because hydrogen-bonding of the large oxometal species is discouraged by sterics (Fig. 3). As was mentioned previously, the *syn* selectivity of dihydroxylation of hindered allylic trichloroacetamides is increased when TMEDA, a bidentate ligand, is replaced by quinuclidine, a monodentate ligand. Even though the OsO_4•quinuclidine complex displays weaker inherent hydrogen bond accepting ability, the reduced steric bulk provides moderate *syn* selectivity in this system.



(Eq. 13)

Conditions		dr
OsO_4, TMEDA, CH_2Cl_2, –78° to rt	(97%)	1.7:1
OsO_4, quinuclidine, CH_2Cl_2, –78°	(66%)	4.9:1

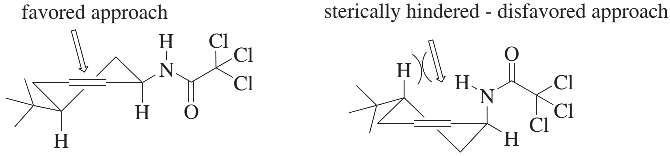
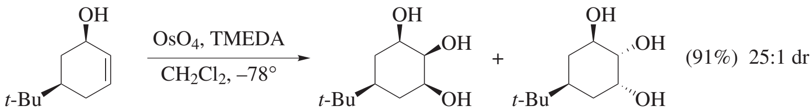
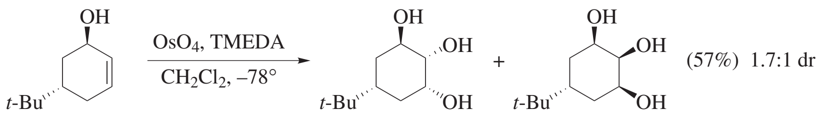


Figure 3. Steric effects in a conformationally locked substrate.

The same lack of *syn* selectivity is also observed with pseudo-axially biased alcohol **5** (Eqs. 14 and 15).[15,21]



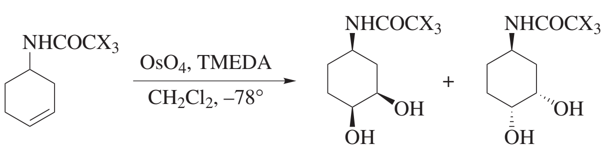
(Eq. 14)



5

(Eq. 15)

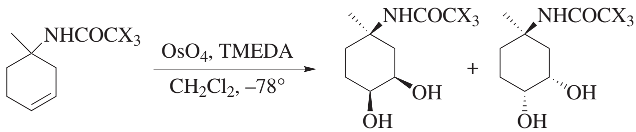
Clearly, the directing functionality must also be placed in a position where it can interact freely with the osmium complex. In contrast to allylic substrates, the directing group in homoallylic substrates needs to be in an axial position to deliver the oxidant intramolecularly. For example, poor selectivity is observed when 4-trichloroacetamido-1-cyclohexene is oxidized, probably because the bulky amide group has to adopt an unfavored axial position in order to deliver the oxidant (Eq. 16).[22] However, when the trichloroacetamide is replaced by the smaller and more acidic trifluoro derivative (approximate pKa of $Cl_3C(O)CNHR = 11.2$ and $F_3C(O)CNHR = 10.7$), the oxidation proceeds with excellent *syn* selectivity (Eq. 16).[22]



X		dr
Cl	(92%)	1.2:1
F	(98%)	>20:1

(Eq. 16)

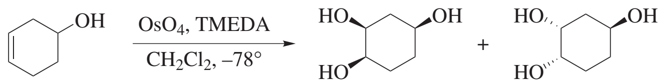
It is noteworthy that in both the trichloroacetamide and trifluoroacetamide cases, the *syn* selectivity is greatly affected by the presence of an alkyl group on the carbon bearing the amide functionality (Eq. 17).[22] In this example, the directing group may be able to adopt the preferred axial conformation, but cannot point the N–H group towards the alkene without encountering steric hindrance from the geminal alkyl group, which leads to dramatic reduction of *syn* selectivity.[22,23,24]



X		dr
Cl	(92%)	1:5
F	(67%)	3:1

(Eq. 17)

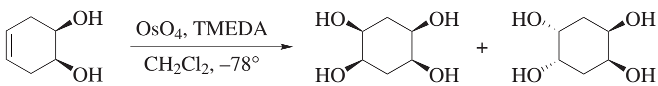
The requirement for an axial directing group would also explain the difference in selectivity between substrate **7** (which must always have one hydroxy group in an axial position) and substrate **6** (Eqs. 18 and 19).[22,25]



6

(92%) 3:1 dr

(Eq. 18)

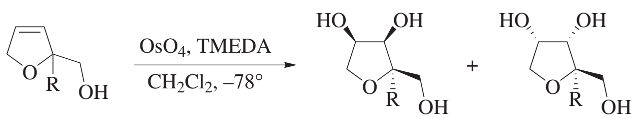


7

(82%) 12.4:1 dr

(Eq. 19)

With the five-membered ring homoallylic alcohol **8**, the dihydroxylation using OsO_4•TMEDA proceeds unselectively (Eq. 20). The exocyclic methylene side-chain may be sufficiently bulky to interfere with effective directed dihydroxylation. This hypothesis is supported by the results of substrate **9**, wherein an alkyl substituent has been introduced to block the face of the alkene opposite to the hydroxymethyl group. As expected, the directed dihydroxylation then proceeds well and with good *syn* selectivity. Furthermore, the directed dihydroxylation of substrate **10** confirms this rationale as the *p*-methoxybenzyl group completely blocks *anti* attack and therefore excellent *syn* selectivity is obtained.[22,25]

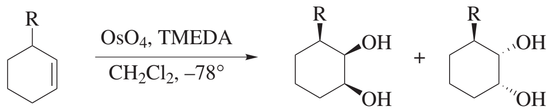


(Eq. 20)

	R		dr
8	H	(55%)	1:1
9	Me	(83%)	6:1
10	*p*-$MeOC_6H_4CH_2$	(82%)	99:1

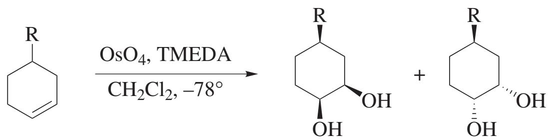
Nature of the Substrate

Allylic versus Homoallylic Substrates. As a rule, allylic substrates lead to better stereoselectivity than homoallylic substrates. The main reason for this is that the directing group in the latter is now positioned further away from the double bond where it cannot influence the approach of the oxidant as easily. In cyclic homoallylic systems, it is more difficult for the hydrogen bond donor group to adopt a position that allows the osmium complex to attack the double bond in a *syn* selective fashion whilst participating in hydrogen-bonding. This issue has been already detailed in the "Steric Effects" section. Eqs. 21 and 22 directly compare examples of allylic and homoallylic alcohols.[22,25]



R		dr
OH	(98%)	9:1
$NHCOCCl_3$	(99%)	24:1

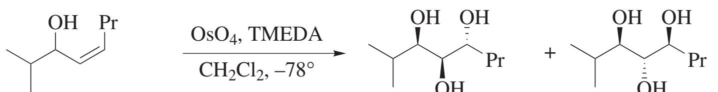
(Eq. 21)



R		dr
OH	(92%)	3:1
$NHCOCCl_3$	(92%)	1.2:1

(Eq. 22)

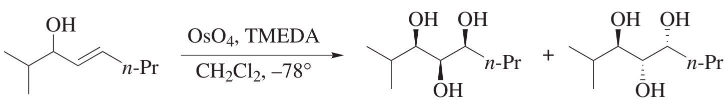
Conformational Factors Determined by the Alkene Substitution Pattern. In cyclic systems, the rigidity of the structure and consequent steric effects lead to high levels of *syn* selectivity. In acyclic systems, the alkene substitution pattern is crucial to obtaining high *syn* stereoselectivity. It is interesting to note that the *syn* selectivity increases dramatically in acyclic systems when the double bond bears a *cis* substituent, as in substrate **11** (Eqs. 23 and 24).[24,26]



11

(79%) 25:1 dr

(Eq. 23)



(84%) 3:1 dr

(Eq. 24)

Within each type of alkene, the levels of *syn* selectivity reported in the literature for directed epoxidation with peracid (most notably *m*-CPBA) are similar to those observed for directed dihydroxylation. It is suggested that, in the transition structure, the dihedral angle between the C–O and the C=C is most favorable at approximately 120°. The two possible transition structures are distinguished by the difference in $A^{[1,3]}$ strain between the R group and the R_{cis} substituent

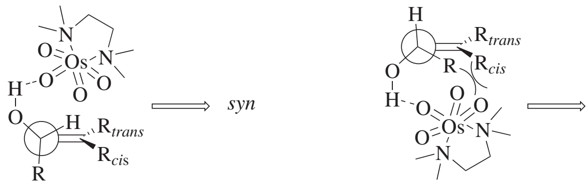
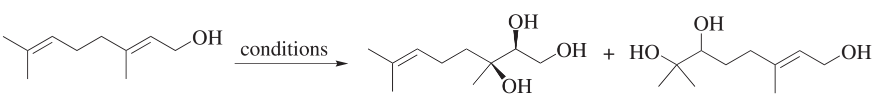


Figure 4. The two possible transition structures for directed dihydroxylation.

and explains why a large group in the R_{cis} position leads to higher levels of stereocontrol than the same group in the R_{trans} position (Fig. 4).[24]

Site Selectivity of the Directed Dihydroxylation Reaction. The directed dihydroxylation also expresses high site selectivity. Treatment of geraniol (**12**) with the OsO_4•TMEDA complex leads to highly selective oxidation of the 2,3-alkene (Eq. 25).[21] When the same substrate is oxidized under Sharpless asymmetric dihydroxylation conditions, the site selectivity is reversed, and oxidation of the most electron-rich double bond is observed.[27]



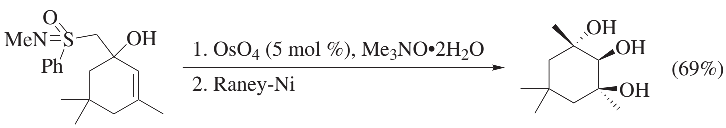
12 **I** **II**

Conditions		I:II
OsO_4, TMEDA, CH_2Cl_2, –78° to rt	(74%)	>25:1
OsO_4 (1 mol %), $(DHQD)_2$-PHAL (5 mol %), $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, t-BuOH/H_2O, 0°	(89%)	1:>49

(Eq. 25)

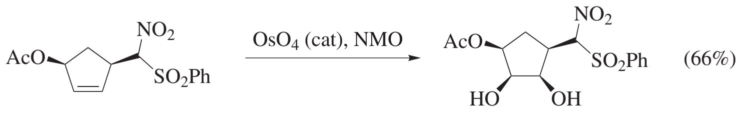
Alternative Directing Groups

Dihydroxylation reactions of allylic alcohols normally give the *anti* product under standard osmium tetroxide oxidation conditions.[6,7] However, scattered reports in the literature suggest that the natural steric bias of certain substrates may be overcome when heteroatomic substituents such as sulfoximines and nitro groups are present within the molecule and a reagent–substrate interaction is postulated to occur. Sulfoximine-directed dihydroxylation of alkene **13**, followed by desulfurization affords triol **14** as a single diastereomer (Eq. 26).[28] Osmium tetroxide oxidation of cyclopentene **15** unexpectedly gives all-*syn* product **16** (Eq. 27).[29] Although association of OsO_4 with the nitrosulfone side-chain is suggested to account for this selectivity,[29] the results from oxidizing a number of simpler analogs do not support a substrate–oxidant association and are interpreted in terms of substrate conformation.[30]



(Eq. 26)

13 **14**



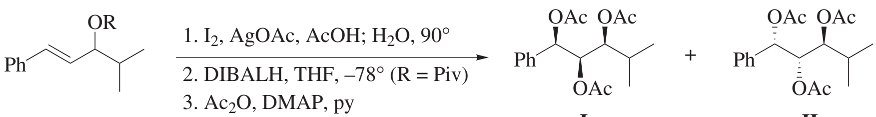
15 **16**

(Eq. 27)

Although interesting, these findings are of limited utility because they cannot be easily interpreted, rationalized, and extended; whereas hydrogen-bonding may come into play in some cases, steric effects are sometimes sufficient to account for the configuration of the products. On the contrary, the OsO_4•TMEDA system relies unequivocally on the hydrogen-bonding ability of the metal complex and shows broad applicability over a large number of allylic alcohol and amine derivatives and enhanced reactivity towards alkenes even at very low temperature.

COMPARISON WITH OTHER METHODS

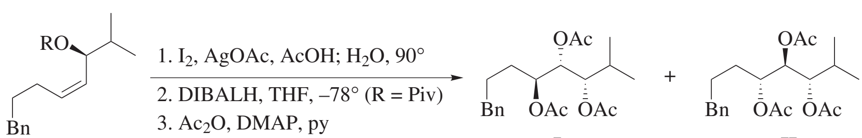
It is noteworthy that the modified Woodward alkene oxidation,[12] which involves the reaction of the alkene with AgOAc and I_2 in HOAc, followed by the addition of H_2O, affords moderate levels of *syn* selectivity in the *cis*-dihydroxylation of some allylic alcohols (Eqs. 28 and 29).[31] Selectivities depend upon the alkene substituents and configuration and the size of the *O*-protecting group, and are generally modest. The *syn* selectivity reflects attack of the iodonium ion on the face of the alkene that is opposite to the –OR group, followed by neighboring group attack within the initially formed β-acetoxy iodocompound. The reversal of stereoselectivity when the same protocol is applied to the free alcohol is attributed to hydrogen-bonding between the –OH and the electrophile.



I **II**

R		I:II
H	(—)	1:12
Ac	(71%)	2.5:1
Piv	(65%)	4:1

(Eq. 28)

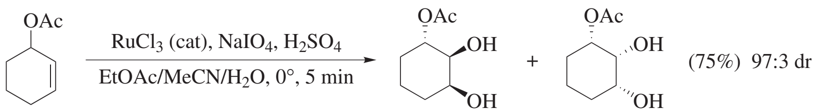


I **II**

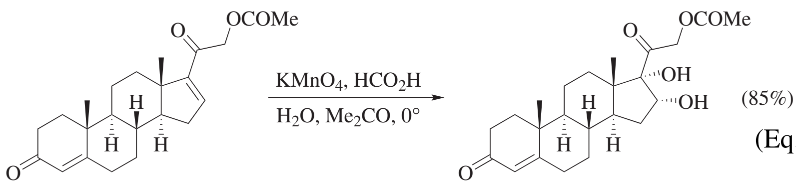
R		I:II
H	(75%)	1:2.6
Ac	(90%)	14.3:1
Piv	(85%)	12.4:1

(Eq. 29)

Alternative, direct oxidations of an alkene to a *syn*-diol have been reported in the literature; we restricted our search to reactions of prochiral substrates possessing a stereogenic center in the allylic position. Although stereocontrolled reactions involving other high-valent metal oxidants are known, no coordination-induced directing effect has been described. For example, ruthenium(VIII)-promoted dihydroxylation leads to *anti* selectivity with respect to the original stereocenter (Eq. 30),[32] and stereocontrolled permanganate-mediated oxidation of a steroidal enone is presumably sterically directed away from the angular methyl group (Eq. 31).[33]



(Eq. 30)



(Eq. 31)

EXPERIMENTAL CONDITIONS

The osmium-mediated dihydroxylation reaction is carried out under an inert atmosphere such as argon or nitrogen and the solvents (CH_2Cl_2, acetone, THF) must be anhydrous. *Osmium tetroxide is toxic, volatile, and sublimes quite easily; it should therefore be handled in a well-ventilated fume-hood. The aqueous layers from the osmium-mediated reactions and any other waste materials should be disposed of properly.*

EXPERIMENTAL PROCEDURES

General Procedure for Stoichiometric Dihydroxylation

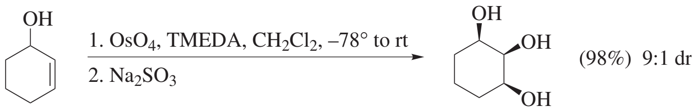
OsO_4·TMEDA.[15] To a solution of substrate (0.50 mmol) and TMEDA (0.55 mmol) in CH_2Cl_2 precooled to $-78°$ was added a solution of OsO_4 (0.53 mmol) in CH_2Cl_2 (~1 mL). The solution turned deep red and then brown-black. It was stirred until the reaction was complete (TLC analysis, ca. 1 h) before being allowed to warm to rt.

Isolation Procedures for 0.50 mmol of Substrate

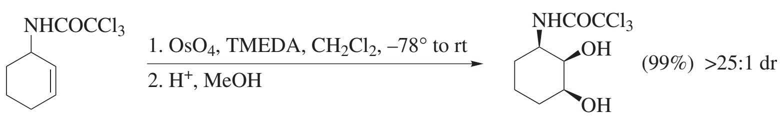
Sodium Sulfite.[15] After completion of the oxidation, the solvent was removed under vacuum and replaced with THF (10 mL) and sodium sulfite (aq saturated solution, 10 mL). This mixture was heated at reflux for 3 h and the work-up completed as indicated.

Acidic Methanol.[15] After completion of the oxidation, the solution was concentrated under vacuum and the resulting residue was dissolved in MeOH (10 mL) before addition of HCl (concentrated, ~5 drops). The solution was stirred for 2 h, concentrated under vacuum, and the product isolated as indicated.

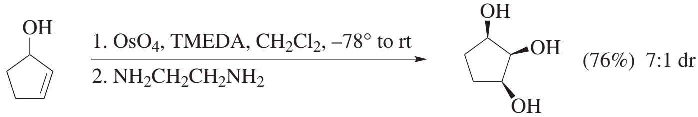
Ethylenediamine.[15] After completion of the oxidation, ethylenediamine (5.0 equiv) was added to the crude reaction mixture at rt and the resulting solution was stirred for 48 h during which time a brown precipitate formed. The solution was then concentrated under vacuum and the product isolated as indicated.



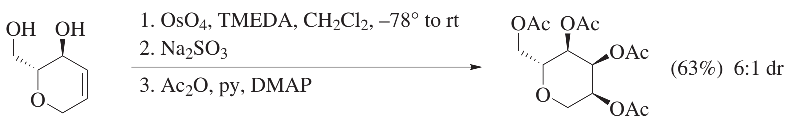
(1*R, 2*S**, 3*S**)-Cyclohexane-1,2,3-triol [Directed Dihydroxylation of an Allylic Cyclic Alcohol Using OsO_4·TMEDA].**[15] 2-Cyclohexene-1-ol (50 mg, 0.51 mmol) was oxidized with OsO_4•TMEDA using the sodium sulfite work-up. The crude reaction mixture was then concentrated under vacuum to afford a grey powder; EtOH (30 mL) was added and the suspension stirred at rt for 1 h. Filtration of the resulting suspension through Celite and concentration of the filtrate under vacuum gave a colorless solid (80 mg). Purification by column chromatography (SiO_2, EtOAc/petroleum ether 7:1) afforded the title compound as an inseparable mixture of isomers (66 mg, 98%, *syn/anti* 9:1): IR (film) 3192, 2927 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 3.81 (t, $J = 2.6$ Hz, 1H), 3.52 (ddd, $J = 10.0, 4.6, 2.6$ Hz, 2H), 1.80–1.00 (m, 6H); ^{13}C NMR (75 MHz, D_2O) δ 72.6, 70.3, 26.3, 18.8; CIMS (m/z): $[M + NH_4]^+$ 150 (100); CI (m/z): $[M + NH_4]^+$ calcd for $C_6H_{16}NO_3$, 150.1130; found, 150.1128.



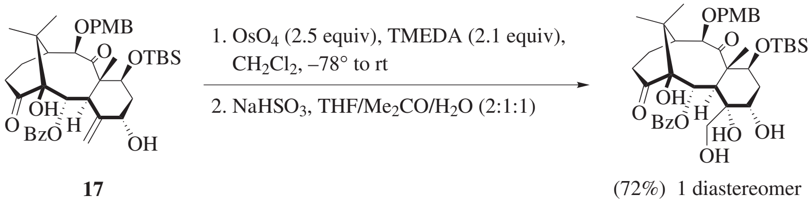
2,2,2-Trichloro-*N*-[(1*R, 2*R**, 3*S**)-2,3-dihydroxycyclohexyl]acetamide [Directed Dihydroxylation of an *N*-Allylic Cyclic Amide Using OsO_4·TMEDA].**[15] 2,2,2-Trichloro-*N*-(cyclohex-2-enyl)acetamide (100 mg, 0.412 mmol) was oxidized with OsO_4•TMEDA using the methanolic work-up; the resulting orange mixture was purified by column chromatography (SiO_2, petroleum ether/EtOAc 1.5:1) to yield the title product (111 mg, 99%) as a colorless oil: IR (film) 3407, 2942, 1698, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 4.06–3.86 (m, 3H), 3.70–3.00 (m, 2H), 1.84–1.58 (m, 5H), 1.46–1.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 92.6, 70.8, 70.3, 52.1, 28.4, 26.1, 18.2; CIMS (m/z): 295 (91), $[M + NH_4]^+$ 293 (100); CI (m/z): $[M + H]^+$ calcd for $C_8H_{13}NO_3Cl_3$, 275.9961; found, 275.9966.



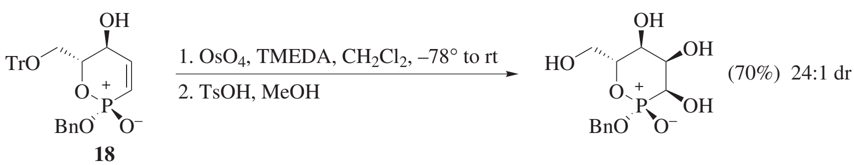
(1*R, 2*S**, 3*S**)-Cyclopentane-1,2,3-triol [Directed Dihydroxylation of an Allylic Cyclic Alcohol Using OsO_4·TMEDA].[15]** Cyclopent-2-enol (100 mg, 1.19 mmol) was oxidized with OsO_4•TMEDA using the ethylenediamine work-up. The residue was redissolved by sonication in a mixture of EtOH (7.5 mL) and EtOAc (40 mL); the resulting solution was filtered through Celite and concentrated under vacuum. Column chromatography (SiO_2, EtOAc) afforded the title compound as a clear oil (66 mg, 76%, *syn*/*anti* 7:1, by ^{1}H NMR). (1*R**, 2*S**, 3*S**)-Cyclopentane-1,2,3-triol was obtained by repeated chromatography: IR (neat) 3365, 2962, 2926 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.09–4.02 (m, 2H), 3.82 (t, $J = 5$ Hz, 1H), 1.95–1.76 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 71.9, 69.9, 27.1; CIMS (m/z): $[M + NH_4]^+$ 154 (100), 90(40); CI (m/z): $[M + NH_4]^+$ calcd for $C_5H_{14}NO_3$, 136.0974; found, 136.0979.



(2*R, 3*R**, 4*S**, 5*S**)-2-(Acetoxymethyl)tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate [Directed Dihydroxylation of an Allylic Cyclic Alcohol Using OsO_4·TMEDA and Subsequent Peracetylation].[15]** (2*R**, 3*S**)-2-(Hydroxymethyl)-3,6-dihydro-2*H*-pyran-3-ol (100 mg, 0.771 mmol) was oxidized with OsO_4•TMEDA using the sodium sulfite work-up. The aqueous mixture was concentrated under vacuum to a grey solid, which was powdered before the sequential addition of pyridine (10 mL), Ac_2O (5 mL) and DMAP (cat). The resulting black suspension was stirred at rt under an atmosphere of nitrogen for 48 h; Et_2O (100 mL) was then added and the mixture filtered through Celite (washing further with Et_2O (200 mL)). The filtrate was washed with HCl (aq solution, 2M, 100 mL), $NaHCO_3$ (aq saturated solution, 100 mL) and brine (100 mL). The organic extracts were dried ($MgSO_4$) and concentrated under vacuum to afford a light-brown oil (201 mg) as a mixture of isomers (*syn*/*anti* 6:1 by ^{1}H NMR). Purification by column chromatography (SiO_2, petroleum ether/EtOAc 6:1) gave the title product (161 mg, 63%) as a colorless oil: $[\alpha]^{27}{}_D + 7.5$ (*c* 0.2, $CHCl_3$); IR (film) 2996, 1747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (t, $J = 2.6$ Hz, 1H), 4.95 (ddd, $J = 10.0, 5.5, 2.6$ Hz, 1H), 4.84 (ddd, $J = 10.0, 5.5, 2.6$ Hz, 1H), 4.14–4.10 (m, 2H), 3.88–3.78 (m, 2H), 3.60 (t, $J = 10.0$ Hz, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.69, 169.89, 169.30, 169.11, 71.71, 67.77, 66.40, 66.27, 63.45, 62.49, 20.70 (2) and 20.55 (2); CIMS (m/z): $[M + NH_4]^+$ 350(10), 249(100); CI (m/z): $[M + NH_4]^+$ calcd for $C_{14}H_{24}NO_9$, 350.1451; found, 350.1454.

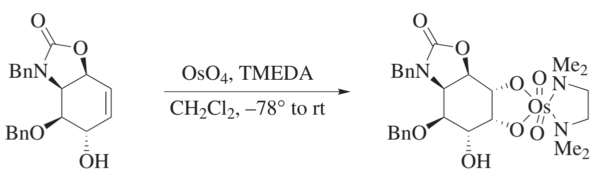


Tricyclic Tetraol [Directed Dihydroxylation of an Exocyclic Allylic Alcohol Using OsO_4·TMEDA].[17] A solution of alkene **17** (590 mg, 0.842 mmol) in CH_2Cl_2 (32.4 mL) was cooled to −78° and treated sequentially with TMEDA (0.32 mL, 2.1 mmol) and OsO_4 (531 mg, 2.09 mmol). The reaction mixture was stirred at this temperature for 2 h, allowed to warm to rt over 15 min, and concentrated under vacuum. The residue was taken up in THF (80 mL), acetone (40 mL), and water (40 mL), treated with sodium bisulfite (7.5 g), and stirred for 3 h. Water (100 mL) and EtOAc (100 mL) were then added, the aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic phases were concentrated under vacuum. THF (80 mL), acetone (40 mL), water (40 mL), and sodium bisulfite (4.0 g) were added, and the mixture was stirred at rt for 20 h. The resultant mixture was filtered through a pad of Celite and the residue rinsed with EtOAc (3 × 150 mL). The layers were separated, the aqueous phase was extracted with EtOAc (2 × 50 mL), the combined organic phases were evaporated, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc 1.2:1) to give the title product as a colorless oil (460 mg, 72%). The spectroscopic properties of the tricyclic tetraol were identical to those previously reported:[34] $[\alpha]^{20}_D$ +5.2 (*c* 0.56, $CHCl_3$); IR (neat) 3470, 1719, 1706, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.2 Hz, 2H), 7.54–7.52 (m, 1H), 7.44–7.40 (m, 2H), 7.26 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 5.71 (d, J = 5.8 Hz, 1H), 4.79 (d, J = 4.0 Hz, 1H), 4.55 (dd, J = 4.3, 11.6 Hz, 1H), 4.43 (d, J = 10.5 Hz, 1H), 4.06 (d, J = 10.6 Hz, 1H), 3.99 (s, 1H), 3.87 (br s, 1H), 3.82 (d, J = 5.8 Hz, 1H), 3.74 (s, 3H), 3.56 (d, J = 10.2 Hz, 1H), 3.43–3.41 (m, 1H), 3.36 (s, 1H), 3.16–3.06 (m, 1H), 2.77 (s, 1H), 2.77–2.72 (m, 1H), 2.36–2.26 (m, 2H), 2.18–2.16 (m, 1H), 1.94–1.93 (m, 1H), 1.88–1.80 (m, 1H), 1.80–1.70 (m, 1H), 1.30 (s, 3H), 1.03 (s, 3H), 0.87 (s, 3H), 0.78 (s, 9H), 0.01 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 208.9, 165.2, 159.4, 152.8, 133.8, 129.8, 129.5, 128.98, 128.9, 113.8, 84.2, 81.6, 75.2, 74.0, 73.5, 71.5, 67.2, 62.9, 58.7, 55.2, 51.3, 42.1, 38.9, 38.0, 32.9, 31.0, 29.6, 25.7, 22.7, 18.2, 10.0, −2.1, −4.2; ES HRMS (m/z): [M + Na^+] calcd for $C_{40}H_{56}O_{11}SiNa$, 763.3490; found, 763.3432.

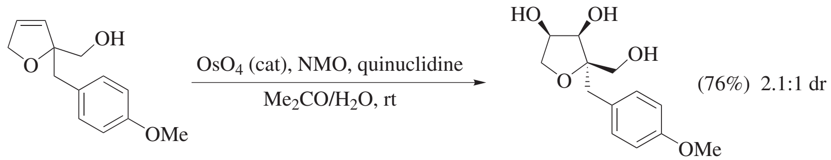


($2S_P^*$,$3S^*$,$4R^*$,$5S^*$,$6R^*$)-2-Phenylmethoxy-6-(hydroxymethyl)-3,4,5-trihydroxy-1,2-oxaphosphorinane-2-oxide) [Directed Dihydroxylation of an Allylic Cyclic Alcohol Using OsO_4·TMEDA].[35] To a solution of OsO_4

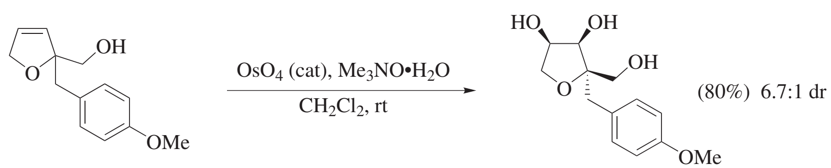
(43 mg, 0.17 mmol) in CH_2Cl_2 (0.6 mL) at $-78°$ was added TMEDA (22 mg, 0.19 mmol) followed by the alcohol **18** (68 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 3 h at $-78°$, warmed to rt, and stirred for 15 min. The solution was concentrated under vacuum to give the crude osmate ester, which was dissolved in MeOH (1 mL) and treated with citric acid (40 mg, 0.21 mmol) for 24 h. The solution was concentrated under vacuum; the residue was dissolved in a small amount of MeOH, and filtered through silica gel (EtOAc/MeOH 9:1). The crude product was dissolved in MeOH (1 mL), treated with a catalytic amount of TsOH•H_2O, and stirred for 8 h. The solution was then concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, EtOAc/MeOH 9:1) to afford the title compound (28 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.31 (m, 5H), 5.21–5.11 (m, 2H), 4.55–4.50 (m, 1H), 4.24 (dt, $J = 33.7$, 2.7 Hz, 1H), 4.01 (dd, $J = 9.8$, 3.4 Hz, 1H), 3.90 (ddd, $J = 12.5$, 4.4, 2.9 Hz, 1H), 3.75 (dd, $J = 9.8$, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (d, $J_{CP} = 6.4$ Hz), 129.7, 129.6, 129.2, 78.4 (d, $J_{CP} = 4.4$ Hz), 75.5 (d), 71.4, 69.6 (dt, $J_{CP} = 6.4$ Hz), 69.0 (d), 67.7 (d, $J_{CP} = 144.5$ Hz), 62.8 (dt, $J_{CP} = 8.0$ Hz); ^{31}P NMR δ 24.5; HRMS-FAB (m/z): $[M + H]^+$ calcd for $C_{38}H_{36}O_8P$, 651.2148; found, 651.2131.



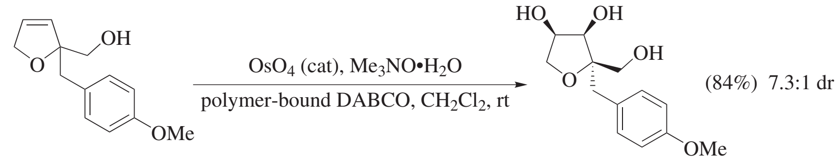
Osmate ester of (3a*R,4*S**,5*S**,6*R**,7*R**,7a*R**)-3-Benzyl-4-benzyloxy-5,6,7-trihydroxyhexahydrobenzo[*d*]oxazol-2(3*H*)-one [Preparation of an Osmate Ester Using OsO_4·TMEDA].[36]** A solution of OsO_4 (140 mg, 0.551 mmol) in CH_2Cl_2 (0.7 mL) was added to a solution of (3a*S**, 4*S**, 5*S**,7a*S**)-3-benzyl-4-(benzyloxy)-5-hydroxy-3,3a,4,5-tetrahydrobenzo[*d*]oxazol-2(7a*H*)-one (184 mg, 0.532 mmol) and TMEDA (87.0 μL, 0.580 mmol) in CH_2Cl_2 at $-78°$ and the reaction mixture was stirred for 2 h. The solution was allowed to warm to rt, concentrated onto silica and the crude material was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 19:1) to afford the title compound as a brown foam (379 mg, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.18 (m, 10H), 4.90 (dd, $J = 8.8$, 4.8 Hz, 1H), 4.84 (d, $J = 15.2$ Hz, 1H), 4.75 (d, $J = 11.6$ Hz, 1H), 4.68 (t, $J = 5.6$ Hz, 1H), 4.56 (dd, $J = 11.2$, 5.6 Hz, 1H), 4.53 (m, 1H), 4.48 (d, $J = 12.0$ Hz, 1H), 4.01 (app quart, 1H), 4.01 (app quart, 1H), 3.93 (d, $J = 15.2$ Hz, 1H), 3.76, (d, $J = 2.8$ Hz, 1H), 3.16–3.08 (m, 4H), 2.93 (s, 3H), 2.90 (s, 3H), 2.89 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 138.0, 136.4, 128.6, 128.4, 128.1, 128.0, 127.7, 127.6, 87.9, 82.1, 75.2, 74.6, 72.9, 68.0, 64.7, 64.3, 53.6, 52.6, 52.3, 52.0, 51.6, 46.8; ESI$^+$ (m/z): $[M + MeCN + NH_4]^+$ 724 (100); ESI$^+$ (m/z): $[M + MeCN + NH_4]^+$ calcd for $C_{27}H_{38}N_3O_8Os$, 724.2274; found, 724.2278.



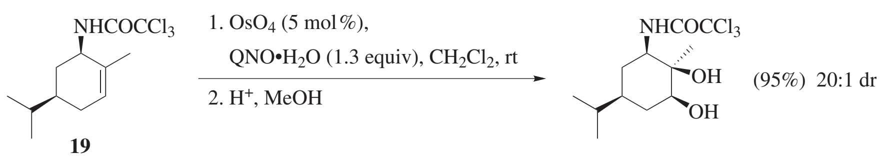
($2R^*$,$3R^*$,$4R^*$)-2-Hydroxymethyl-2-(4-methoxybenzyl)tetrahydrofuran-3,4-diol [Directed Dihydroxylation of a Homoallylic Alcohol Using Catalytic OsO_4·Quinuclidine and NMO].[37] 4-Methylmorpholine-*N*-oxide (240 mg, 2.01 mmol) was added to a stirred solution of 2-hydroxymethyl-2-(4-methoxybenzyl)-2,5-dihydrofuran (150 mg, 0.681 mmol) in acetone (20 mL) and water (5 mL) at rt, followed by quinuclidine (5 mg, 7 mol %) and OsO_4 (5 mg, 3 mol %). The reaction mixture was stirred overnight. Acetone was removed under vacuum before the addition of EtOAc (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to give the crude product as a mixture of diastereomers (*syn*/*anti* 2.1:1, by HPLC). Purification by column chromatography (SiO_2, CH_2Cl_2/*i*-PrOH 19:1) gave (2*R**,3*S**,4*S**)-2-hydroxymethyl-2-(4-methoxybenzyl)tetrahydrofuran-3,4-diol (41 mg, 24%) as a crystalline solid, mp 103–105°, and (2*R**, 3*R**, 4*R**)-2-(hydroxymethyl)-2-(4-methoxybenzyl)tetrahydrofuran-3,4-diol (89 mg, 52%) as a crystalline solid, mp 93–95°. Analytical data for the major isomer: R_f (CH_2Cl_2/*i*-PrOH 95:5) 0.26; IR 3232, 1249 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.20–7.16 (m, 2H), 6.85–6.81 (m, 2H), 4.04 (d, $J = 5.3$ Hz, 1H), 3.81 (dd, $J = 8.3, 4.7$ Hz, 1H), 3.76 (s, 3H), 3.71–3.61 (m, 3H), 3.52 (d, $J = 11.4$ Hz, 1H), 2.81 (d, $J = 13.9$ Hz, 1H), 2.71 (d, $J = 13.9$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.9, 131.7, 129.1, 113.5, 85.4, 75.2, 71.9, 71.8, 64.3, 54.6, 40.2; ESI$^+$ (m/z): [M + Na$^+$] 277 (100); ESI$^+$ (m/z): [M + Na]$^+$ calcd for $C_{13}H_{18}O_5Na$, 277.1046; found, 277.1046; Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.37; H, 7.16.



($2R^*$,$3R^*$,$4R^*$)-2-Hydroxymethyl-2-(4-methoxybenzyl)tetrahydrofuran-3,4-diol [Directed Dihydroxylation of a Homoallylic Alcohol Using Catalytic OsO_4 and TMO].[37] Trimethylamine-*N*-oxide dihydrate (5.7 g, 51 mmol) was added to a stirred solution of 2-hydroxymethyl-2-(4-methoxybenzyl)-2,5-dihydrofuran (3.78 g, 17.2 mmol) in CH_2Cl_2 (200 mL) at rt. OsO_4 (50 mg, 0.20 mmol) was then added and the mixture stirred overnight. Sodium sulfite (aq saturated solution, 20 mL) was added and the mixture stirred for 20 min. The organic layer was dried ($MgSO_4$) and concentrated under vacuum to give the crude product as a mixture of diastereomers (*syn*/*anti* 6.7:1, by HPLC). Purification by column chromatography (SiO_2, CH_2Cl_2/*i*-PrOH 19:1) gave the *anti*-triol (0.45 g, 10%) and the *syn*-triol (3.04 g, 70%).



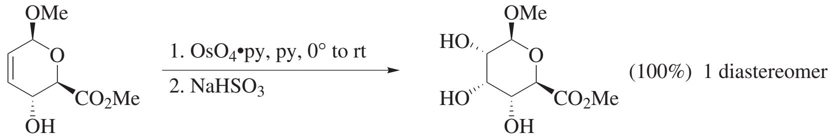
(2*R,3*R**,4*R**)-2-Hydroxymethyl-2-(4-methoxybenzyl)tetrahydrofuran-3,4-diol [Directed Dihydroxylation of a Homoallylic Alcohol Using Catalytic OsO_4, TMO, and Polymer-Bound DABCO].[37]** Polymer-bound 1,4-diazabicyclo[2.2.2]octane chloride (100 mg, 1% DVB, 100-200 mesh) was added to a solution of OsO_4 (26 mg) in cyclohexane (5 mL); the solvent was then evaporated, and the solid so obtained (100 mg, ~10 mol % OsO_4) was added to a solution of 2-hydroxymethyl-2-(4-methoxybenzyl)-2,5-dihydrofuran (100 mg, 0.451 mmol) in CH_2Cl_2 (15 mL) at rt. Trimethylamine-*N*-oxide dihydrate (150 mg, 1.40 mmol) was added and the mixture was shaken overnight; the polymer was then removed by filtration and the filtrate was concentrated under vacuum to give the crude product as a mixture of diastereomers (*syn*/*anti* 7.3:1, by HPLC). Purification by column chromatography (SiO_2, CH_2Cl_2/*i*-PrOH 19:1) gave the *anti*-triol (12 mg, 10%) and the *syn*-triol (85 mg, 74%).



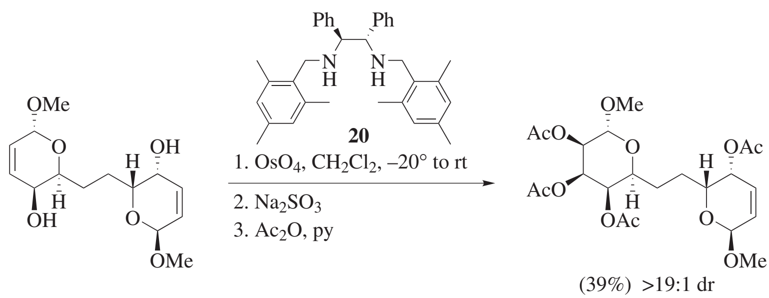
2,2,2-Trichloro-*N*-((1*R, 2*R**, 3*S**, 5*S**)-2,3-dihydroxy-5-isopropyl-2-methylcyclohexyl)acetamide [Directed Dihydroxylation of an Allylic Cyclic Amide Using Catalytic OsO_4 and QNO].[19]** Quinuclidine (1.00 g, 9.01 mmol) was dissolved in CH_2Cl_2 (20 mL) under nitrogen and cooled to −78° before the addition of recrystallised *m*-CPBA (1.94 g, 11.24 mmol) in one portion. The mixture was stirred for 30 min and then allowed to warm to rt. The crude reaction mixture was flushed through a column of silica gel using CH_2Cl_2 as eluent until all of the benzoic acid byproduct was removed, then the solvent gradient was increased (CH_2Cl_2/MeOH 2.3:1) to strip quinuclidine-*N*-oxide from the column. Concentration under vacuum produced a brown oil, which crystallised on standing under high vacuum conditions to produce QNO as an off-white solid (1.25 g, 95%) and this was stored under reduced pressure. KF analysis showed this hygroscopic material contained 11% water by weight (~QNO•H_2O), and on standing open to air this increased to 40% water by weight (~QNO•$5H_2O$).

Quinuclidine-*N*-oxide monohydrate (0.36 g, 2.18 mmol) was added in one portion to a stirred solution of trichloroacetamide **19** (0.50 g, 1.68 mmol) in

CH_2Cl_2 at rt. OsO_4 (0.02 g, 0.08 mmol) was then added and the reaction mixture was stirred until complete consumption of the starting amide was observed by TLC. MeOH (10 mL) and HCl (concd, 4 drops) were added and the resulting solution was stirred for 2 h and then concentrated under vacuum to afford a dark yellow, viscous oil. Purification by column chromatography (SiO_2, petroleum ether/Et_2O 1:4) yielded the title compound (0.53 g, 95%, *syn*/*anti* 20:1, by HPLC) as a colorless crystalline solid. The analytical data for the product was not reported in this reference.



(2*R, 3*R**, 4*S**, 5*S**, 6*S**)-Methyl 3,4,5-Trihydroxy-6-methoxytetrahydro-2*H*-pyran-2-carboxylate [Directed Dihydroxylation of an Allylic Cyclic Alcohol Using OsO_4·Pyridine].[38]** (2*R**, 3*R**, 6*S**)-Methyl 3-Hydroxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-carboxylate (50 mg, 0.25 mmol) in pyridine (4 mL) was added to an OsO_4 (70 mg, 0.28 mmol, 1.1 equiv) solution in pyridine (0.5 mL). After 2 h at rt, the reaction was quenched with $NaHSO_3$ (aq saturated solution, 1 mL) and dry loaded onto SiO_2. Purification by column chromatography (SiO_2, CH_2Cl_2/MeOH 9:1) gave the title compound as a colorless oil (60 mg, 0.25 mmol, 100%): IR (neat) 3418, 2930, 1736, 1084, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.56 (d, $J = 6.8$ Hz, 1H), 4.26–4.16 (m, 3H), 3.86 (dd, $J = 3.0, 9.0$ Hz, 1H), 3.49 (s, 3H), 3.47 (dd, $J = 3.4, 7.1$ Hz, 1H), 2.78 (br s, 3H), 1.26 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 102.4, 73.5, 71.0, 69.7, 69.5, 62.2, 57.8, 14.4; EIMS (m/z): [M−H_2O] 218 (1), [M + H−MeOH] 205 (2), 71 (100). CIMS (m/z): $[M + H]^+$ 237 (1), [M + H−MeOH] 205 (18), 187 (100).



(2*R, 3*S**, 4*S**, 5*S**, 6*S**)-2-{2-[(2*S**, 3*S**, 6*R**)-3-Acetoxy-6-methoxy-3, 6-dihydro-2*H*-pyran-2-yl]ethyl}-3,4,5-triacetoxy-6-methoxytetrahydropyran [Directed Dihydroxylation Using OsO_4 and a Chiral Amine].[39]** A solution of diamine **20** (33.9 mg, 0.071 mmol) in CH_2Cl_2 (0.5 mL) was added to a stirred solution of OsO_4 (20 mg, 0.071 mmol) in CH_2Cl_2 (1.5 mL). The yellow solution was cooled to −20°; ($2R^*, 3S^*, 6R^*$)-2-(2-(($2R^*, 3R^*, 6S^*$)-3-hydroxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl)ethyl)-6-methoxy-3,6-dihydro-2*H*-pyran-3-ol (20 mg, 0.071 mmol) was added in one portion and the reaction mixture was stirred for 5 h, warmed to rt, stirred for 2 d and evaporated under vacuum. The residue was dissolved in THF/sodium sulfite (aq saturated solution, 1:1, 2 mL), refluxed for 2 h and evaporated under vacuum to give a crude product. Crude ($2R^*, 3R^*, 4R^*, 5R^*, 6R^*$)-2-(2-(($2R^*, 3R^*, 6S^*$)-3-hydroxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl)ethyl)-6-methoxytetrahydro-2*H*-pyran-3,4,5-triol was dissolved in a mixture of Ac_2O (2 mL) and pyridine (1 mL), stirred for 5 h at rt, and evaporated under vacuum to give the crude product. Purification by column chromatography (petroleum ether/EtOAc 2.3:1) afforded the title product (13.2 mg, 39%) as a viscous colorless oil: $[\alpha]_D^{20}$ +90.9 (*c* 0.033, $CHCl_3$); R_f 0.31 (petroleum ether/EtOAc 2.3:1); IR (thin film) 2960, 2924, 2853, 1742, 1678, 1455, 1373, 1259, 1083 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (ddd, $J = 10.0$, 5.5, 1.0 Hz, 1H), 6.00 (ddd, $J = 10.0$, 3.0, 0.4 Hz, 1H), 5.27 (t, $J = 3.8$ Hz, 4H), 5.21 (dd, $J = 3.8$, 1.2 Hz, 1H), 5.10 (dt, $J = 3.8$, 1.2 Hz, 1H), 4.91 (d, $J = 3.0$ Hz, 1H), 4.76 (d, $J = 1.2$ Hz, 1H), 4.02 (td, $J = 9.3$, 2.6 Hz, 1H), 3.97 (ddd, $J = 9.3$, 3.8, 1.0 Hz, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 2.14 (s, 3H), 2.14 (s, 3H), 2.08 (s, 3H), 1.99 (s, 3H) and 1.77–1.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.4, 170.1, 169.6, 130.4, 125.9, 99.4, 95.2, 68.8, 68.3, 67.5, 66.0, 64.5, 55.7, 55.2, 27.1, 26.4, 21.0, 20.8, 20.7, 20.6; ESI^+ (m/z): $[M + Na]^+$ 511 (100); ESI^+ (m/z): $[M + Na]^+$ calcd for $C_{22}H_{32}O_{12}Na$, 511.1791; found, 511.1768.

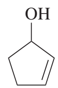
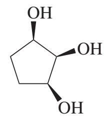
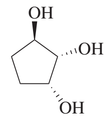
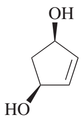
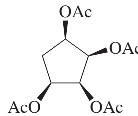
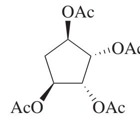
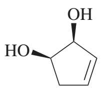
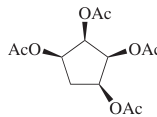
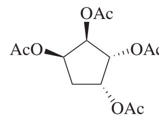
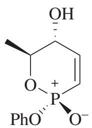
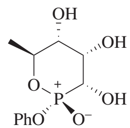
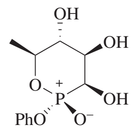
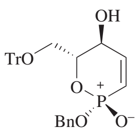
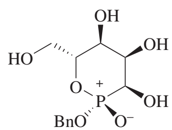
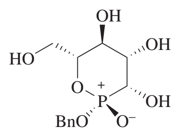
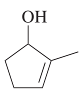
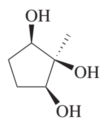
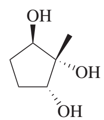
TABULAR SURVEY

The literature has been covered through the end of September 2007. The tables are organized by substrate type. Entries in the tables are in order of increasing number of carbons. Protecting groups and *O*-methyl groups are excluded from the count. The symbol (—) indicates that no yield was reported and the symbol — indicates that no dr (*syn*/*anti*) was reported.

Abbreviations used in the tables are as follows:

ee	enantiomeric excess
eq	equivalents
QNO	quinuclidine *N*-oxide
TBDPS	*tert*-butyldiphenylsilyl

TABLE 1. DIRECTED DIHYDROXYLATION OF ALLYLIC CYCLIC ALCOHOLS

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_5 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then $NH_2(CH_2)_2NH_2$	 **I** +  **II** **I** + **II** (76), **I**:**II** = 7:1	21, 15
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then $NH_2(CH_2)_2NH_2$ 2. Ac_2O, py	 **I** +  **II** **I** + **II** (73), **I**:**II** = 25:1	15
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then $NH_2(CH_2)_2NH_2$ 2. Ac_2O, py	 **I** +  **II** **I** + **II** (67), **I**:**II** = 2:1	15
	OsO_4, TMEDA, CH_2Cl_2, –60° to rt; then citric acid, MeOH	 **I** +  **II** **I** + **II** (70), **I**:**II** = 13.5:1	35
	OsO_4, TMEDA, CH_2Cl_2, –60° to rt; then TsOH, MeOH	 **I** +  **II** **I** + **II** (70), **I**:**II** = 24:1	35
C_6 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then $NH_2(CH_2)_2NH_2$	 **I** +  **II** **I** + **II** (88), **I**:**II** = 25:1	15

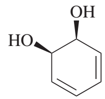
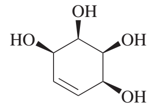
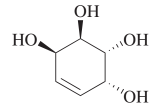
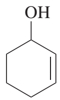
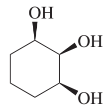
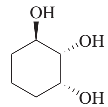
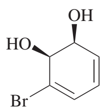
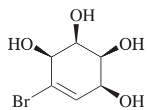
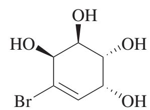
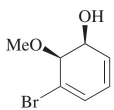
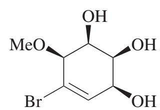
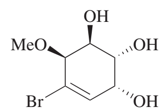
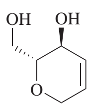
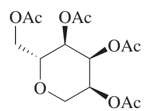
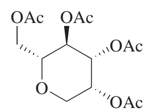
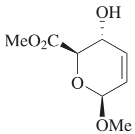
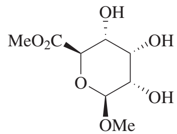
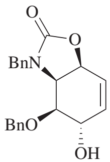
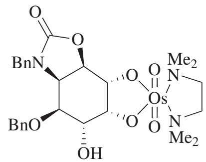
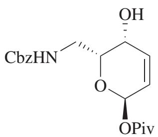
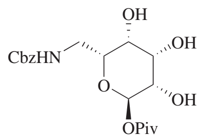
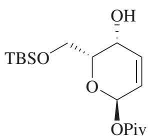
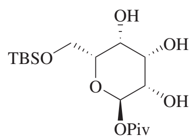
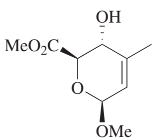
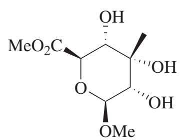
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then Na_2SO_3	 **I** +  **II**	**I** + **II** (54), **I**:**II** = 16:1	21, 15
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then Na_2SO_3	 **I** +  **II**	**I** + **II** (98), **I**:**II** = 9:1	15
	OsO_4 (cat), $Me_3NO{\bullet}2H_2O$, CH_2Cl_2	 **I** +  **II**	**I** + **II** (79), **I**:**II** = 4.6:1	21
	OsO_4, quinuclidine, CH_2Cl_2, –78°	 **I** +  **II**	**I** + **II** (71), **I**:**II** = 2.2:1	40
	OsO_4 (cat), $Me_3NO{\bullet}2H_2O$, CH_2Cl_2	**I** + **II** (40), **I**:**II** = 2:1		40
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then Na_2SO_3 2. Ac_2O, py	 **I** +  **II**	**I** + **II** (63), **I**:**II** = 6:1	21, 15

TABLE 1. DIRECTED DIHYDROXYLATION OF ALLYLIC CYCLIC ALCOHOLS (*Continued*)

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)		Refs.
C_6 	OsO_4•py, py, 0° to rt; then $NaHSO_3$		(100), 1 diastereomer	38
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt		(100), 1 diastereomer	36
	OsO_4, TMEDA, CH_2Cl_2, –78°; then $NH_2(CH_2)_2NH_2$		(47), 1 diastereomer	41
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then Na_2SO_3		(80), 1 diastereomer	42, 20, 15
C_7 	OsO_4•py, py, 0° to rt; then $NaHSO_3$		(60), 1 diastereomer	38

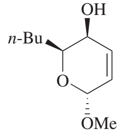
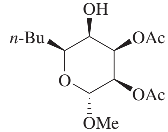
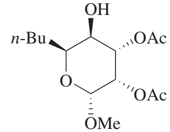
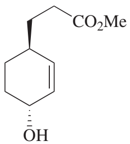
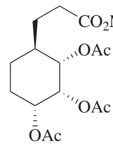
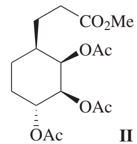
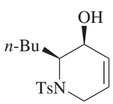
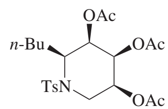
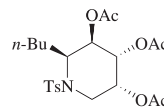
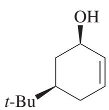
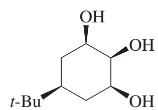
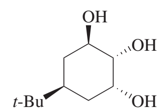
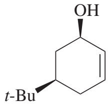
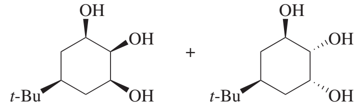
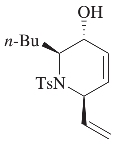
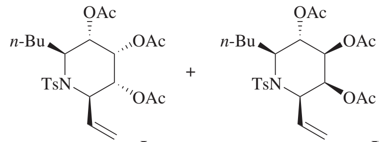
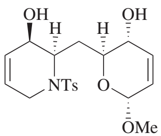
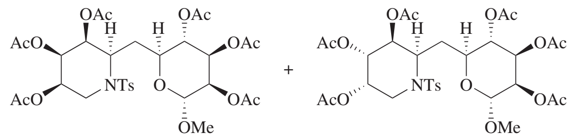
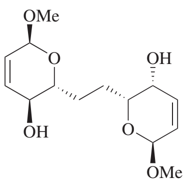
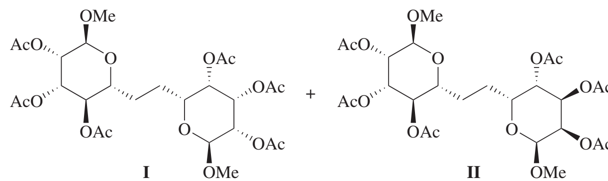
C_9 	1. OsO_4, TMEDA, CH_2Cl_2, –78° 2. Ac_2O, py	 **I** +  **II** **I + II** (94), **I:II** = >19:1	43
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then Na_2SO_3 2. Ac_2O, py	 **I** (—), 1 diastereomer	44
	1. OsO_4•py, py, 0° to rt; then $Na_2S_2O_5$ 2. Ac_2O, DMAP, py	**I** +  **II** **I + II** (32), **I:II** = 1:1	44
	1. OsO_4, TMEDA, CH_2Cl_2, –78° 2. Ac_2O, py	 **I** +  **II** **I + II** (74), **I:II** = 24:1	45, 46
C_{10} 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then Na_2SO_3	 **I** +  **II** **I + II** (95), **I:II** = 25:1	21, 15

TABLE 1. DIRECTED DIHYDROXYLATION OF ALLYLIC CYCLIC ALCOHOLS (*Continued*)

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_{10} 	OsO_4, amine, CH_2Cl_2, 0° to rt; then Na_2SO_3	 **I** **II** **I** + **II** (—) Amine / **I**:**II**: TMEDA 4.6:1; Me_3N 1.2:1; $Me_2NCH_2NMe_2$ 1.6:1; $Me_2N(CH_2)_2OH$ 1.1:1; $Me_2N(CH_2)_2OMe$ 1.1:1; $Me_2N(CH_2)_3NMe_2$ 2.8:1	15
C_{12} 	1. OsO_4, TMEDA, CH_2Cl_2, –78° 2. Ac_2O, py	 **I** **II** **I** + **II** (25), **I**:**II** = 3:1	45, 46
	1. OsO_4, TMEDA, CH_2Cl_2, –78° 2. Ac_2O, py	 **I** **II** **I** + **II** (17), **I**:**II** = 24:1	45, 46
	1. OsO_4, TMEDA, CH_2Cl_2, –78° 2. Ac_2O, py	 **I** **II** **I** + **II** (83), **I**:**II** = 19:1	47, 48

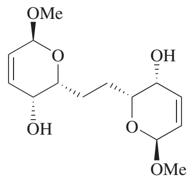
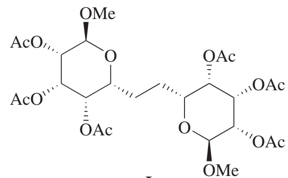
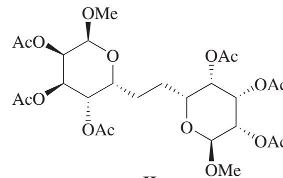
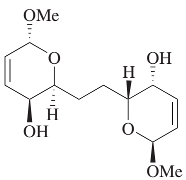
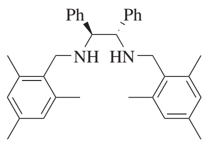
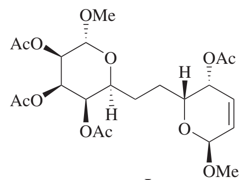
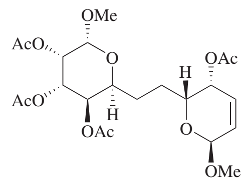
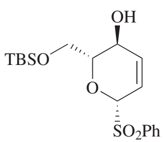
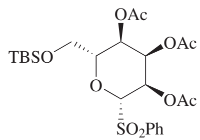
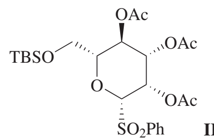
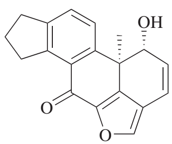
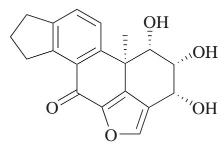
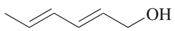
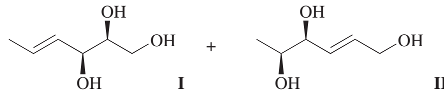
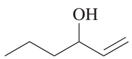
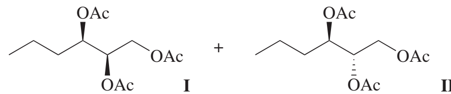
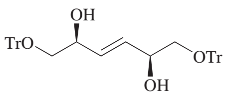
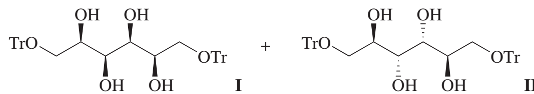
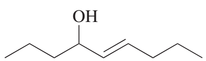
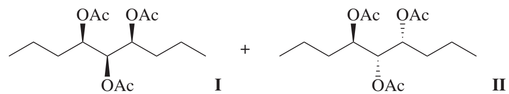
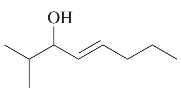
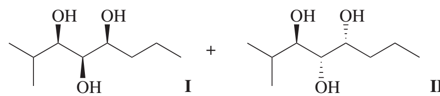
	1. OsO_4, TMEDA, CH_2Cl_2, –78° 2. Ac_2O, py	 **I** +  **II** **I** + **II** (78), **I**:**II** = 24:1	47, 48
	1. , OsO_4, CH_2Cl_2, –20° 2. Ac_2O, py	 **I** +  **II** **I** + **II** (39), **I**:**II** = 19:1	39
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (82), **I**:**II** = 25:1	15
C_{19}			
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then py/H_2O/$NaHSO_3$ (35:30:2)	 (76), 1 diastereomer	49

TABLE 2. DIRECTED DIHYDROXYLATION OF ACYCLIC AND EXOCYCLIC ALLYLIC ALCOHOLS

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_6			
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I + II** (70), **I**:**II** = 5:1	21
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I + II** (74), **I**:**II** = 5:1	50
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I + II** (95), **I**:**II** = 1.1:1	51
C_9			
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I + II** (83), **I**:**II** = 3:1	50
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I + II** (84), **I**:**II** = 3:1	50

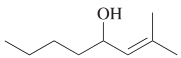
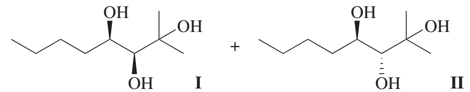
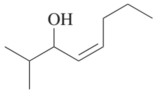
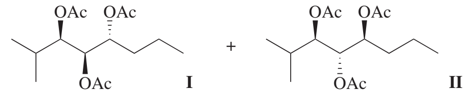
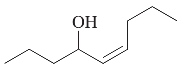
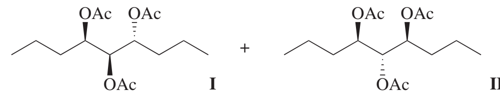
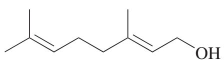
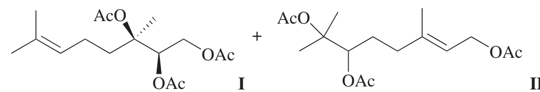
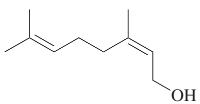
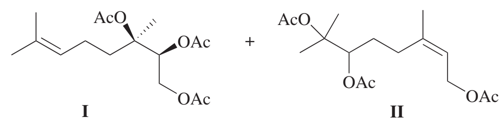
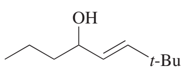
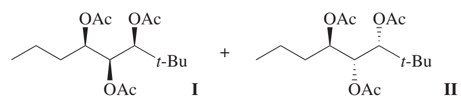
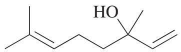
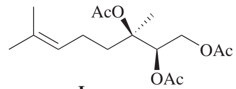
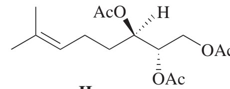
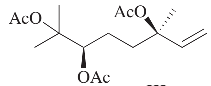
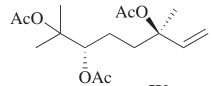
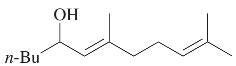
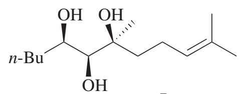
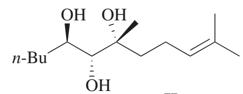
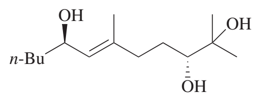
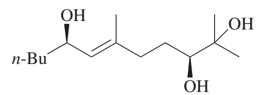
		OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I + II** (78), **I**:**II** = 25:1	50
		1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I + II** (79), **I**:**II** = 25:1	50
		1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I + II** (74), **I**:**II** = 25:1	50
C_{10}		1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I + II** (74), **I**:**II** = >25:1	21
		1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I + II** (68), **I**:**II** = 4:1	21
		1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I + II** (75), **I**:**II** = 4:1	50

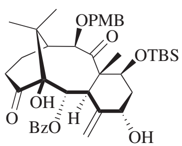
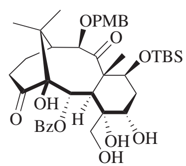
TABLE 2. DIRECTED DIHYDROXYLATION OF ACYCLIC AND EXOCYCLIC ALLYLIC ALCOHOLS (*Continued*)

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_{10} 	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** +  **III** +  **IV**	21

I + II	**I:II**	**III + IV**	**III:IV**
(70)	2.5:1	(6)	—

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_{14} 	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** +  **III** +  **IV**	50

I + II	**I:II**	**III + IV**	**III:IV**
(70)	24:1	(<5)	—

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_{19} 	OsO_4 (2.5 eq), TMEDA (2.1 eq), CH_2Cl_2, –78° to rt; then $NaHSO_3$, THF/acetone/H_2O (2:1:1)	 (72), 1 diastereomer	17

C$_{22}$

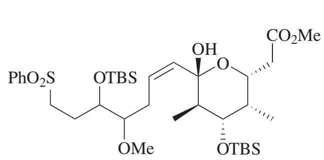
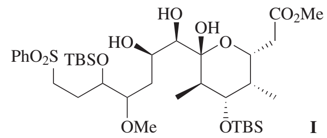
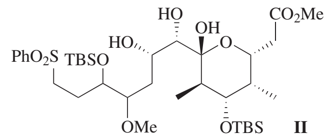
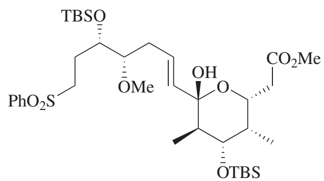
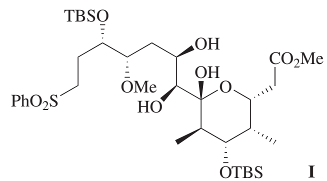
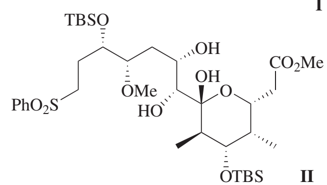
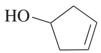
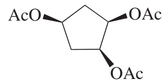
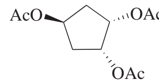
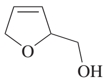
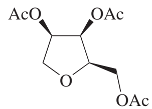
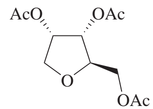
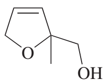
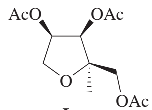
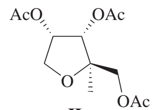
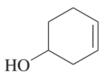
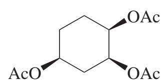
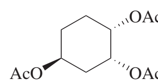
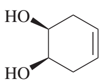
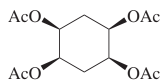
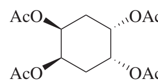
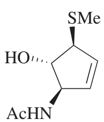
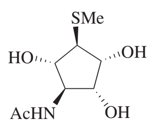
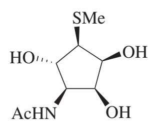
	OsO_4 (1.0 eq), TMEDA (1.1 eq), CH_2Cl_2, –78° to rt; then $NaHSO_3$	 **I** +  **II** **I** + **II** (100), **I**:**II** = 9:1	52
	OsO_4 (1.0 eq), TMEDA (1.1 eq), CH_2Cl_2, –78° to rt; then $NaHSO_3$	 **I** +  **II** **I** + **II** (100), **I**:**II** = 5:1	52

TABLE 3. DIRECTED DIHYDROXYLATION OF HOMOALLYLIC CYCLIC ALCOHOLS

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_5			
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (71), **I**:**II** = 25:1	25, 22
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (55), **I**:**II** = 1:1	25, 22
C_6			
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (83), **I**:**II** = 6:1	25, 22
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (92), **I**:**II** = 3:1	25, 22
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (55), **I**:**II** = 12.4:1	25, 22
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt	 **I** +  **II** **I** + **II** (71), **I**:**II** = 6:1	53

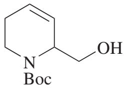
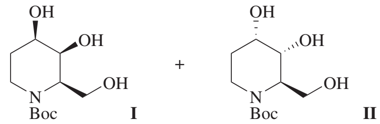
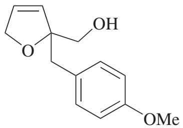
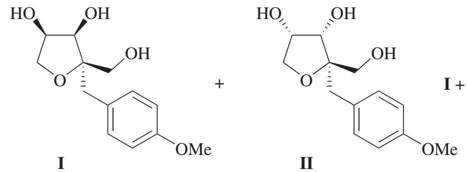
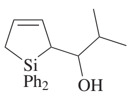
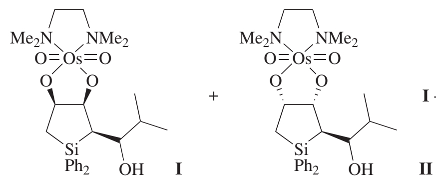
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** + **II**; **I + II** (86), **I**:**II** = 2:1	54
C_{12} 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** + **II**; **I + II** (82), **I**:**II** = 99:1	37
	OsO_4 (cat), quinuclidine, acetone/H_2O	**I + II** (76), **I**:**II** = 2.1:1	37
	OsO_4 (cat), $Me_3NO{\bullet}2H_2O$, CH_2Cl_2	**I + II** (80), **I**:**II** = 6.7:1	37
	OsO_4 (cat), $Me_3NO{\bullet}2H_2O$, polymer-bound DABCO, CH_2Cl_2	**I + II** (84), **I**:**II** = 7.3:1	37
C_{20} 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt	 **I** + **II**; **I + II** (—), **I**:**II** = 1.2:1	55

TABLE 4. DIRECTED DIHYDROXYLATION OF HOMOALLYLIC EXOCYCLIC ALCOHOLS

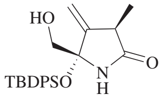
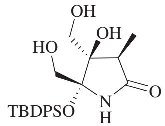
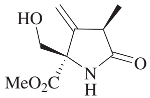
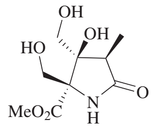
Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_7 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 (99), 1 diastereomer	56
C_8 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 (35), 1 diastereomer	56

TABLE 5. DIRECTED DIHYDROXYLATION OF *N*-ALLYLIC AMINE DERIVATIVES

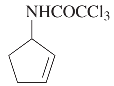
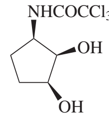
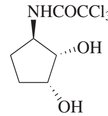
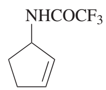
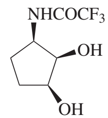
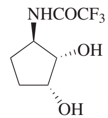
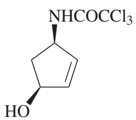
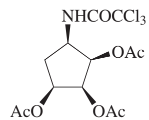
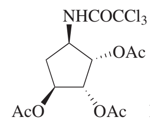
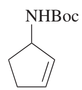
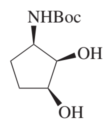
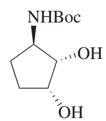
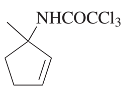
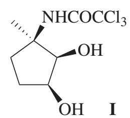
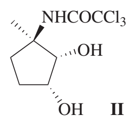
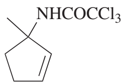
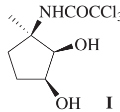
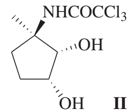
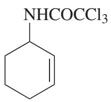
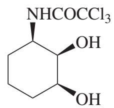
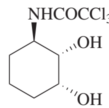
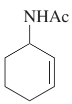
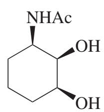
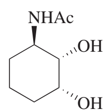
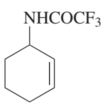
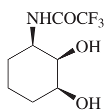
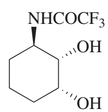
Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_5 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** +  **II** **I** + **II** (80), **I**:**II** = 24:1	20, 15
	OsO_4 (cat), $Me_3NO•2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (84), **I**:**II** = 7.8:1	19
	OsO_4 (0.05 eq), $QNO•H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (69), **I**:**II** = 13:1	19
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then aq Na_2SO_3, reflux	 **I** +  **II** **I** + **II** (—), **I**:**II** = 25:1	15
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (83), **I**:**II** = 17:1	15
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then aq Na_2SO_3, reflux	 **I** +  **II** **I** + **II** (—), **I**:**II** = 9:1	15
C_6 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** +  **II** **I** + **II** (81), **I**:**II** = 24:1	15

TABLE 5. DIRECTED DIHYDROXYLATION OF *N*-ALLYLIC AMINE DERIVATIVES (*Continued*)

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_6 	OsO_4 (cat), $Me_3NO•2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH	 **I** +  **II** **I** + **II** (81), **I**:**II** = 9:1	19
	OsO_4 (0.05 eq), $QNO•H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (69), **I**:**II** = 13:1	19
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** +  **II** **I** + **II** (99), **I**:**II** = 24:1	20, 15
	OsO_4 (cat), $Me_3NO•2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (93), **I**:**II** = 3:1	19
	OsO_4 (0.05 eq), $QNO•H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (86), **I**:**II** = 4.3:1	19
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then aq Na_2SO_3, reflux	 **I** +  **II** **I** + **II** (—), **I**:**II** = 1.8:1	15
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then aq Na_2SO_3, reflux	 **I** +  **II** **I** + **II** (—), **I**:**II** = 24:1	15

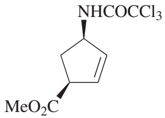
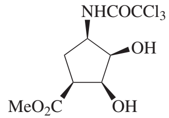
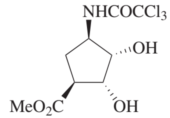
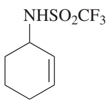
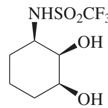
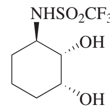
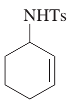
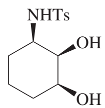
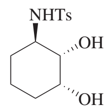
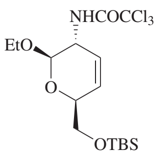
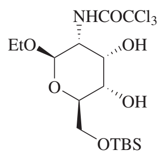
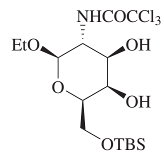
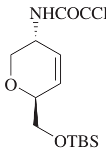
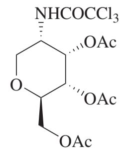
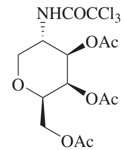
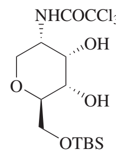
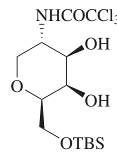
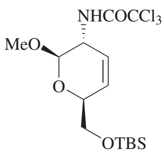
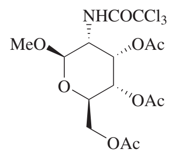
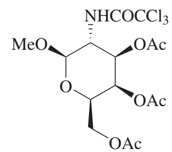
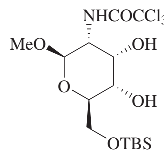
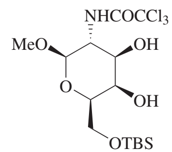
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** +  **II** **I** + **II** (93), **I**:**II** = 5:1	20, 15
	OsO_4 (cat), Me_3NO•$2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (81), **I**:**II** = 1.5:1	19
	OsO_4 (0.05 eq), QNO•H_2O (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (69), **I**:**II** = 1.6:1	19
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then aq Na_2SO_3, reflux	 **I** +  **II** **I** + **II** (—), **I**:**II** = 4.2:1	15
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then aq Na_2SO_3, reflux	 **I** +  **II** **I** + **II** (—), **I**:**II** = 3.5:1	15
	OsO_4 (cat), Me_3NO•$2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH	 **I** +  **II** **I** + **II** (80), **I**:**II** = 20:1	19
	OsO_4 (0.05 eq), QNO•H_2O (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (91), **I**:**II** = 20:1	19

TABLE 5. DIRECTED DIHYDROXYLATION OF *N*-ALLYLIC AMINE DERIVATIVES (*Continued*)

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_6 	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O	 **I** +  **II** **I** + **II** (78), **I**:**II** = 24:1	20
	OsO_4 (cat), $Me_3NO•2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH	 **I** +  **II** **I** + **II** (85), **I**:**II** = 20:1	19
	OsO_4 (0.05 eq), $QNO•H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (89), **I**:**II** = 25:1	19
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O	 **I** +  **II** **I** + **II** (92), **I**:**II** = 4:1	57
	1. OsO_4, quinuclidine (1.1 eq), CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O	**I** + **II** (90), **I**:**II** = 24:1	57
	OsO_4 (cat), $QNO•H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	 **I** +  **II** **I** + **II** (80), **I**:**II** = 20:1	57

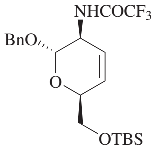
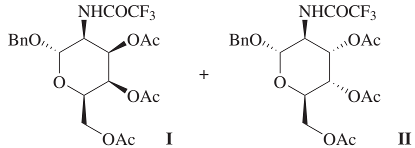
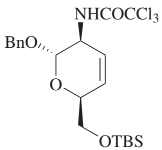
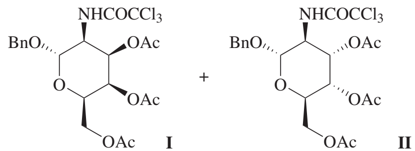
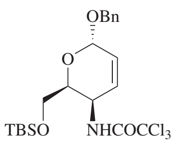
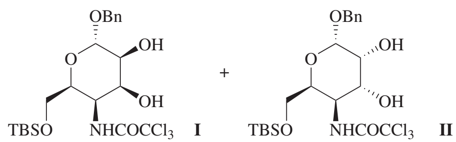
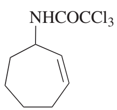
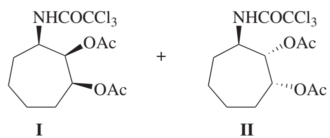
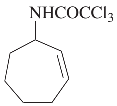
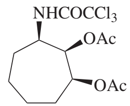
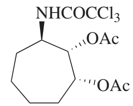
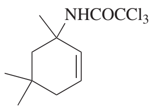
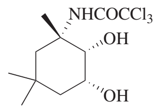
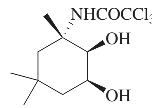
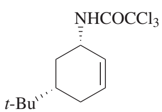
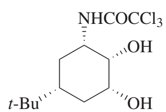
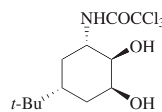
		OsO_4 (cat), $Me_3NO{\cdot}2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH		**I** + **II** (87), **I**:**II** = 14:1	57
		1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O		**I** + **II** (82), **I**:**II** = 25:1	15
		1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O		**I** + **II** (89), **I**:**II** = 25:1	57
		OsO_4 (cat), $Me_3NO{\cdot}2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH		**I** + **II** (90), **I**:**II** = 2:1	19
		OsO_4 (0.05 eq), $QNO{\cdot}H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH		**I** + **II** (94), **I**:**II** = 2.4:1	19
C_7		1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py		**I** + **II** (78), **I**:**II** = 25:1	15

TABLE 5. DIRECTED DIHYDROXYLATION OF *N*-ALLYLIC AMINE DERIVATIVES (*Continued*)

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_7 	1. OsO_4 (cat), $Me_3NO•2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (87), **I**:**II** = 10:1	19
	1. OsO_4 (0.05 eq), $QNO•H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH 2. Ac_2O, py	**I** + **II** (82), **I**:**II** = 17:1	19
C_9 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** +  **II** **I** + **II** (92), **I**:**II** = 24:1	20, 15
	OsO_4 (cat), $Me_3NO•2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (81), **I**:**II** = 11:1	19
	OsO_4 (0.05 eq), $QNO•H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (79), **I**:**II** = 20:1	19
C_{10} 	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** +  **II** **I** + **II** (96), **I**:**II** = 24:1	20, 15

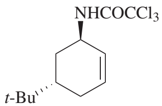
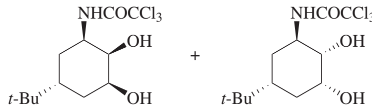
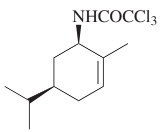
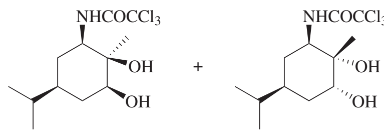
	OsO_4 (cat), $Me_3NO \cdot 2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (81), **I**:**II** = 6:1	19
	OsO_4 (0.05 eq), $QNO \cdot H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (77), **I**:**II** = 13:1	19
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** **II** **I** + **II** (97), **I**:**II** = 1.7:1	20, 15
	OsO_4, quinuclidine, CH_2Cl_2, –78°; then HCl, MeOH	**I** + **II** (66), **I**:**II** = 4.9:1	20
	OsO_4 (cat), $Me_3NO \cdot 2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (91), **I**:**II** = 1.6:1	19
	OsO_4 (0.05 eq), $QNO \cdot H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (88), **I**:**II** = 2.1:1	19
	OsO_4 (cat), $Me_3NO \cdot 2H_2O$ (1.5 eq), CH_2Cl_2, rt; then HCl, MeOH	 **I** **II** **I** + **II** (84), **I**:**II** = 13:1	19
	OsO_4 (0.05 eq), $QNO \cdot H_2O$ (1.3 eq), CH_2Cl_2, rt; then HCl, MeOH	**I** + **II** (95), **I**:**II** = 20:1	19

TABLE 5. DIRECTED DIHYDROXYLATION OF *N*-ALLYLIC AMINE DERIVATIVES (*Continued*)

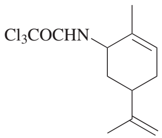
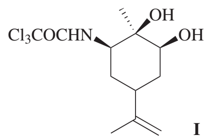
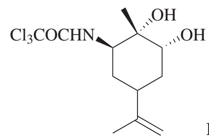
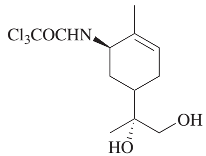
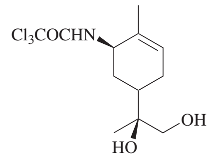
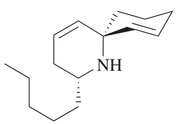
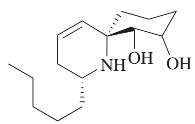
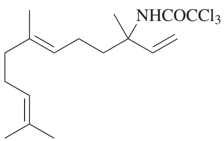
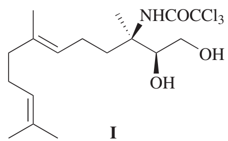
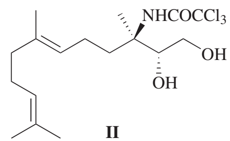
Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_{10}			
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** +  **II**  **III** +  **IV** **I + II** (71), **I:II** 25:1, **III + IV** (<3), **III:IV** —	58
C_{15}			
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 (60), 1 diastereomer	59
	OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH	 **I** +  **II** **I + II** (68), **I:II** = 13:1	58

TABLE 6. DIRECTED DIHYDROXYLATION OF *N*-HOMOALLYLIC CYCLIC AMIDES

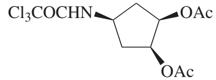
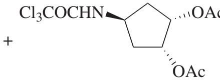
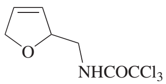
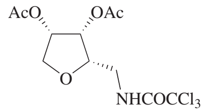
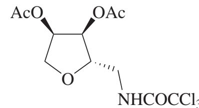
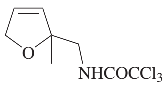
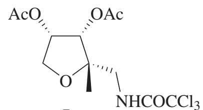
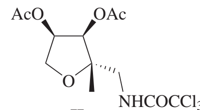
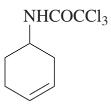
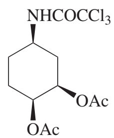
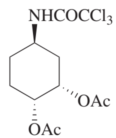
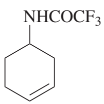
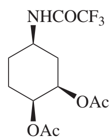
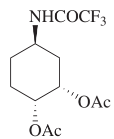
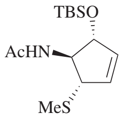
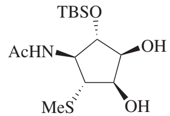
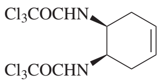
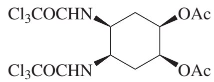
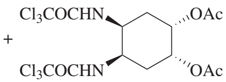
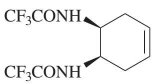
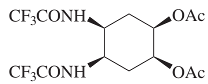
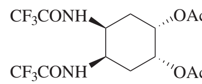
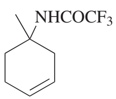
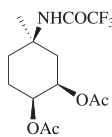
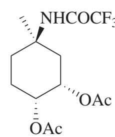
Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_5 	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (94), **I**:**II** = >25:1	22
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (72), **I**:**II** = 2:1	22
C_6 	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (88), **I**:**II** = >25:1	22
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (92), **I**:**II** = 1.2:1	22
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (90), **I**:**II** = >20:1	22

TABLE 6. DIRECTED DIHYDROXYLATION OF *N*-HOMOALLYLIC CYCLIC AMIDES (*Continued*)

Substrate	Conditions	Product(s), Yield(s) (%), and dr (*syn*:*anti*)	Refs.
C_6 	OsO_4•py, py, rt; then $Na_2S_2O_5$, THF/H_2O, 65°	 (81), 1 diastereomer	53
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (100), **I**:**II** = 3:1	22
	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (95), **I**:**II** = >25:1	22
C_7 	1. OsO_4, TMEDA, CH_2Cl_2, –78° to rt; then HCl, MeOH 2. Ac_2O, py	 **I** +  **II** **I** + **II** (67), **I**:**II** = 5:1	22

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CHAPTER 2

TRANSITION-METAL-CATALYZED α-ARYLATION OF ENOLATES

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INTRODUCTION

The last three decades have witnessed increasing efforts to develop highly efficient and selective tools for the catalyzed formation of carbon–carbon and carbon–heteroatom bonds. Among the latter, outstanding results have been obtained in the field of soft, non-organometallic nucleophiles.[1] The formation of carbon–oxygen, –nitrogen, –sulfur, –phosphorus, –boron, or –silicon bonds has become as widely used as the well-known Suzuki, Corriu–Kumada–Tamao, Stille, Negishi, Hiyama, and Sonogashira cross-coupling reactions. One of the major challenges is the α-arylation of soft carbon nucleophiles such as stabilized carbon enolates and related functional groups. Although α-arylated carboxylic acids (and keto derivatives) are prevalent in natural products (for example, lucuminic acid,[2] welwistatin,[3] and chloropeptin and vancomycin[4]) and are important building blocks in a number of drugs (such as the anti-inflammatory agents Naproxen and Ibuprofen,[5] the anesthetic Scopolamine,[6] and *p*-malonylphenylalanine (Pmf,[7] a potent phosphotyrosine mimetic), catalytic α-arylation of stabilized carbon enolates had, until recently, been described only rarely (Fig. 1).

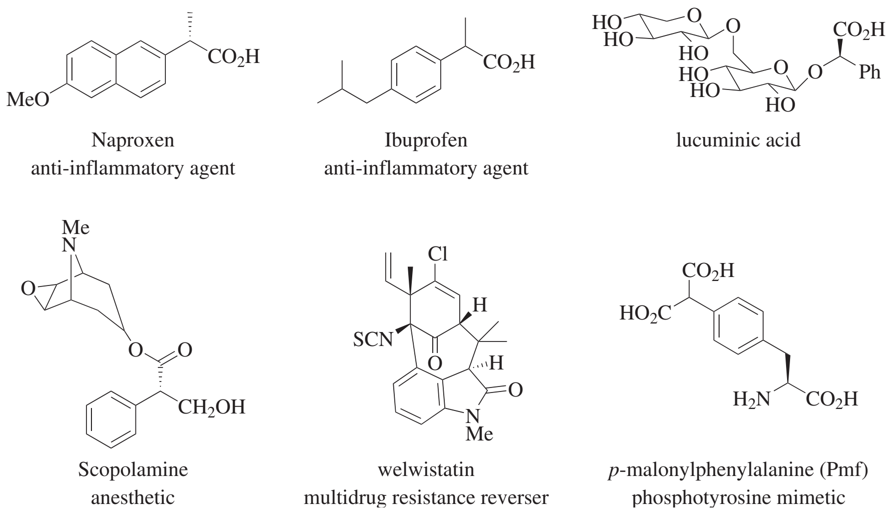
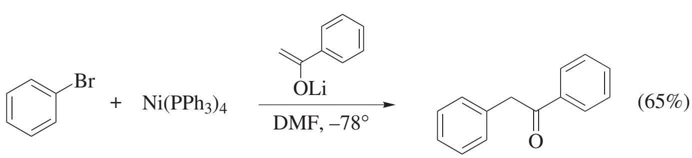


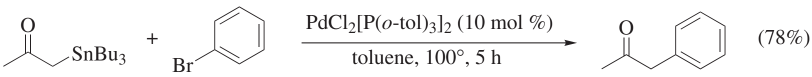
Figure 1. Natural products and drugs bearing α-arylated carboxylic acid derivatives.

The first examples of both inter- and intramolecular arylation of ketone enolates were reported in 1973 by Semmelhack using a nickel catalyst.[8] The reaction of the oxidative addition product of bromobenzene and $Ni(PPh_3)_4$ with the lithium enolate of acetophenone afforded the arylated ketone in modest yield (Eq. 1). An intramolecular version was also reported as the key step of the total synthesis of cephalotaxinine. The natural product was obtained in only 30% yield and required the use of a stoichiometric amount of $Ni(cod)_2$.[8]



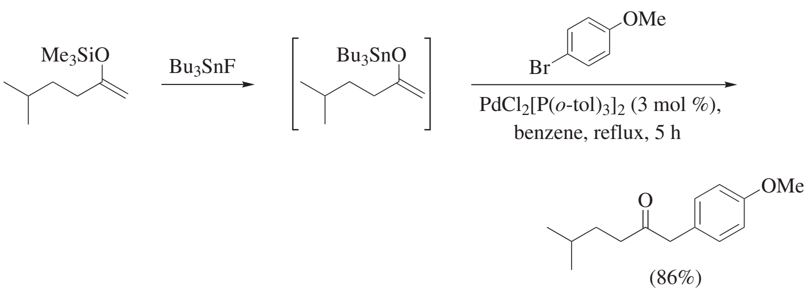
(Eq. 1)

This pioneering work was followed by several examples of transition-metal-mediated α-arylations of ketones or their derivatives including the catalyzed arylation of vicinal bromotrimethylsilylalkenes[9] and acetonyltributyltin (Eq. 2),[10] as well as the arylation of 2-trimethylsilyloxyallyl halides with stoichiometric reagents.[11]



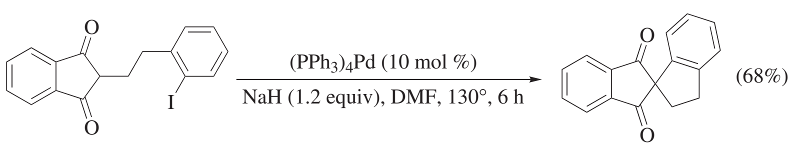
(Eq. 2)

One variant of these reactions involves the site selective arylation of silyl enol ethers of methyl ketones with aryl halides under palladium catalysis in the presence of trialkyltin fluorides (Eq. 3).[12,13] The latter are assumed to generate tin enolates in situ via silyl/stannyl exchange followed by arylation with the aryl halide.



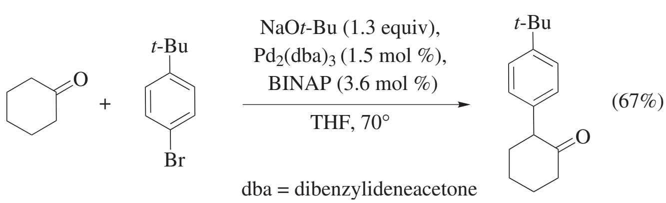
(Eq. 3)

Later, the use of malonate-type nucleophiles in the palladium-catalyzed α-arylation of ketones in inter- and intramolecular modes was reported (Eq. 4).[14,15]



(Eq. 4)

In 1997, five seminal papers dealing with inter- and intramolecular palladium-catalyzed arylation of ketones appeared.[16−20] This method could then be extended to ketones and esters under milder conditions and with a wider scope (Eq. 5).



(Eq. 5)

The more recent developments of this method concern not only the use of a large number of related nucleophiles such as amides, lactones and lactams, malonates, cyanoacetates, aldehydes, α-amino esters, nitriles, sulfones, and nitroalkanes, but also activated benzylic and vinylogous γ-arylations. Current efforts are mainly devoted to multiple arylation sequences, intramolecular α-arylations, and enantioselective α-arylations. Although palladium-catalyzed reactions have received a great deal of attention, several other efficient, competitive, and enantioselective nickel-, copper-, or ruthenium-based catalytic systems have recently emerged.

In addition, the transition-metal-catalyzed introduction of aromatic groups at the position α to enolizable moieties has found applications in the total synthesis of natural products, demonstrating the utility of this general synthetic method. The aim of this chapter is to present an up-to-date overview of the transition-metal-catalyzed α-arylation of enolates and their derivatives. Because palladium is the transition metal predominantly employed, this chapter focuses on palladium-assisted synthetic transformations. However, the most relevant α-arylations involving other catalytic systems are also detailed. Several accounts have recently appeared covering some aspects of palladium-catalyzed α-arylations.[21–23] The literature up to the beginning of 2008 is covered in the Tabular Survey.

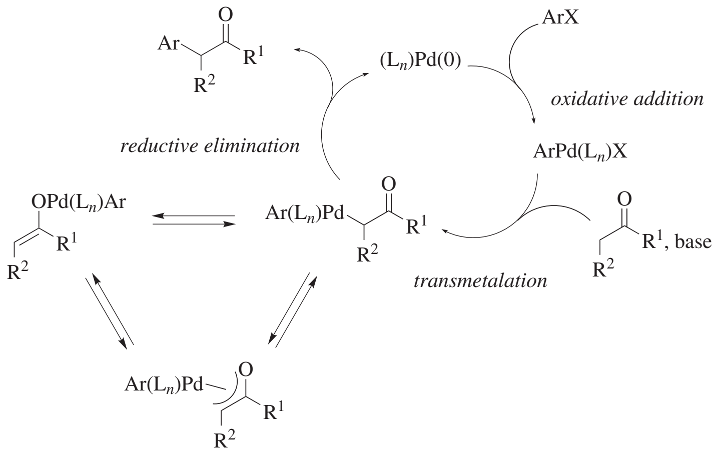
MECHANISM AND STEREOCHEMISTRY

Palladium is the most widely used transition metal in catalyzed α-arylations. Relevant mechanistic studies are almost exclusively carried out with this metal. The main features of reactions mediated by other transition metals are discussed in the corresponding sections.

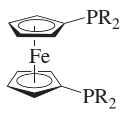
The general mechanism of the palladium-catalyzed arylation of enolates is rather classical involving the well-known oxidative addition, transmetalation, and reductive elimination sequence (Scheme 1).[23] Although the general mechanism is well accepted, a number of questions about particular aspects of the catalytic cycle are still under discussion.

The first issue concerns the number of phosphines coordinated to the palladium atom. Initially, bidentate phosphines such as dppf (**1**) or BINAP (**2**) (Fig. 2) were used to form strongly chelated intermediates to prevent β-elimination.[16] However, during further synthetic and mechanistic studies, a monochelated intermediate involving the DtBPF ligand (**3**) was observed by ^{31}P NMR spectroscopy.[23] This observation led to the introduction of very efficient mono- and bidentate ligands **4–11** (Fig. 2). Such bulky, electron-rich monodentate ligands are involved in the formation of monoligated (12 electrons) [PdL] species that can undergo rapid oxidative additions with ArX, including aryl chlorides.[24,25] Ligandless reactions are also possible in some non-demanding reactions.[18]

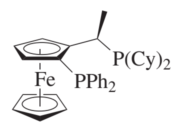
The second issue concerns the nature of the palladium species undergoing reductive elimination in the catalytic cycle. In general, main group metal and early transition metals favor the *O*-bound enolate whereas late transition metals favor



Scheme 1



Ligand	R
1	Ph
3	*t*-Bu



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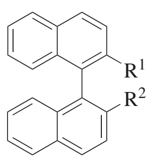
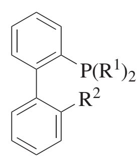


Ligand	R^1	R^2
2	PPh_2	PPh_2
5	P(*p*-tol)$_2$	P(*p*-tol)$_2$
6	NMe_2	P(*t*-Bu)$_2$



Ligand	R^1	R^2
7	*t*-Bu	H
8	*t*-Bu	Me
9	Cy	H
10	Cy	Me
11	Cy	*i*-Pr

Figure 2. Phosphine ligands for palladium-catalyzed α-arylations.

the *C*-bound form.[23] Indeed, with the exception of hindered α,α′-disubstituted ketones and complexes where the enolate oxygen is located *trans* with respect to the aryl group, the *C*-bound isomers are favored.[23] Competition experiments involving isolated palladium enolates showed that their relative stability is controlled by the number of substituents on the α-position of the keto group (Fig. 3).[23]

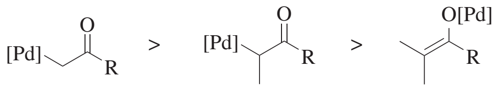
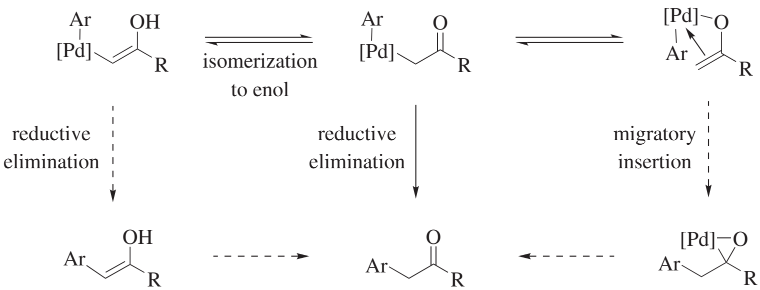


Figure 3. Relative stability of palladium enolates.

The reductive elimination step was investigated for various isolated *C*- and *O*-bound palladium enolates.[26] By comparison of the elimination rates, alternative mechanisms (such as isomerization to the enol or migratory insertion could be ruled out and the classical concerted reductive elimination was confirmed (Scheme 2).[23,27]



Scheme 2

The influence of electronic effects was also investigated. As illustrated in Fig. 4, acyl substituents (aryl, alkoxy, amino) on the palladium enolates have little influence on the reductive elimination rates.[28] In these cases, the observed differences in reactivity in the palladium-catalyzed arylation of ketones, esters, and amides must result from the rate of formation of the α-palladated species. On the other hand, striking differences are observed in the reductive eliminations of methyl, ketomethyl, cyanomethyl, and malonyl arylpalladium complexes.[23,29] Increasing the electron-withdrawing ability of the substituent lowers the reductive elimination rate. This effect is particularly impressive in malonate-type complexes where no reductive elimination is observed. In such reactions, this effect must be counteracted by ligands that are efficient in promoting reductive elimination, such as bulky, electron-rich monophosphines, as exemplified by the DPPBz ligand (**12**) (Fig. 4).[23,29]

Because enantiomerically enriched α-substituted carbonyl compounds are important structural features in drugs and natural products, the creation of tertiary and quaternary stereogenic centers α to carbonyl groups through the asymmetric arylation of enolates is of significant interest. Initial attempts employed BINAP-type ligands for this transformation.[30] Modest enantioselectivities are obtained using 10 to 20 mol % of palladium precatalyst, and 12 to 24 mol % of ligands **2** or **13** (Eq. 6).

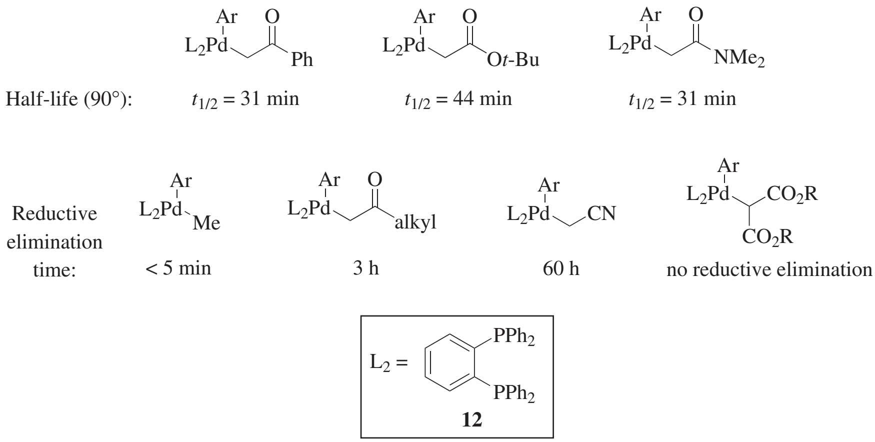
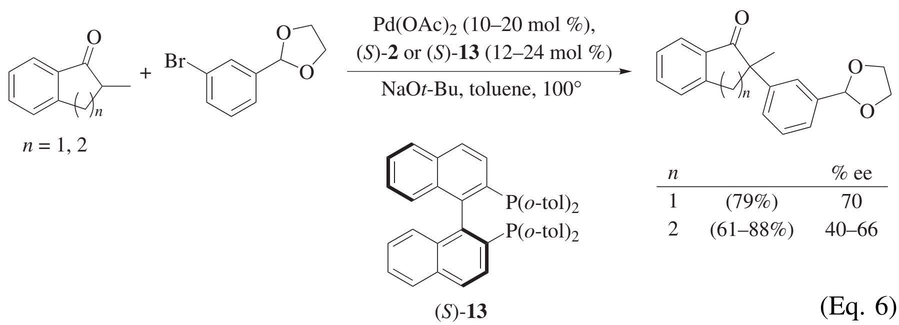
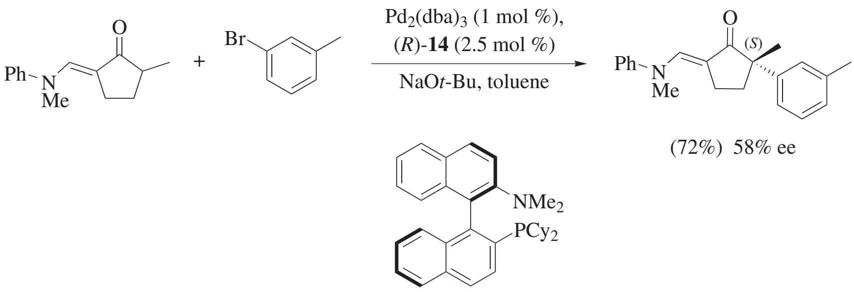


Figure 4. Electronic effects on the rate of reductive elimination.



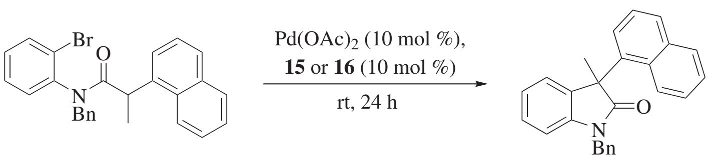
(Eq. 6)

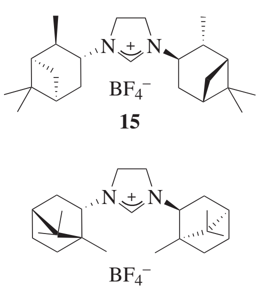
These transformations require the use of an excess of the aryl halide to ensure complete conversions because of the competitive homocoupling of the aryl bromide to afford biphenyl derivatives.[30a] In addition, these arylations are restricted to the formation of quaternary stereocenters. The acidity of the remaining proton in the tertiary arylation products leads to lower enantioselectivities under basic conditions.[30a] The arylation reactions proceed with high yields and high to excellent enantioselectivities in the case of blocked α-methylcyclopentanones (Eq. 7).[31] In such substrates, the use of a methylene group that can be easily removed can prevent arylation at the less substituted carbon of α-methylcyclopentanones. Toluene and sodium *tert*-butoxide is the most suitable combination of solvent and base in these transformations. Whereas arylations using *m*- and *p*-substituted aryl bromides generally proceed with high enantioselectivities (80–94% enantiomeric excess), the *o*-substituted derivatives react with low yields and enantioselectivities. Similar enantiomeric excesses (88–93%) are observed in couplings of ketones bearing methyl, *n*-propyl, and *n*-pentyl α-substituents, indicating that enantiomeric excesses are insensitive to the size of the α-alkyl moiety.[30a] Although BINAP is often used, reactions using palladium catalysts based on dialkyl monophosphines such as **14** can be employed under milder conditions (room temperature) and are more efficient in terms of substrate range and precatalyst loadings. As exemplified in Eq. 7, best results are obtained using monophosphine ligands. Although attempts to rationalize the sense of asymmetric induction are still inconclusive, it should be noted that reversed stereoselectivity is observed using diphosphine-type ligands such as BINAP.[30a] These observations suggest an asymmetric induction mechanism that is significantly different for monophosphine and diphosphine ligands, respectively, depending on the chelation mode in the enantiodetermining step.



(*R*)-**14** (Eq. 7)

An interesting alternative approach involves the use of chiral *N*-heterocyclic carbene (NHC) ligands in intramolecular arylation reactions for the asymmetric synthesis of oxindoles. Ligands **15** and **16**, derived from (−)-isopinocampheylamine and (+)-norbornylamine, respectively, display complementary induction under mild conditions, and afford products of opposite absolute configuration (Eq. 8).[32]

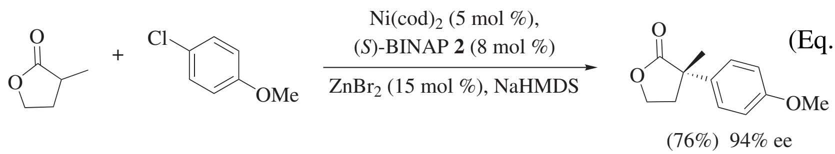




Ligand		% ee
15	(88%)	67
16	(80%)	71

(Eq. 8)

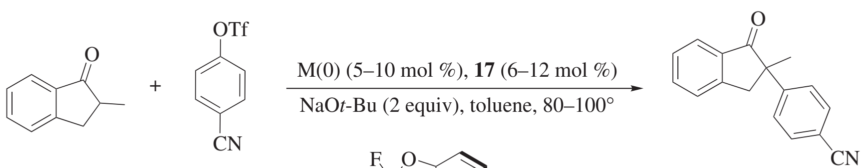
In addition to palladium-catalyzed asymmetric arylations, nickel- and copper-catalyzed processes have recently emerged as alternative approaches.[33] Substitution of palladium(0) with nickel(0) catalysts leads to very efficient, enantioselective α-arylation of γ-butyrolactones. The use of Ni(BINAP) catalytic systems provides the products in modest to good yields, but with high enantiomeric excesses (Eq. 9).[33] The increase in the enantioselectivity is attributed to the greater influence of the ligand in the stereodetermining step resulting from the smaller nickel-center. Interestingly, aryl chlorides can be used instead of bromides with comparable reaction rates.[34] Moreover, addition of substoichiometric amounts of zinc salts increases the reaction rate. Zinc halide species are assumed to act as Lewis acids to facilitate halide abstraction from the oxidative addition product, thus generating a more reactive cationic complex at an early stage of the transmetalation step (Eq. 10).[33]

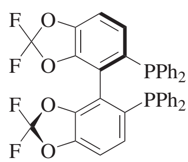


(Eq. 9)

$$(\mathrm{BINAP})\mathrm{Ni(Ar)(Br)} \xrightarrow{\mathrm{ZnBr_2}} [(\mathrm{BINAP})\mathrm{Ni(Ar)}]^+ \,\mathrm{ZnBr_3}^- \qquad \text{(Eq. 10)}$$

The highly enantioselective arylation of ketones using ligand **17** and electron-poor aryl triflates in the presence of nickel-based catalysts, or electron-rich aryl triflates in the presence of palladium-based complexes, has been recently described (Eq. 11).[34]



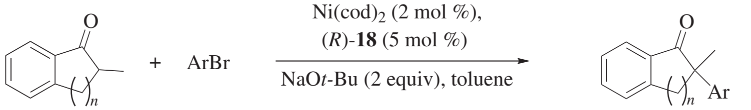


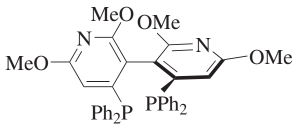
17

M(0)		% ee
Ni(cod)	(84%)	95
$Pd(dba)_2$	(79%)	78

(Eq. 11)

Highly enantioselective nickel-catalyzed α-arylations of ketone enolates involving the Ni-P-Phos catalytic system (P-Phos = structure **18**) have been applied to the 2-methylindanone, -tetralone, and -benzosuberone series leading to the formation of quaternary centers with enantiomeric excesses up to 98% (Eq. 12).[35]



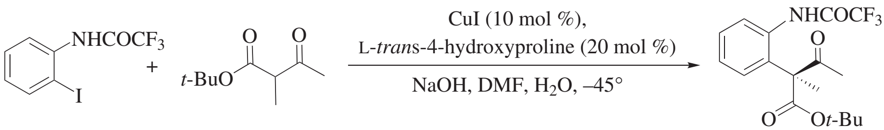


(*R*)-**18**

n		% ee
1	(69–80%)	67–88
2	(59–94%)	70–98
3	(70–74%)	60–73

(Eq. 12)

Copper-catalyzed arylations of acetoacetates in the presence of L-*trans*-4-hydroxyproline as the ligand proceed in high yield (29–87%) and enantiomeric excesses (60–93%) (Eq. 13).[36] It is worth noting that traces of water in the solvents are beneficial to the reaction rates, allowing the reactions to proceed smoothly at low temperature. Temperatures as low as −45° provide the carbon–carbon bond formation with enhanced enantiomeric composition.[36]



(79%) 93% ee

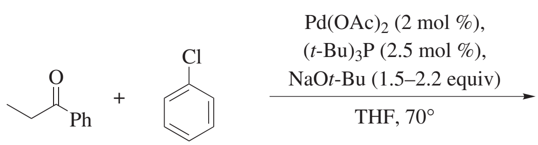
(Eq. 13)

SCOPE AND LIMITATIONS

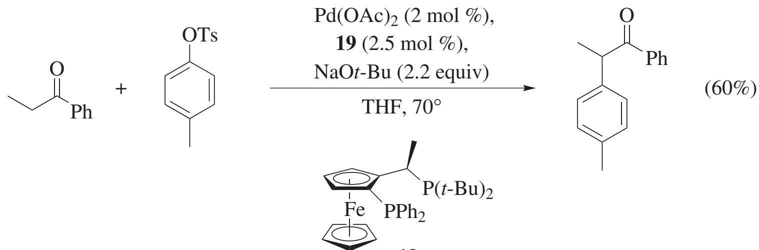
Palladium-Catalyzed α-Arylation

α-Arylation of Ketones. This section focuses mainly on the direct, catalyzed arylation of ketone enolates; recent developments on the use of stoichiometric reagents[37–39] are not covered. In the period since their seminal 1997 papers, Hartwig, Buchwald, and Miura have tried to develop "universal conditions" for a wide range of substrates under mild reaction conditions.

On the basis of their mechanistic studies (see above), the Hartwig group has reported a simple and active catalytic system for the arylation of ketones: **3**/Pd(dba)$_2$ or (t-Bu)$_3$P/Pd(OAc)$_2$ (in a 1:1.25 Pd/L ratio) in THF (Eq. 14).[40] These conditions allow the reaction of a wide range of aryl bromides and chlorides (including electron-rich ones) to take place. One example of the coupling of an aryl tosylate with propiophenone is also described, but requires the use of ligand **19** at 70° (Eq. 15).[40] Under these conditions, monoarylated ketones can be obtained in good yields starting from cyclohexanone, 3-methyl-2-propanone, acetophenone, propiophenone, and isobutyrophenone. The limits of these conditions are found with methyl alkyl ketones, which form diarylated compounds.



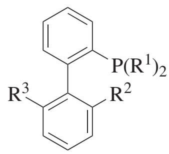
(78%) (Eq. 14)



19

(Eq. 15)

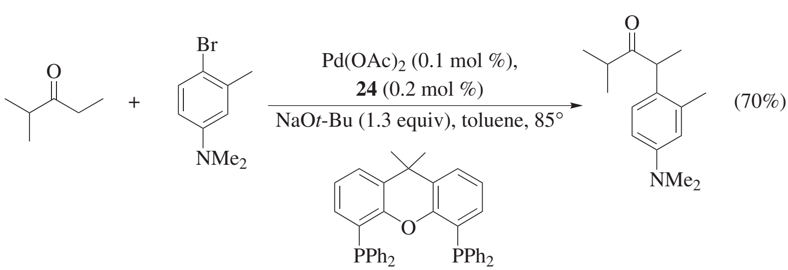
Buchwald et al. have developed electron-rich monophosphine ligands **7–11** (Fig. 2) and **20–23** (Fig. 5) that possess a biphenyl skeleton. These ligands facilitate rapid oxidative additions with aryl halides, including aryl chlorides.[41]



Ligand	R^1	R^2	R^3
20	Ph	NMe_2	H
21	*t*-Bu	NMe_2	H
22	Cy	NMe_2	H
23	Cy	OMe	OMe

Figure 5. Electron-rich monophosphine ligands.

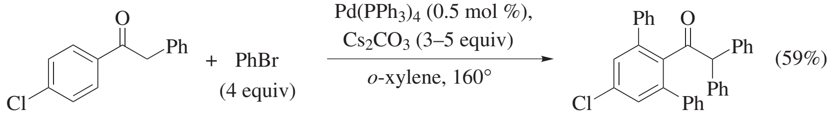
A wide range of substrates (electron-rich, electron-poor, and 2-substituted aryl bromides and chlorides with aromatic, aliphatic, and cyclic ketones) can be successfully combined under typical conditions: Xantphos (**24**), $Pd(OAc)_2$, NaO*t*-Bu, 70° in toluene (Eq. 16).[42] For reactions involving base-sensitive substrates, a milder base such as K_3PO_4 can be used in the presence of **24**/$Pd_2(dba)_3$.[43] Most of the non-demanding reactions (typically propiophenone and pinacolone with aryl bromides) can be carried out in the absence of a ligand. However, the use of bidentate ligands such as Xantphos (**24**) is essential in α-arylations of ketones bearing two enolizable methylene or methyl groups.[42] A major limitation of this method is the use of cyclopentanone, where self-aldolization is the major process (for an example where the cyclopentanone enolate is generated in situ through a 1,4-addition, see Ref. 44). The α-arylations of methyl or cyclic ketones with 2-halonitroarenes require the use of a substoichiometric amount (20%) of 4-methoxyphenol to be efficient.[45]



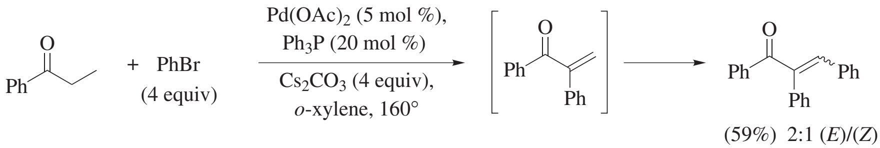
24

(Eq. 16)

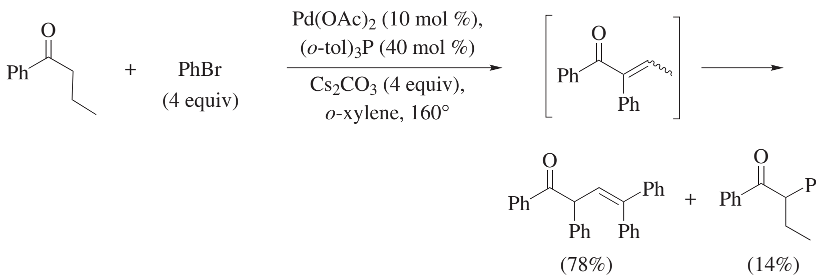
Miura et al. have mainly focused their efforts on multiple arylations of phenyl ketone derivatives. Benzyl phenyl ketones undergo a triarylation sequence: the expected α-arylation but also two *o*-arylations (Eq. 17).[46] With alkyl aryl ketones, multiple arylation is also observed: after the initial α-arylation process, a second palladium-enolate is formed, which undergoes a β-elimination to form a double bond. This double bond then reacts further through a Heck reaction (Eq. 18), or a vinylogous γ-arylation (Eq. 19).[47]



(Eq. 17)

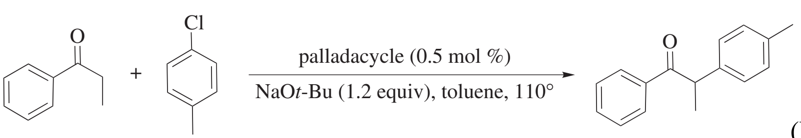


(Eq. 18)

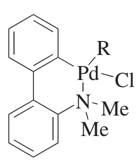


(Eq. 19)

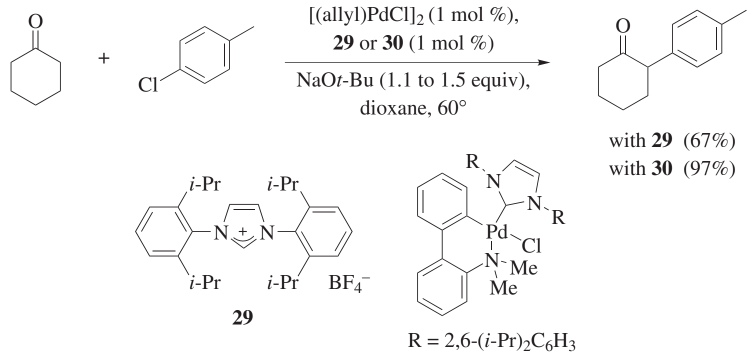
Robust catalytic systems capable of practical (industrial) applications, especially with aryl chlorides, are of great value. The use of the *n*-BuP(adamantyl)$_2$ electron-rich phosphine,[48] palladacycles possessing a tertiary phosphine, such as **25**,[49] or secondary phosphines **26**–**28**,[49] NHC ligand **29**,[50,51] or palladacycle **30**[52] provide efficient arylation of non- and deactivated aryl chlorides (Eqs. 20, 21).



(Eq. 20)



Palladacycle	R	
25	P(Cy)$_3$	(99%)
26	PH(Cy)$_2$	(69%)
27	PH(*t*-Bu)$_2$	(60%)
28	PH(2-norbornyl)$_2$	(100%)

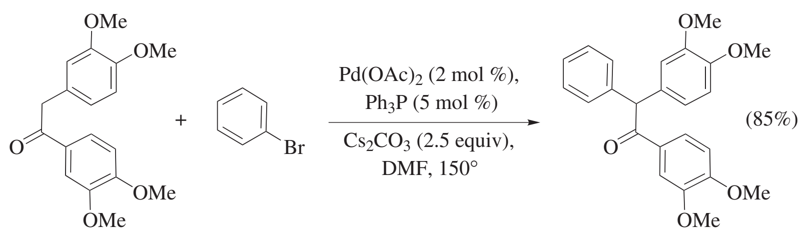


29

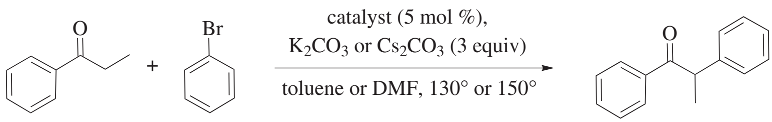
R = 2,6-(i-Pr)$_2C_6H_3$
30

(Eq. 21)

The selective mono-arylation of 1,2-diarylethanones has been studied, and byproducts (*o*-arylation, multiple arylation, and dehalogenation) can be minimized by a careful choice of reaction conditions (Eq. 22). Originally, homogeneous conditions (Pd(OAc)$_2$, Ph$_3$P, Cs$_2$CO$_3$) were described, but these reactions can also be performed with polystyrene-derived catalyts **31**–**33** (Eq. 23).[53–55] More recently, the same group has also described the use of phosphinite PCP-pincer complexes.[56] In addition, arylations on solid supports have been described using immobilized 4-bromobenzamide.[57]

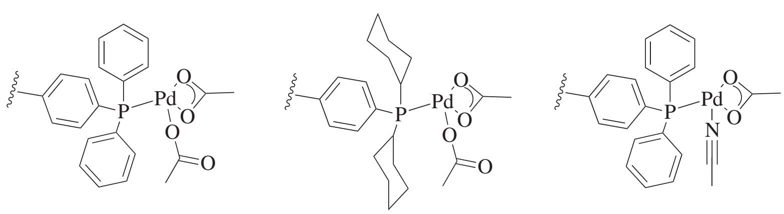


(Eq. 22)



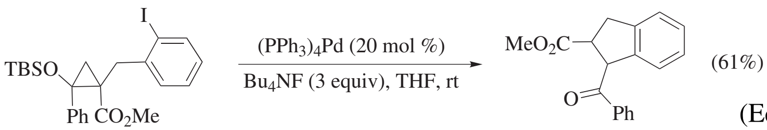
Catalyst	
31	(43%)
32	(16%)
33	(85%)

(Eq. 23)

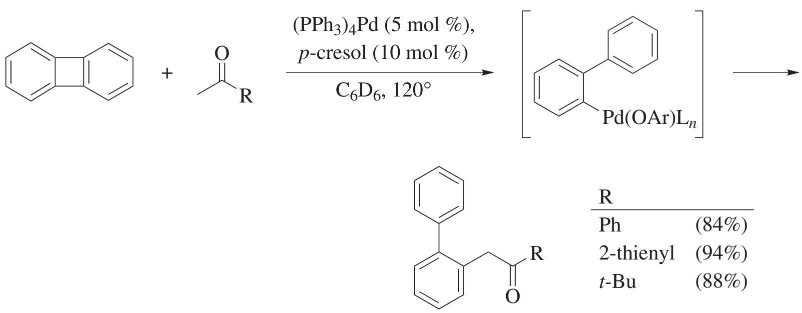


31 **32** **33**

In some instances, either the ketone enolate or the aryl palladium species can be generated from alternative precursors. In Eq. 24, the ketone enolate is obtained in situ through a cyclopropanol ring-opening reaction.[58] Biphenylene can also be used as an aryl halide surrogate in the presence of *p*-cresol (Eq. 25).[59]



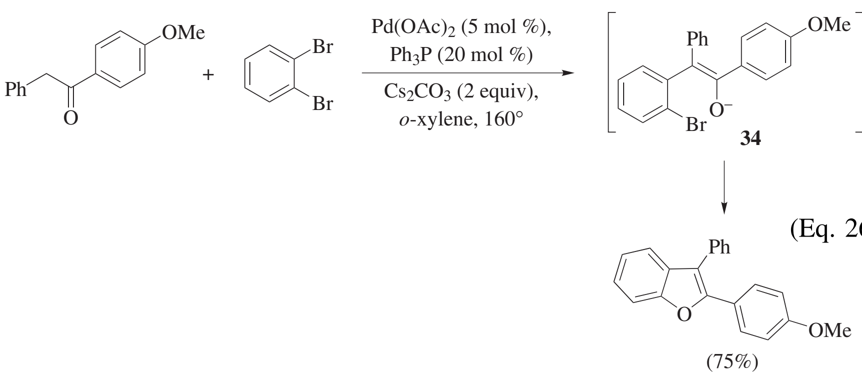
(Eq. 24)



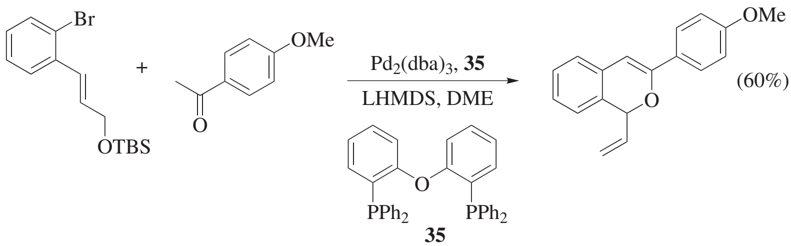
(Eq. 25)

R	
Ph	(84%)
2-thienyl	(94%)
t-Bu	(88%)

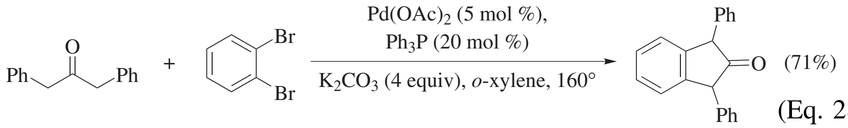
Using 1,2-dibromobenzenes, tandem reactions can be envisioned through two successive palladium-catalyzed reactions. In the formation of benzofurans from aryl benzyl ketones, the mechanism involves first an α-arylation followed by a second deprotonation of the more acidic proton and finally the intramolecular arylation of the *O*-enolate intermediate **34** (Eq. 26).[60] An extension of this method to non-aromatic cyclic and acyclic ketones has been described using DPEphos (**35**).[61,62] A tandem alkylation of the *O*-enolate intermediate is reported in the synthesis of a small library of 1-vinyl-1*H*-isochromene derivatives as illustrated in Eq. 27.[63] Two carbon−carbon single bond formations are also possible as illustrated in Eq. 28.[60]



(Eq. 26)

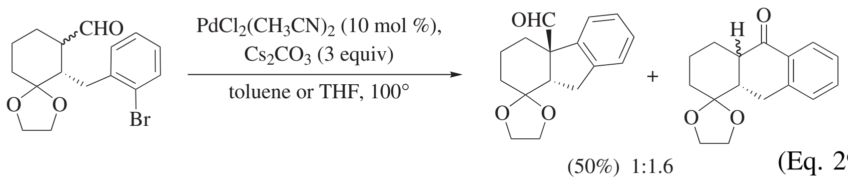


(Eq. 27)



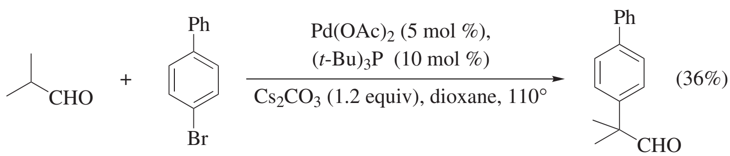
(Eq. 28)

α-Arylation of Aldehydes. Because of the propensity of aldehydes to undergo aldol self-condensations under basic conditions, arylation of aldehydes has received less attention. In the intramolecular arylation of aldehydes, a mixture of α-arylation and carbonyl-arylation is obtained (Eq. 29).[64]



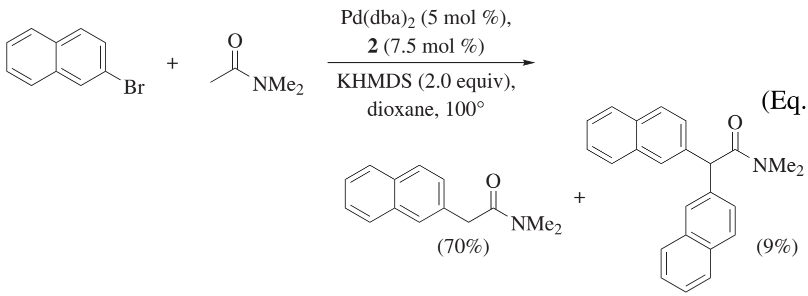
(Eq. 29)

In intermolecular, α-selective arylation of aldehydes (Eq. 30), the use of dioxane and $(t\text{-Bu})_3P$ are essential to prevent aldolization and to promote the reaction (no reaction is observed in the presence of Cy_3P).[65]



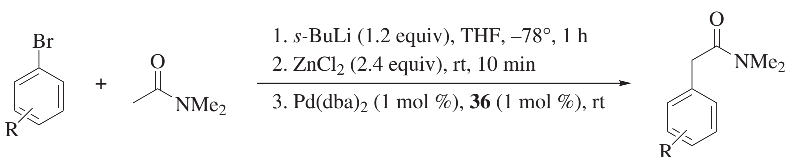
(Eq. 30)

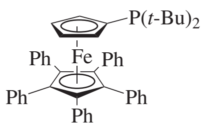
α-Arylation of Amides. On the basis of the arylation of ketones and aldehydes, several groups have explored the extension of the method to carboxylic acid derivatives. In these studies and in contrast to ketones, the arylation of amides and esters is not plagued by site selectivity and such reactions would appear to be less challenging. Disappointingly, the first attempts to arylate amides gave rather low yields, even in intramolecular versions. This lack of reactivity can be attributed to the higher pK_a's of the amide moiety compared to that of ketones,[66] requiring the use of stronger bases. KHMDS is more efficient than LiTMP (lithium 2,2,6,6-tetramethylpiperidide) and the more classical NaO*t*-Bu. The α-arylation of *N*,*N*-dialkylacetamide has been reported in moderate to good yields.[67] Side-products such as diarylated amides and/or dehydrohalogenated arenes are observed along with the expected arylation products (Eq. 31).



(Eq. 31)

The scope of the reaction is limited by the use of strongly basic conditions that preclude the use of base-sensitive and/or electrophilic substituents and lead to catalyst deactivation or decomposition. The aforementioned problems have recently been overcome by moving to the less basic zinc enolates. The higher functional group tolerance of these nucleophiles allows an extended scope of such coupling processes. Indeed, ketone, nitrile, ester, and nitro derivatives can be used as substrates in one-pot procedures starting from *N*,*N*-dialkylamides or α-bromo *N*,*N*-dialkylamides.[68] Under these conditions ($Pd(dba)_2$, **36**), no side-products from diarylation of the enolate are observed (Eq. 32).



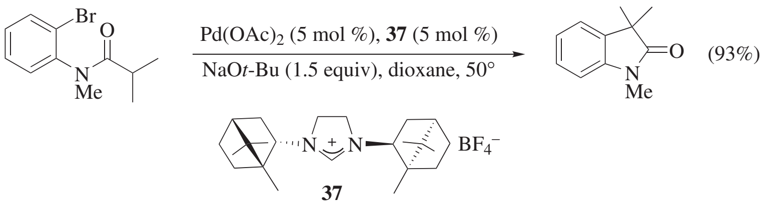


36

(Eq. 32)

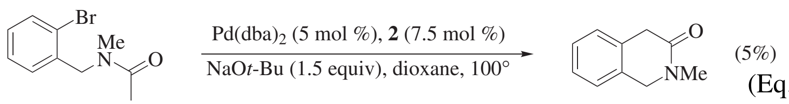
R	
4-CO_2Me	(95%)
2-CN	(84%)
4-CN	(89%)
4-COPh	(92%)
4-NO_2	(90%)

Apart from the use of zinc enolates, the α-arylation of amides has been limited to intramolecular reactions and/or lactam substrates. Intramolecular reactions have been used in the synthesis of oxindoles and tetrahydroisoquinoline derivatives. In the oxindole series, a wide range of aryl substituents (with respect to both steric and electronic properties) are tolerated in these intramolecular reactions. Standard conditions involving BINAP and NaO*t*-Bu are used, but sterically hindered alkyl phosphines[67] or hindered imidazolium carbene precursors like **37**[32,69,70] generate more active catalytic systems, providing higher arylation rates (Eq. 33).

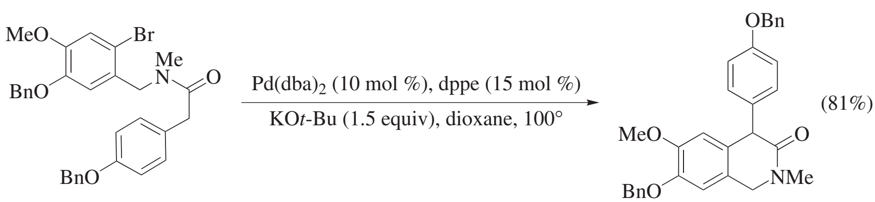


(Eq. 33)

In the tetrahydroisoquinoline series, more disparate yields have been observed. Poor yields (5%) of the expected cyclized product from a non-stabilized enolate using the $Pd(dba)_2$, BINAP, NaO*t*-Bu catalytic system are observed (Eq. 34).[67] In contrast, stabilization of the enolate allows yields ranging from 54 to 81% (Eq. 35).[71]

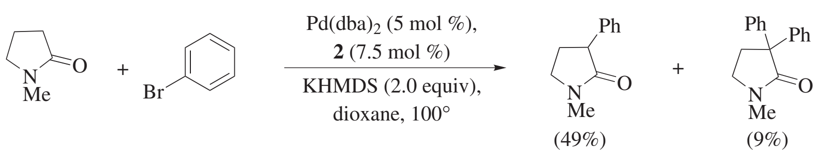


(Eq. 34)



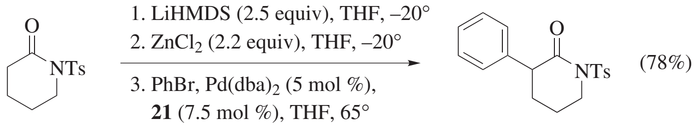
(Eq. 35)

Arylation of lactams is also possible. *N*-Methylpyrrolidinone (NMP) reacts with bromobenzene to give the expected arylation product in 49% yield, along with 9% of the diarylation product (Eq. 36).[67]



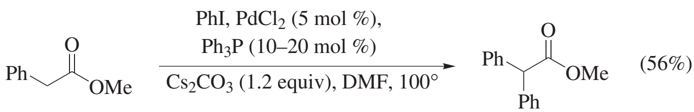
(Eq. 36)

Arylpiperidones can also be prepared by palladium-assisted α-arylation of the derived zinc enolates (Eq. 37).[72] No diarylation byproducts are observed. The α-arylation process seems not to be dependent on the nitrogen atom substitution. In contrast, steric hindrance around the aryl halide has a significant impact on yields: a modest 46% yield is observed with 2-methylbromobenzene whereas no arylation occurs with 2,6-dimethylbromobenzene.



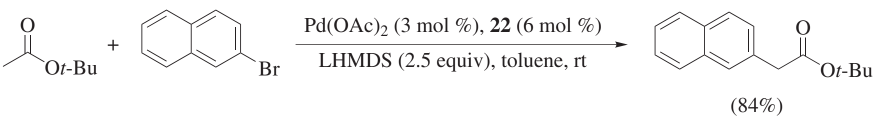
(Eq. 37)

α-Arylation of Esters. α-Arylation of methyl phenyl acetate, which involves a doubly-stabilized anion, using a $PdCl_2{-}Ph_3P$ catalytic system and Cs_2CO_3 as the base, affords the expected arylated ester in a modest 56% yield (Eq. 38).[73]

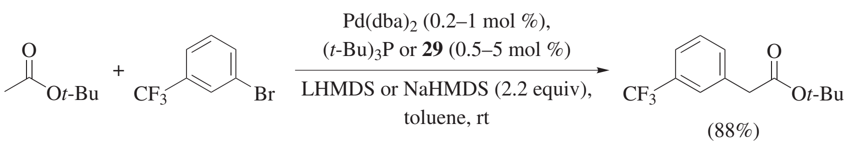


(Eq. 38)

The use of hindered phosphines (Eq. 39), bidentate phosphines, or carbene-based ligands (Eq. 40) has been extended to the α-arylation of ester substrates.[74,75] *tert*-Butyl acetate or propionate reacts with a wide range of aryl bromides at room temperature in high yields. Although 2.2 to 2.5 equivalents of base are necessary to ensure complete conversion, diarylated byproducts are not observed.

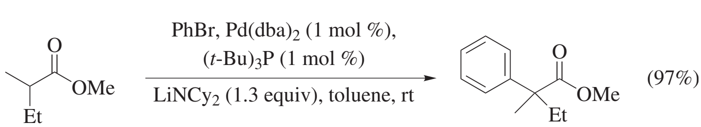


(Eq. 39)



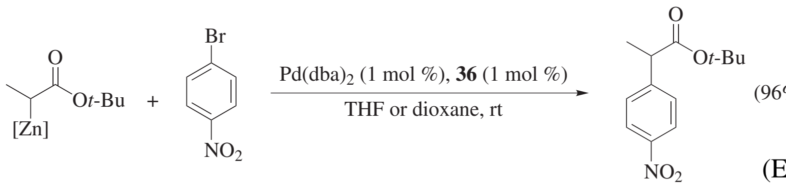
(Eq. 40)

Generation of the enolate prior to the coupling with a stronger hindered amide base, such as $LiNCy_2$, greatly improves the reaction and allows the formation of quaternary carbon atoms (Eq. 41).[23,74] Heterocycles such as furans, thiophenes, and pyridines are well-tolerated using this method. Moreover, high yields are generally obtained using low catalyst loadings and slight excesses of both ester and base.



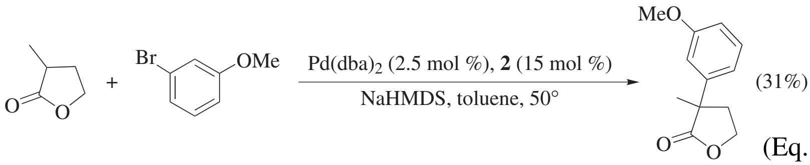
(Eq. 41)

For aryl halides bearing base-sensitive or electrophilic substituents, the use of zinc enolates again improves the yield (Eq. 42).[76] In addition, these conditions also prove satisfactory for aryl halides bearing acidic and basic substituents, such as bromophenols, bromoanilines, and substituted pyridines.



(Eq. 42)

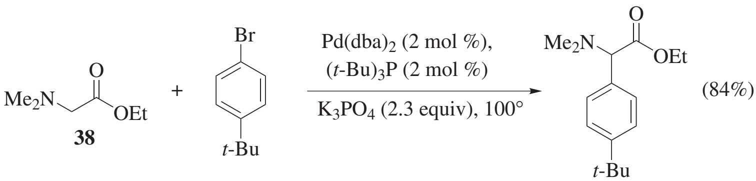
The arylation of lactones under palladium catalysis appears in a single report; however, only modest yields are obtained using the Pd/BINAP, NaHMDS catalytic system (Eq. 43).[33]



(Eq. 43)

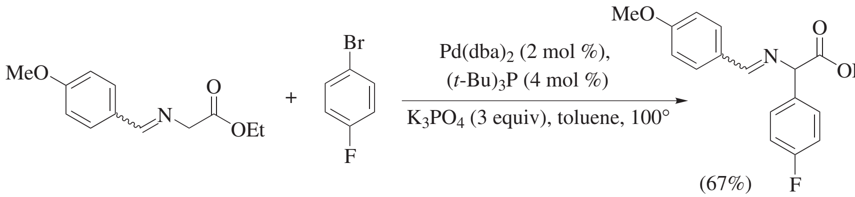
More successful nickel-catalyzed α-arylations of esters have been developed, and this point will be discussed below.

α-Arylation of Amino Acids and Derivatives. Ethyl *N*,*N*-dimethylglycinate (**38**) undergoes facile α-arylation even when using K_3PO_4 as the base (Eq. 44).[77]



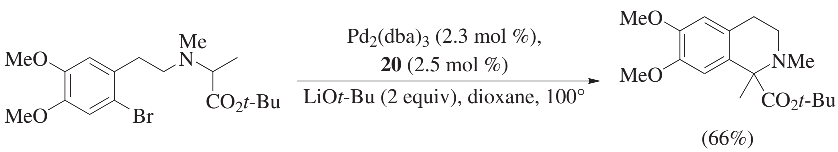
(Eq. 44)

Amino acids with more common nitrogen protecting groups have been evaluated subsequently. Because of their convenient preparation, imino esters derived from benzophenone and benzaldehyde are of particular value. Under the aforementioned conditions ($(t\text{-Bu})_3P$, $Pd(dba)_2$, K_3PO_4), imino ester derivatives are arylated in high yields (Eq. 45).[77] Coordination of the substrate nitrogen atom is assumed to assist both the formation of the enolate and the arylation reaction.



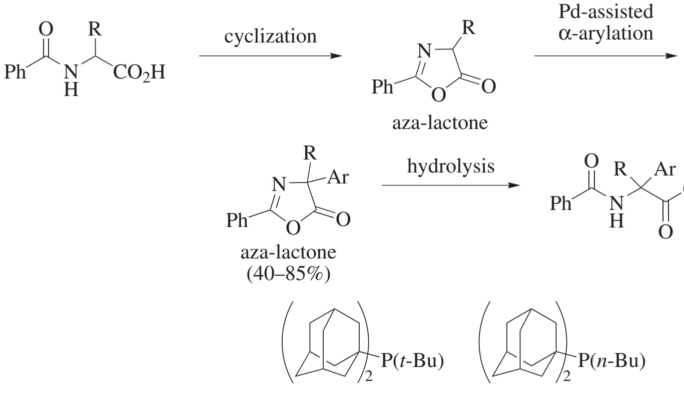
(Eq. 45)

Intramolecular α-arylation of α-amino acid esters provides easy access to 5- and 6-membered dihydroisoindole and tetrahydroisoquinoline derivatives in good to excellent yields using a $Pd_2(dba)_3$/**20** or **22** and LiOt-Bu catalytic system (Eq. 46). In these reactions, LiOt-Bu is superior to other bases such as NaOt-Bu, NaHMDS, phosphates, or carbonates (which cause decomposition of the starting material or lead to poor conversion).[78] In addition, this method allows flexible access to fused tricyclic systems in fair to good yields. Although quaternary carbon centers are accessible via the aforementioned intramolecular route, the analogous intermolecular α-arylation of α-alkyl α-amino acid derivatives is still unreported.



(Eq. 46)

An elegant route to quaternary amino acids, involving a cyclodehydration–arylation–hydrolysis sequence, has been described (Scheme 3).[79] α-Alkyl α-amino acids are first transformed into azalactones. In the second step, the palladium-catalyzed α-arylation affords quaternary carbon centers in good yields

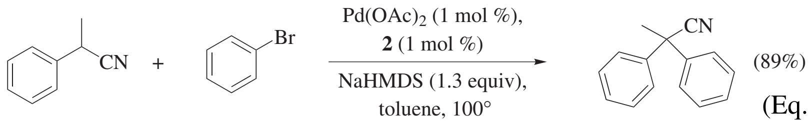


39 **40**

Scheme 3

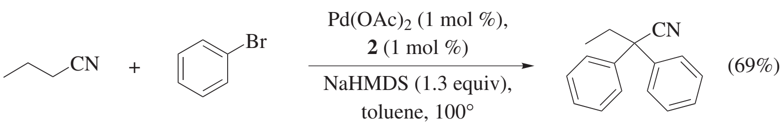
(40–85%). Subsequent hydrolysis gives rise to the quaternary amino acids. The highest yields and fastest rates occur with catalytic systems based on 5 mol % $Pd(dba)_2$ or $Pd(OAc)_2$, 10 mol % of ligand **39** or **40** and 3.3 equivalents of K_2CO_3 or K_3PO_4.

α-Arylation of Nitriles. Aliphatic nitriles are less acidic than ketones[26,66] and thus require the use of stronger bases. For these substrates, the development of catalytic systems was first based on the general method established for ketones and amino acid derivatives. However, hindered alkyl phosphines are less effective than the more common BINAP ligand **2**. Thus, arylation of nitriles is possible using the $Pd(OAc)_2$/**2** catalytic system and affords high to quantitative yields of the expected arylated nitriles (Eq. 47).[26]



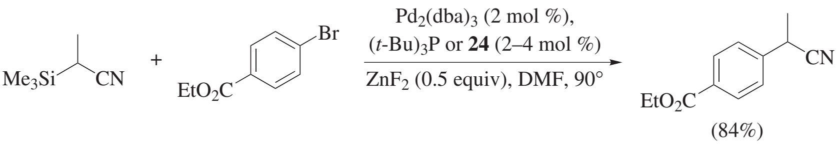
(Eq. 47)

A major limitation to this method is the arylation of linear nitriles. Only the diarylated product is obtained under the previously described conditions because of the increased acidity of the α-CH of the monoarylated product compared to the starting material (Eq. 48).[26]

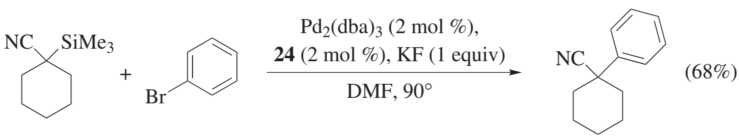


(Eq. 48)

One elegant solution that circumvents the formation of diarylation byproducts is the coupling of aryl halides with silylaceto- or propionitriles.[80] Under these conditions, monoarylation occurs selectively in the presence of $Pd_2(dba)_3/(t\text{-}Bu)_3P$ or **24** and ZnF_2 (Eq. 49). Highly hindered silyl derivatives fail to react under these conditions and require the use of a stronger fluoride source such as KF. Indeed, α-arylation of α-trimethylsilylcyclohexanecarbonitrile occurs in good yields with various aryl bromides as exemplified by Eq. 50.

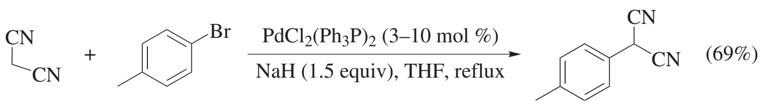


(Eq. 49)



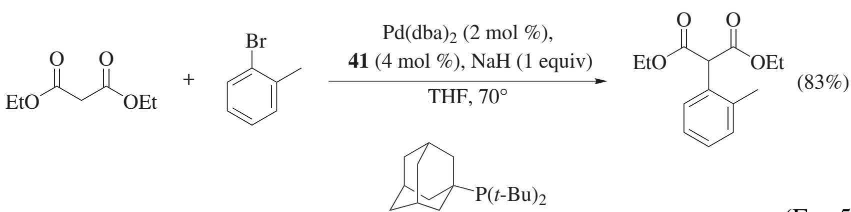
(Eq. 50)

α-Arylation of Active Methylene Compounds. Along with ketones and carboxylic acid derivatives, active methylene compounds such as malonates, β-cyanoesters, malononitriles, and β-diketones represent an important class of nucleophiles that can be arylated, thus considerably expanding the scope of the metal-assisted α-arylation reaction. An example of α-arylation of malononitriles is shown in Eq. 51. The mechanism is assumed to proceed as described in Scheme 1.[14,81]



(Eq. 51)

Recent work has significantly expanded the range of nucleophiles and now allows malonates, acetoacetates, as well as β-cyanoesters to couple with aromatic halides in both an intra- and intermolecular fashion. Complete conversions are obtained using (t-Bu)$_3$P, **3**, **36**, or **41** as ligands (with a palladium to ligand ratio of 1:1 or 1:2) in association with mild bases such as NaH or K_3PO_4 (Eq. 52).[43,82]

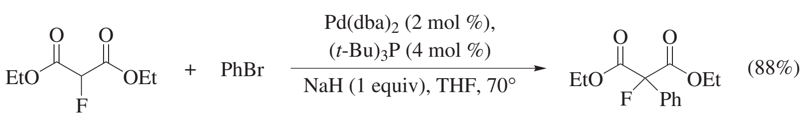


41

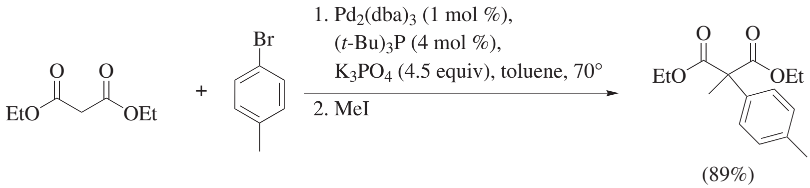
(Eq. 52)

With a view to industrial applications where catalyst and purification costs are of economic importance, the use of heterogeneous conditions has also been explored. Although the results do not rival the most recent developments in homogeneous catalysis, [Pd(NH_3)$_4$]-zeolite in combination with NaOt-Bu, and $PdCl_4{}^{-2}$ in combination with Ba$(OH)_2$, allow the arylation of diethyl malonates in yields ranging from 38–84% and 93–99%, respectively.[83,84] It is worth noting that no diarylated products are observed.

The formation of quaternary carbon centers can be achieved starting from fluoro malonates as shown in Eq. 53.[40] However, attempts to couple alkyl-substituted malonates failed. This lack of reactivity is mainly attributed to steric hindrance, which inhibits the formation of the carbon-bound palladium–malonate complex. This limitation is overcome through a sequential arylation–alkylation process (Eq. 54).[40]

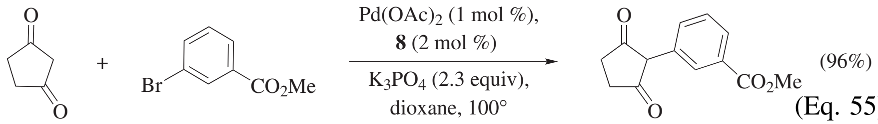


(Eq. 53)



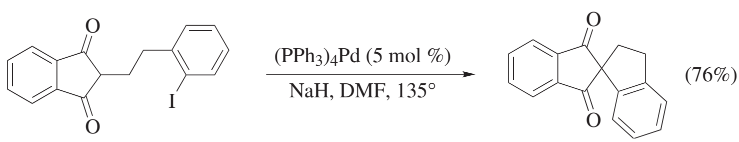
(Eq. 54)

α-Arylation of 1,3-diketones can also be carried out. 1,3-Cyclohexanedione and 1,3-cyclopentanedione undergo monoarylation using the aforementioned procedure (Eq. 55).[43]



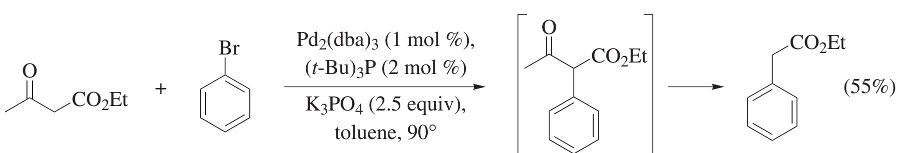
(Eq. 55)

Intramolecular arylation of 1,3-diketones has been described (Eq. 56). Although this strategy requires relatively high temperatures, precluding the use of thermally sensitive substrates, these results paved the way to more recent developments.[15,85]



(Eq. 56)

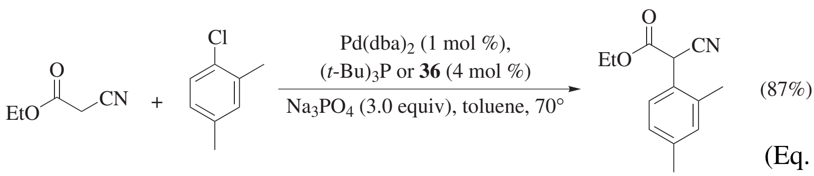
Palladium-catalyzed α-arylations of β-keto esters are rare. However, the key step of an elegant synthesis of the *N*-methylwelwitindolinone skeleton is based on an intramolecular palladium-catalyzed α-arylation of a β-keto ester (see below).[86] Moreover, arylacetic acid esters can be prepared through a one-pot two-step strategy involving a palladium-catalyzed α-arylation of acetoacetate followed by an in situ base-catalyzed deacylation of the arylacetoacetate intermediate **42** (Eq. 57).[87]



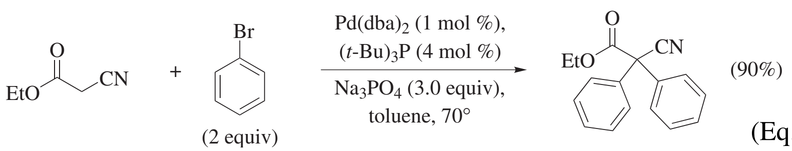
42

(Eq. 57)

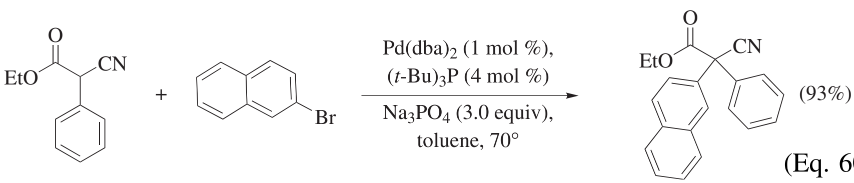
Although the arylation of cyanoacetates using $Pd(PPh_3)_2Cl_2$/KO*t*-Bu as the catalytic system in 1,2-dimethoxyethane (monoglyme) proceed in low to good yields (8–88%),[88,89] recent advances allow selective access to monoarylated as well as symmetrical and unsymmetrical diarylated cyanoacetates. Optimization using high-throughput screening led to the development of a high-yielding arylation of cyanoacetates using $Pd(dba)_2/(t\text{-}Bu)_3P$ (Eq. 58).[90] However, reactions of aryl halides bearing electron-withdrawing groups generate varying amounts of diarylated side products. The selectivity of this method can be improved by switching from $(t\text{-}Bu)_3P$ to ligand **36**, without a noticeable decrease in the arylation yield. The reaction of 2 equivalents of aryl halide and ethyl cyanoacetate produces symmetrical diarylcyanoesters (Eq. 59) and the reaction of 1 equivalent of aryl halide with monoarylcyanoacetates cleanly affords the corresponding unsymmetrical diarylated cyanoacetates (Eq. 60).[90]



(Eq. 58)

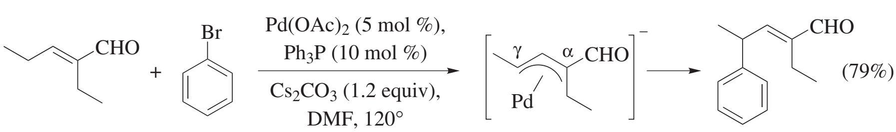


(Eq. 59)

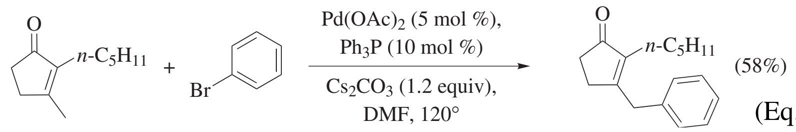


(Eq. 60)

Vinylogy, Phenylogy. Site Selectivity in γ/ω-Arylation. In substrates incorporating vinyl and phenyl groups, arylation may occur at the γ- and ω-position according to vinylogy and phenylogy principles.[91] In α,β-unsaturated carbonyl substrates, where both α- and γ-positions are prone to arylation, only γ-arylation occurs even in substrates having hydrogen available for syn-β-elimination (Eq. 61).[92] Arylation at the β-position (Heck reaction) is not observed. Cyclic enones are also good substrates for γ-arylation (Eq. 62).[92] Mono- or diarylated compounds can be obtained selectively by changing the amount of aryl bromide.

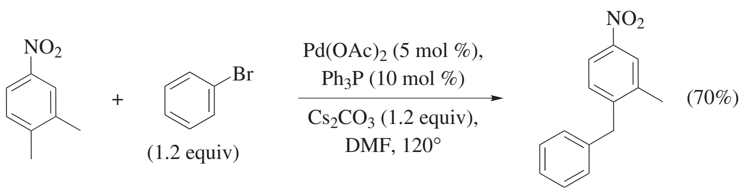


(Eq. 61)



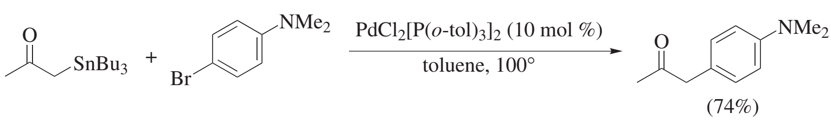
(Eq. 62)

Alkylated nitroaromatic compounds undergo arylation in the side chains (Eq. 63).[93] Although good yields are obtained, the arylation process often affords mixtures of mono- and diarylated products. It is worth noting that selective diarylation may occur when 2 equivalents of the aryl bromide are used. However, this reaction is sensitive to steric factors and depends on the aromatic substitution pattern. Indeed, despite the use of 2 equivalents of the aryl bromide, selective monoarylation is obtained in the presence of neighboring substituents in either the aromatic halide or the nitro-substrate, or at the benzylic position.



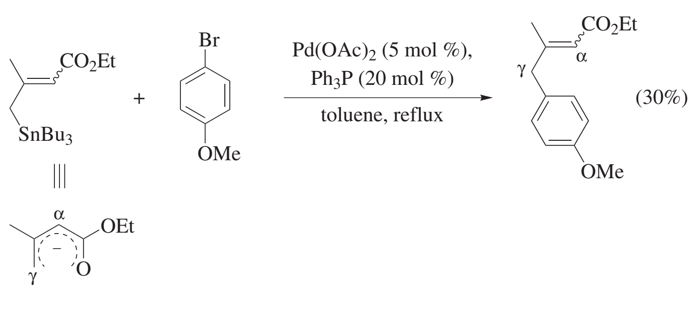
(Eq. 63)

α-Arylation via α-Stannylmethyl Carbonyl Compounds. α-Stannylmethyl ketones are usually considered masked tin enolates. Although this strategy also requires the preparation of the stannylated coupling partner (in some cases such tin derivatives can be prepared in situ), α-aryl ketones are cleanly obtained in yields ranging from 51–91% in the presence of $PdCl_2[P(o\text{-tol})_3]_2$ (Eq. 64).[10]



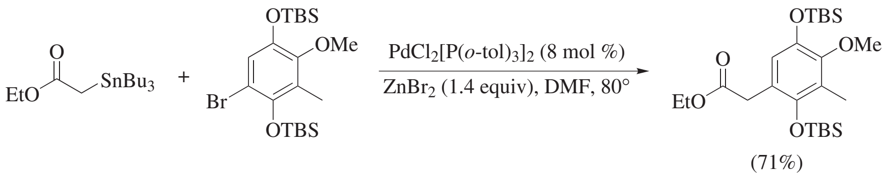
(Eq. 64)

Products arylated at the γ-position of α,β-unsaturated esters have been obtained from the corresponding tin derivatives (Eq. 65). The reaction takes place at the carbon directly bonded to tin. The allylic transposition product (α-arylation) is not detected.[94,95]



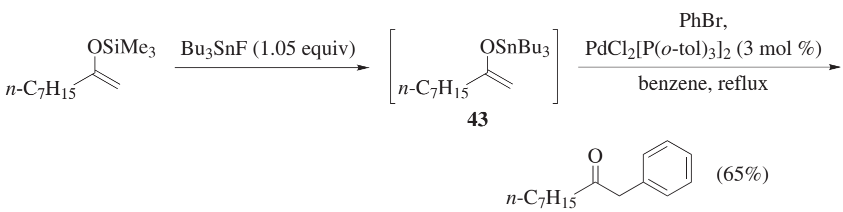
(Eq. 65)

A similar strategy introduces an aromatic group on an acetate moiety.[96,97] Indeed, the preparation of the arylacetic fragment of elisabethin A involves arylation of an acetate ester through tin–zinc transmetallation and a subsequent Negishi-type coupling (Eq. 66).



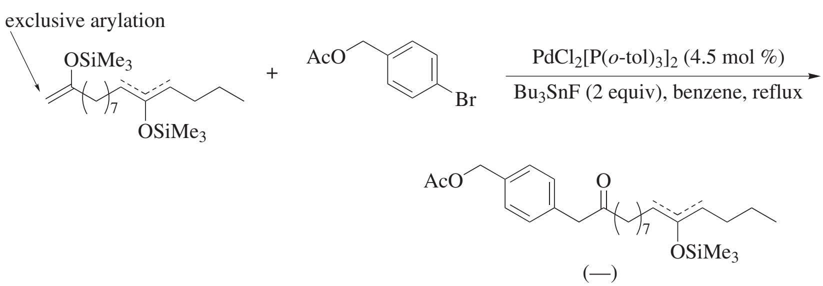
(Eq. 66)

α-Arylation of Silyl Enol Ethers and Ketene Acetals. The α-arylation of silyl enol ethers with aryl halides requires the use of a stoichiometric amount of Bu_3SnF as an additive. The reaction is assumed to proceed by in situ generation of tin enolate **43** via silicon–tin exchange followed by a palladium-catalyzed α-arylation (Eq. 67).[12,13]



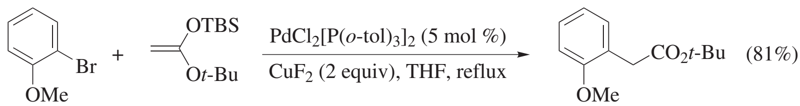
(Eq. 67)

Interestingly, good selectivity is observed in substrates bearing two silyl enol ether groups. Steric interactions between large alkyl groups and the approaching tin fluoride have been postulated to explain the observed selective arylation (Eq. 68).[12,13]



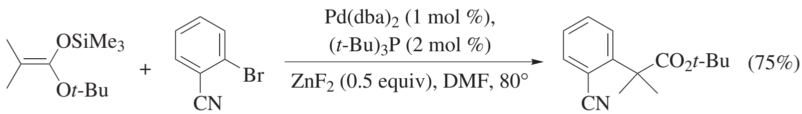
(Eq. 68)

α-Arylation of silyl ketene acetals also requires the use of additives, such as Bu_3SnF or CuF_2 (Eq. 69).[98]



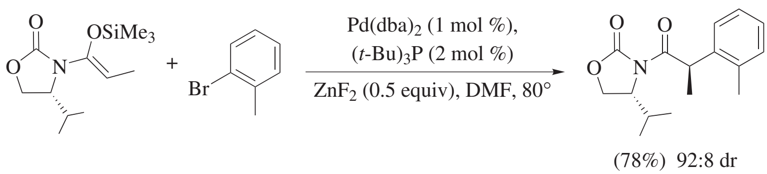
(Eq. 69)

More recently, a general α-arylation procedure for silyl ketene acetals that uses catalytic amounts of a Lewis acid promoter was reported. Thus, 0.25–0.50 equivalents of ZnF_2 or Zn(O*t*-Bu)$_2$ allows complete reaction and arylation in high yields (Eq. 70). Since transmetalation products or accumulation of zinc enolates could not be detected, the exact role of the zinc-based additives is still unclear.[99]

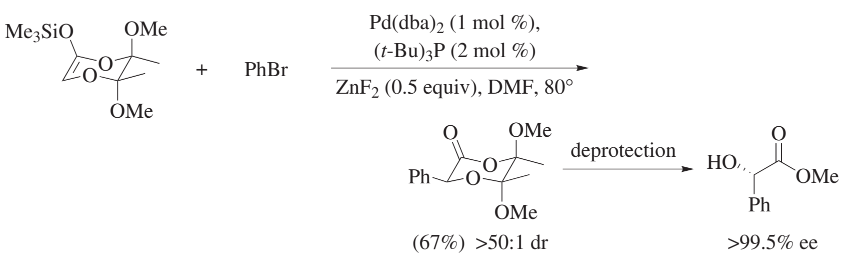


(Eq. 70)

This method has been extended to ketimines and silyl ketene acetals bearing chiral auxiliaries and thus to the diastereoselective formation of tertiary stereogenic centers (Eqs. 71 and 72).

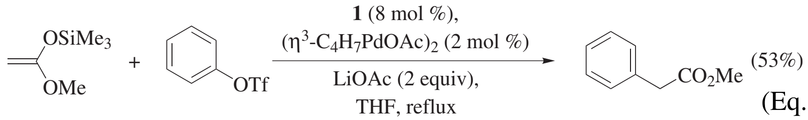


(Eq. 71)



(Eq. 72)

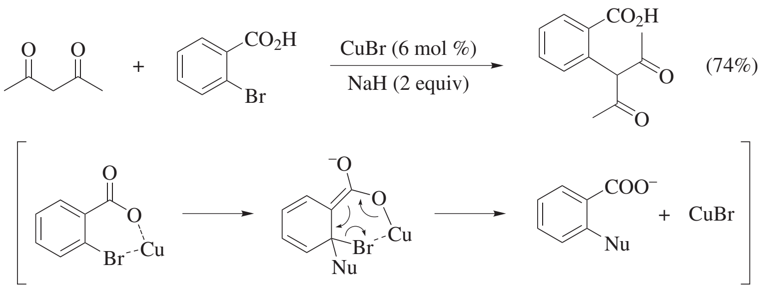
The requirement for metal-based additives can be avoided by the use of aryl triflates. In the presence of palladium(II) and lithium acetate, α-arylated esters are often obtained in high yields (Eq. 73).[100]



(Eq. 73)

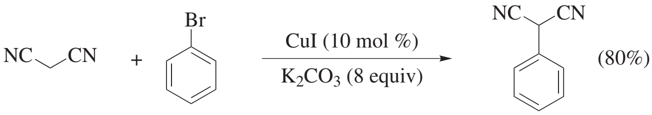
Copper-Catalyzed α-Arylation

Although palladium complexes are the most studied catalytic systems for α-arylation of enolates, nickel and copper catalysts were initially used. Reaction of various halobenzoic acids in the presence of CuBr allows the formation of the expected arylation product (Eq. 74).[101]



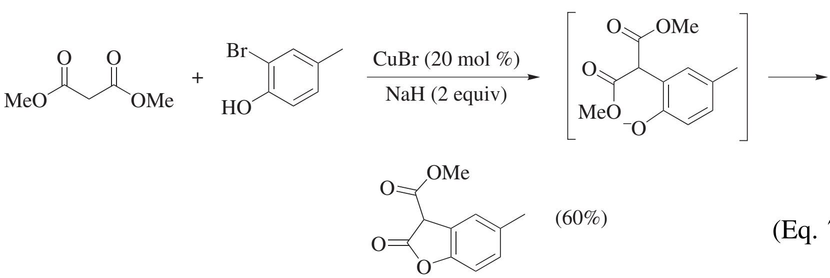
(Eq. 74)

The arylation is assumed to proceed through a copper-assisted nucleophilic displacement of the bromide anion. This strategy is limited to active methylene compounds and requires the presence of an *ortho* carboxylic acid group. This protocal has been extended to the arylation of malononitriles and related substrates,[102] and to the formation of benzofuran-2-ones.[103] The α-arylation of malononitrile and its derivatives proceeds in the presence of a catalytic amount of CuI as shown in Eq. 75.[102]

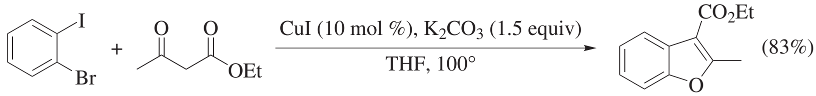


(Eq. 75)

Catalytic amounts of CuBr promote the reaction between dimethyl malonate and 2-bromophenols to afford the corresponding benzofuran-2-ones in one step (Eq. 76). Access to benzofurans from the copper-catalyzed arylation of β-keto esters has also been described (Eq. 77).[104]

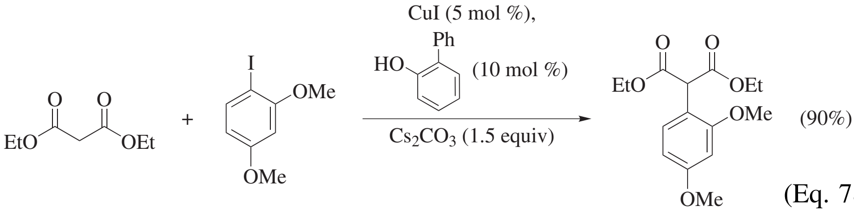


(Eq. 76)



(Eq. 77)

The use of CuI in combination with 2-phenylphenol[105] or 2-nicotinic acid[106] as the ligand allows mild arylations of malonates in high to excellent yields at room temperature (Eq. 78).

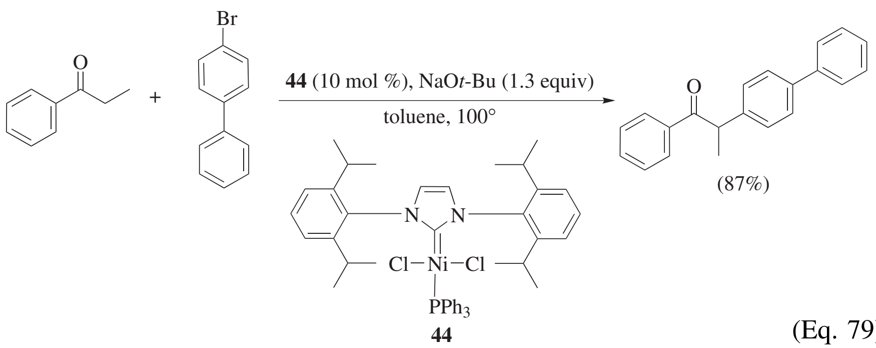


(Eq. 78)

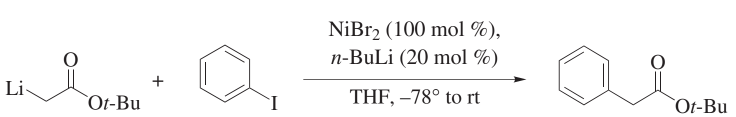
The efficient copper-catalyzed enantioselective α-arylation of β-keto esters was presented earlier (Eq. 13).[36]

Nickel-Catalyzed α-Arylation

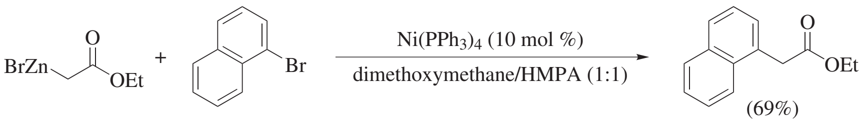
Until the recent development of a Ni–BINAP catalytic, enantioselective α-arylation of lactones (Eq. 9) and the *N*-heterocyclic carbene-based nickel complex **44** promoted α-arylation of acyclic ketones (Eq. 79),[107] examples of nickel-catalyzed arylations of enolates were rare. Two papers independently described the arylation of lithium (Eq. 80)[108] and zinc enolates (Eq. 81).[109]



(Eq. 79)



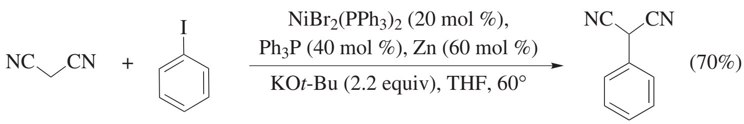
(Eq. 80)



(Eq. 81)

Although the nature of the catalytic system (n-BuLi$-$NiBr$_2$) is still unclear, the arylation of preformed lithium ester enolates with aryl halides occurs in modest to high yields and is viable for both arylation and vinylation reactions (Eq. 80).[108] Preformed zinc enolates (Reformatsky-type reagents) can also be arylated in the presence of nickel(0) catalysts. However, the use of unstable and air sensitive Ni(PPh$_3$)$_4$, even at 10 mol % loading, affords good yields of the expected arylated products (Eq. 81).[109]

An efficient α-arylation of malononitrile has also been described using Ni(PPh$_3$)$_4$ (generated in situ from NiBr$_2$(PPh$_3$)$_2$, Ph$_3$P, and zinc) as the catalyst (Eq. 82).[110]



(Eq. 82)

APPLICATIONS TO SYNTHESIS

Transition-metal-catalyzed α-arylations of carbonyl compounds have found many useful synthetic applications,[15,111] particularly in the synthesis of natural products and biologically active substances. Bonjoch and Wills have described approaches to the syntheses of bridged azabicyclic and 1-vinyl-1H-isochromene compounds, respectively (Fig. 6).[63,112,113] As previously discussed, access to benzofurans (Eq. 26) and benzothiophenes is possible through a C-arylation, O-arylation sequence.[61,62,64]

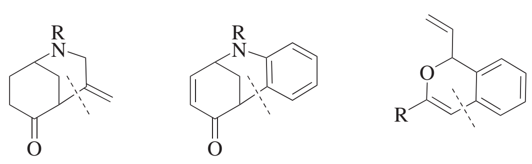
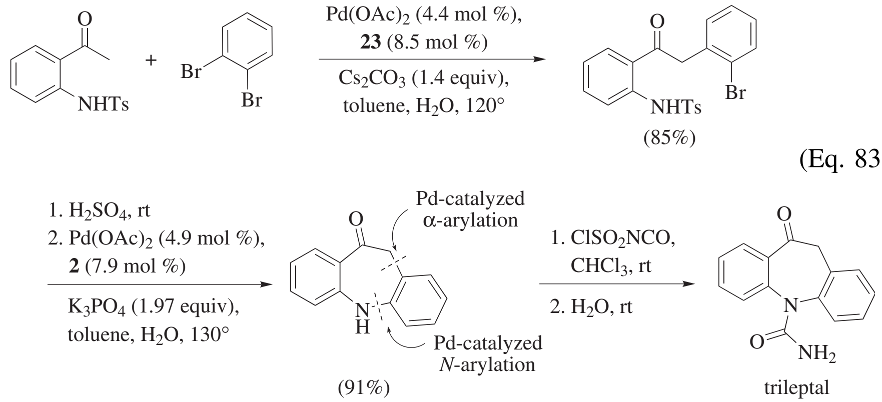


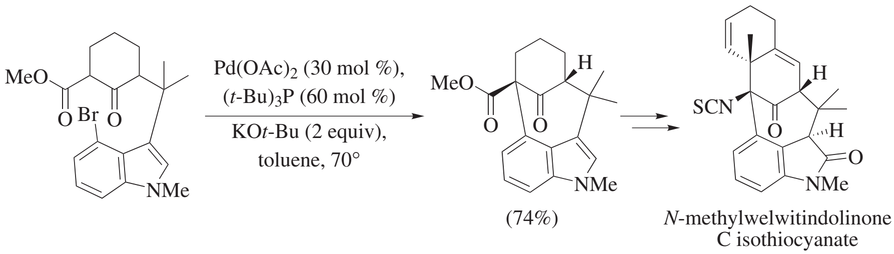
Figure 6. Palladium-assisted bond formation.

An efficient synthesis of trileptal, one of the most widely prescribed drugs for the treatment of epilepsy, involves a palladium-catalyzed α-arylation followed by a palladium-catalyzed N-arylation (Eq. 83).[114]



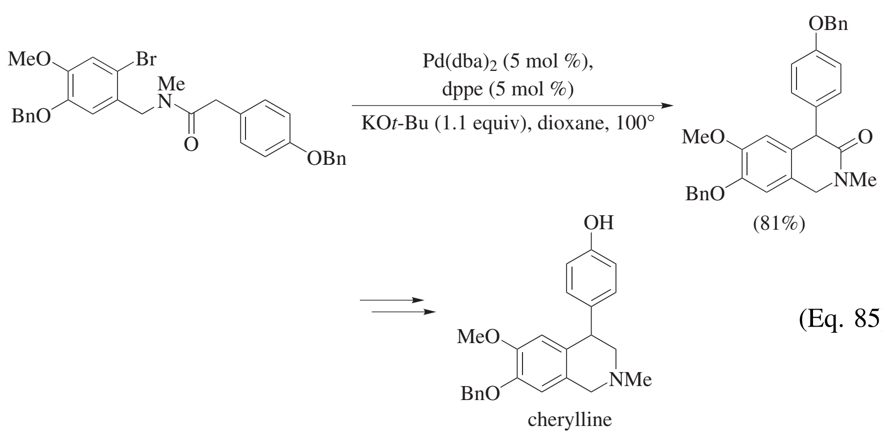
(Eq. 83)

The key step in an approach to the *N*-methylwelwitindoline skeleton involves an intramolecular palladium-catalyzed α-arylation of a cyclic β-keto ester derivative (Eq. 84).[86]

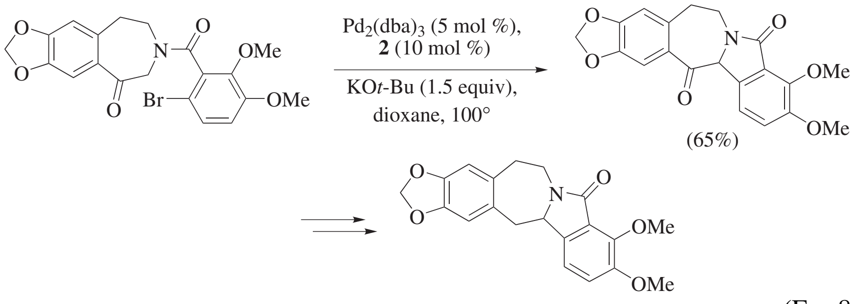


(Eq. 84)

Efficient syntheses of cherylline and latifine use the intramolecular α-arylation of amides (Eq. 85),[71] and a total synthesis of lennoxamine (Eq. 86) employs intramolecular α-arylation of an α-amido ketone.[115]



(Eq. 85)



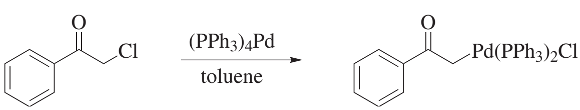
lennoxamine (Eq. 86)

COMPARISON WITH OTHER METHODS

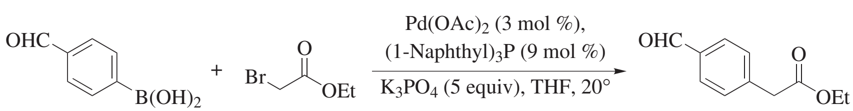
The arylation of enolates has been a challenging subject of research for more than fifty years. The advent of transition-metal-catalyzed carbon–carbon bond formation overcomes many of the drawbacks of existing methods. However, some catalytic, stoichiometric, and metal-free methods represent useful, complementary strategies that also allow the α-arylation of enolates. The following section focuses on: (1) palladium-catalyzed α-arylation from α-halomethyl ketones, (2) α-arylation involving the stoichiometric use of transition metals or metals, (3) miscellaneous methods including photo-induced α-arylation, iodonium salt α-arylation, and nucleophilic aromatic substitution using enolates.

Palladium-Catalyzed α-Arylation via α-Halomethyl Carbonyl Compounds

As shown in Eq. 87, oxidative addition of α-chloro ketones to a palladium(0) species affords *C*-bound "palladium enolates", some of which have been isolated and fully characterized.[116] Adducts of this type, such as that derived from ethyl bromoacetate, are able to couple with arylboronic acids under Suzuki-type reaction conditions ($Pd(OAc)_2$, $P(1\text{-naphthyl})_3$, K_3PO_4) to give the corresponding arylated acetic acid ester derivatives (Eq. 88).[117] The main drawback of this strategy is the required preparation of α-halo carbonyl compounds prior to the coupling reaction.



(Eq. 87)

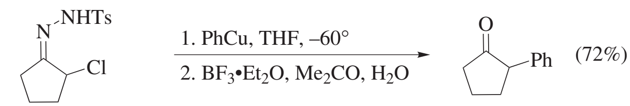


(74%) (Eq. 88)

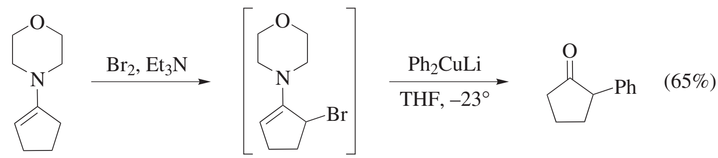
Stoichiometric Transition-Metal- and Metal-Promoted α-Arylation

Copper-Mediated α-Arylation. Stoichiometric, copper-mediated α-arylation of ketones and other carbonyl derivatives has been known for almost a century.

Early reports deal with arylation of acetylacetone, ethyl malonate, and active methylene anions in the presence of copper-bronze or copper acetate.[118–120] More recently, reactions of α-halo tosylhydrazones with an excess of phenylcopper (Eq. 89)[121] or a bromination–phenylation sequence on enamines (Eq. 90)[122] smoothly afford the products, which are converted into the corresponding α-phenyl cycloalkanones.

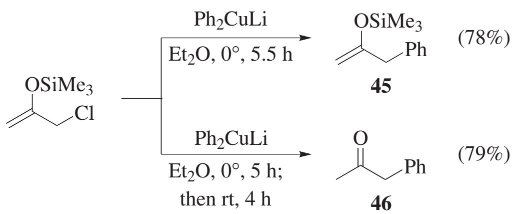


(Eq. 89)



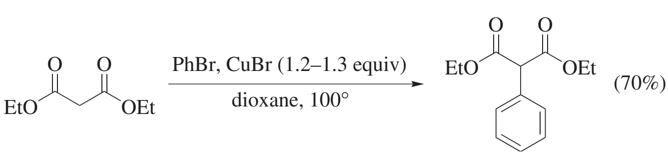
(Eq. 90)

α-Chloromethyl trimethylsilyl enol ethers also undergo arylation using lithium diarylcuprate. Depending on the reaction temperature, the arylated silyl enol ether **45** or the corresponding arylated ketone **46** may be obtained (Eq. 91).[11]



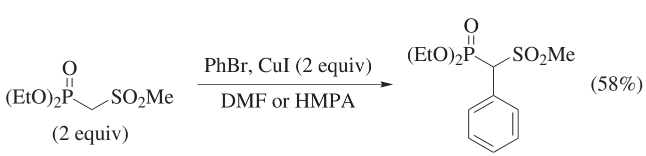
(Eq. 91)

Activation of symmetrical and unsymmetrical active methylene compounds with 1.2 to 1.3 equivalents of CuBr in refluxing dioxane allows the arylation of malonates (Eq. 92).[123,124]



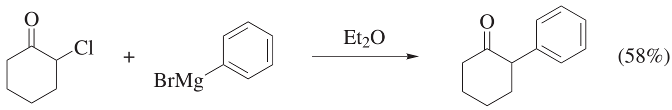
(Eq. 92)

CuI is used as a stoichiometric coupling agent in arylation reactions of unsymmetrical, phosphonyl-stabilized carbanions (Eq. 93). Two equivalents of both CuI and the active methylene reactant are required to obtain good to high yields.[125]



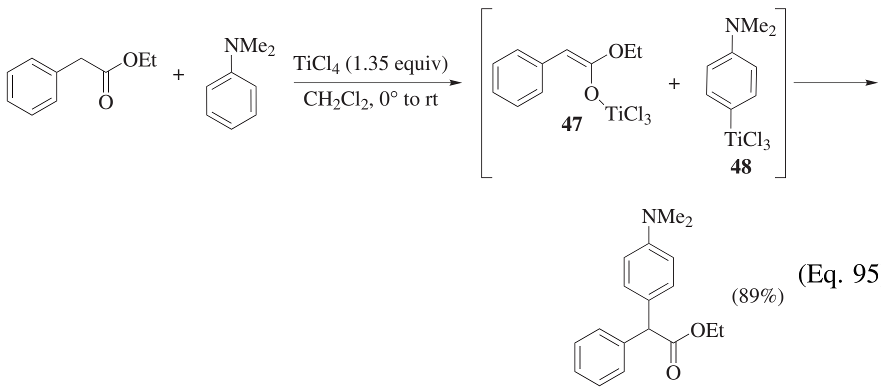
(Eq. 93)

Magnesium- and Titanium-Mediated α-Arylation. Although stoichiometric magnesium- or titanium-based arylations are rare, their use allows easy access to arylated ketones or diarylated esters in some cases. An example is the reaction of 2-chlorocyclohexanone with phenylmagnesium bromide (Eq. 94).[126]



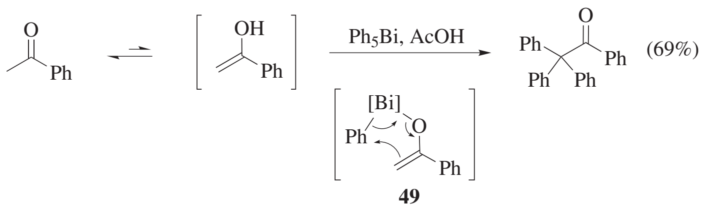
(Eq. 94)

The reaction of α-arylacetic esters with tertiary arylamines in the presence of stoichiometric amounts of $TiCl_4$ affords the corresponding α,α-diarylated ester (Eq. 95).[127] The proposed mechanism involves both the titanium ester enolate **47** and aryltitanium species **48**.



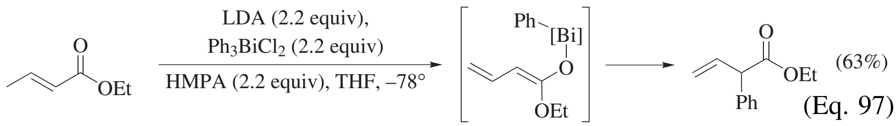
(Eq. 95)

Bismuth-Mediated α-Arylation. Ketones, active methylene derivatives, silyl enol ethers, and silyl ketene acetals are arylated under basic or neutral conditions using stoichiometric amounts of polyarylbismuth(V) compounds such as pentaphenylbismuth, tetraphenylbismuth chloride or triphenylbismuth dichloride as phenylating agents.[128,129] The postulated mechanism involves the O–Bi bonded intermediate **49** (Eq. 96). Internal ligand coupling between the aryl group and the enolate carbon accounts for the observed α-arylated products.



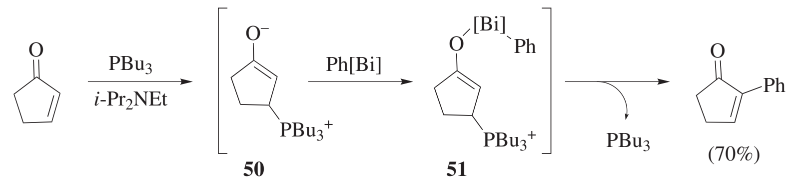
(Eq. 96)

α,β-Unsaturated carbonyl derivatives undergo site selective α-arylation with concomitant deconjugation of the olefinic moiety (Eq. 97).[37,130]



(Eq. 97)

Cyclic α,β-unsaturated ketones react with arylbismuth reagents in the presence of tributylphosphine and Hünig's base to afford α-arylation products (Eq. 98). The reaction likely proceeds by formation of phosphonium intermediate **50** followed by the generation of Bi-enolate **51**, the α-arylation reaction, and subsequent elimination of the phosphine.[38]



50 **51**

(Eq. 98)

Lead-Mediated α-Arylation. Aryllead triacetates effect the construction of α-aryl carbonyl compounds under mild conditions. As shown in Fig. 7, this method introduces aryl groups into various substrates, including β-dicarbonyls, active methylene compounds, lactones, dihydroindoles, benzofurans, and neoflavones.[131–135] In most cases, 1.1 equivalents of the aryllead derivative, obtained through Hg−Pb or Sn−Pb exchange, are required to ensure complete transformation. Reaction rates are significantly enhanced by the use of additional ligands such as 1,10-phenanthrolines.[136]

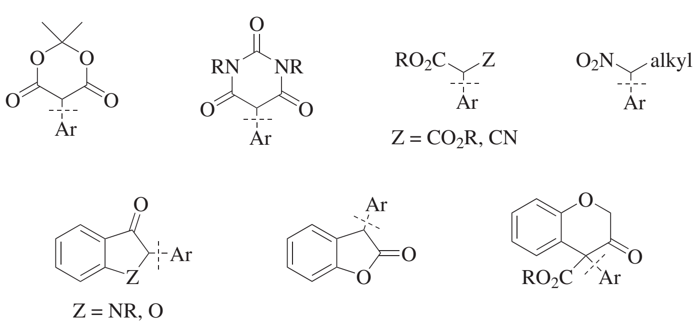
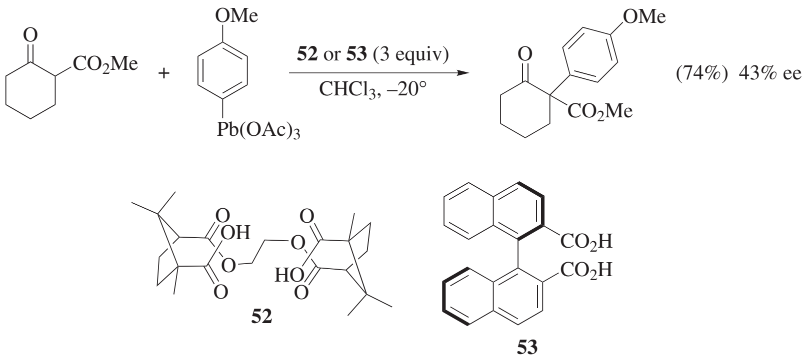


Figure 7. α-Aryl carbonyl compounds formed with aryllead triacetates.

Asymmetric coupling of aryllead reagents with β-keto esters is achieved by replacement of one or more of the labile acetate ligands with enantiomerically pure carboxylic acids such as **52** or the binaphthyl dicarboxylic acid **53** (Eq. 99).[133,137]

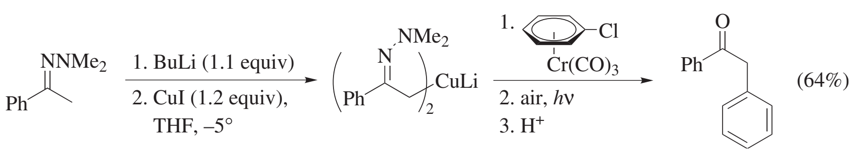


(Eq. 99)

Miscellaneous α-Arylation Methods

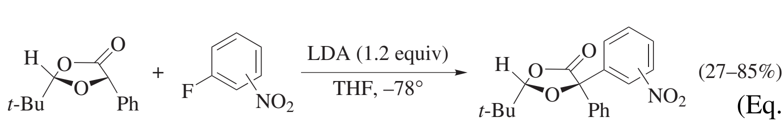
Introduction of aryl groups at the α-carbon of carbonyl compounds may also be accomplished through several non-metallic procedures. The following section briefly illustrates the most relevant ones, including nucleophilic or photo-induced aromatic substitution and α-arylation using iodonium salts.

Nucleophilic aromatic substitution of activated aryl halides by carbon nucleophiles proceeds through Meisenheimer-type intermediates and is followed by rearomatization. This process requires the presence of strong electron-withdrawing groups or complexation of the aromatic system with metallic fragments such as $Cr(CO)_3$. In this context, efficient arylation of ketone hydrazones with η^6-(chlorobenzene)$Cr(CO)_3$ followed by decomplexation and hydrolysis has been reported (Eq. 100).[138]



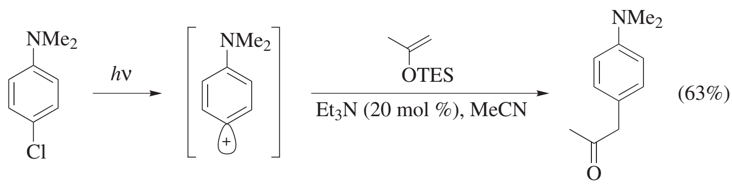
(Eq. 100)

In addition, the diastereoselective arylation of protected mandelic acids with fluoronitrobenzenes under basic conditions affords the expected arylated products (Eq. 101).[139]

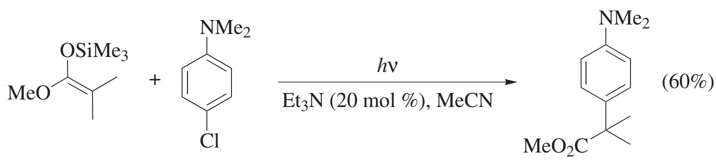


(Eq. 101)

Photo-stimulated formation of carbon–carbon bonds between aromatics and enolate equivalents has also received considerable attention. Photo-induced generation of phenyl cations and subsequent reaction with enamines, silyl enol ethers, or ketene silyl acetals afford the corresponding α-arylated carbonyl compounds (Eqs. 102 and 103).[96,140,141]

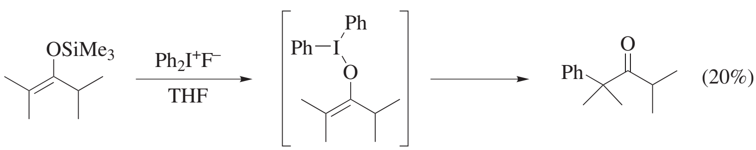


(Eq. 102)



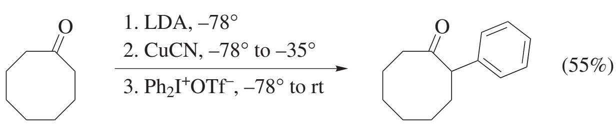
(Eq. 103)

An alternative strategy involves the use of diaryliodonium salts as the "phenyl cation" species. Such species exploit the excellent nucleofugality of the phenyliodonium group, which is about 10 times higher than that of triflate.[142] The treatment of silyl enol ethers with diaryliodonium fluorides affords the expected arylated ketones. Although the mechanism is still unclear, it might involve a trivalent iodine intermediate **54** as suggested in Eq. 104.[143,144]



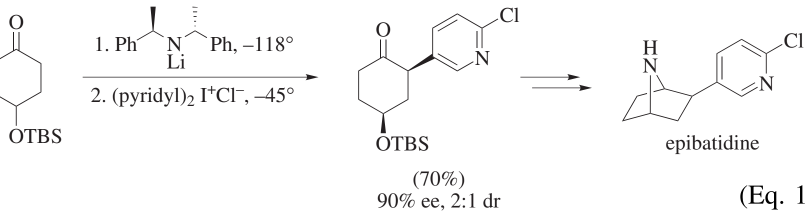
(Eq. 104)

A second alternative, involving deprotonation of cyclic ketones followed by generation of a copper enolate and subsequent coupling using diaryliodonium salts, is shown in Eq. 105.[145]



(Eq. 105)

A recent synthesis of (–)-epibatidine employs a chiral amide base to desymmetrize 4-substituted cyclohexanone derivatives, which then react with a diaryliodonium salt to give the arylated products in high yields, and modest dr and ee (Eq. 106).[146]

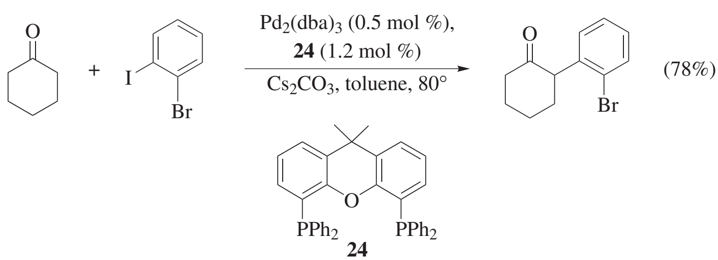


(Eq. 106)

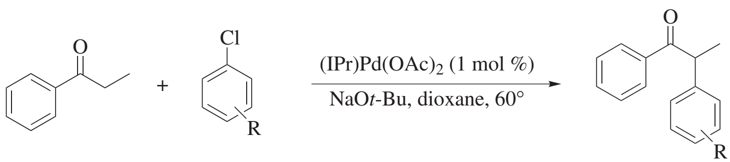
EXPERIMENTAL CONDITIONS

An attractive aspect of the transition-metal-catalyzed α-arylation of enolates is its experimental simplicity. Although the use of a glove-box was initially recommended, most of the reactions can be carried out efficiently using normal Schlenk techniques in anhydrous solvents. As discussed above, a wide variety of different conditions (palladium source, ligand, base, solvent) have been developed, but it appears that $Pd_2(dba)_3$ [(or $Pd(OAc)_2$), $(t\text{-Bu})_3P$ in dioxane (or toluene)] in the presence of an excess of NaO*t*-Bu [(NaHMDS or $LiNCy_2$ in the arylation of esters and amides)] are often the first experimental conditions to be tried.

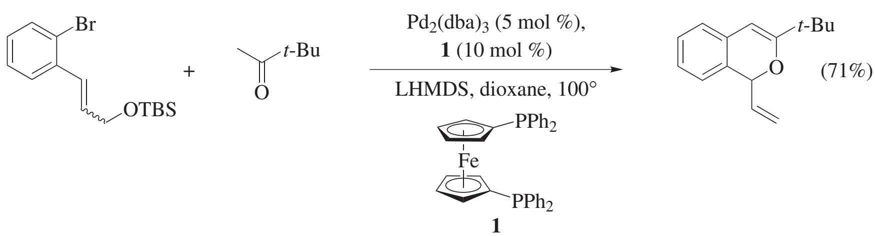
EXPERIMENTAL PROCEDURES



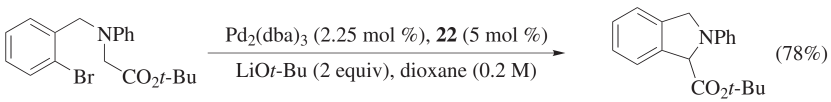
2-(2-Bromophenyl)cyclohexanone [Palladium-Catalyzed α-Arylation of a Ketone].[62] Cesium carbonate (4.570 g, 14.00 mmol) was added to a flask charged with $Pd_2(dba)_3$ (0.030 g, 0.033 mmol) and Xantphos (**24**) (0.040 g, 0.080 mmol) under nitrogen. The reagents were suspended in anhydrous dioxane (6.4 mL); 1-Bromo-2-iodobenzene (1.80 g, 6.37 mmol, 0.82 mL) and cyclohexanone (1.25 g, 12.74 mmol, 1.3 mL) were added under nitrogen, and the reaction mixture was heated at 80° for 24 h. After cooling, the reaction mixture was diluted with Et_2O (ca. 10 mL), filtered through Celite, and the solvents were removed in vacuo. The residue was purified by flash column chromatography (5–10% Et_2O/petroleum ether) to give 1.26 g (78% yield) of the title product: mp 57–58° (MeOH); IR (Nujol) 2920, 2855, 1709, 1566 (w), 1462, 1377, 1281, 1196, 1121, 1070, 1027, 977, 940, 769, 746, 722, 674 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (td, J = 7.9, 1.5 Hz, 1H, Ar–H), 7.31 (td, J = 7.9, 1.1 Hz, 1H, Ar–H), 7.21 (dd, J = 7.9, 1.9 Hz, 1H, Ar–H), 7.12 (ddd, J = 7.9, 7.2, 1.9 Hz, 1H, Ar–H), 4.11 (app. dd, J = 12.4, 5.3 Hz, 1H, Ar–CH), 2.89–2.51 (m, 2H, CH_2CO), 2.35–2.15 (m, 2H, $ArCHCH_2$), 2.10–1.71 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 137.8, 132.1, 128.9, 127.8, 126.8, 124.6, 56.0, 41.8, 33.6, 27.1, 25.1; LRMS (CI^+, NH_3) m/z: $[M + NH_4]^+$ 270, $[M + H{:}^{79}Br]^+$ 253, $[M - {}^{79}Br]^+$ 173, $[M - {}^{79}Br{-}CO]^+$ 145, $[M - {}^{79}Br{-}CO{-}C_2H_4]^+$ 115; HRMS (ES^+): $[M + H]^+$ calcd for $C_{12}H_{14}BrO$, 253.0223; found, 253.0225.

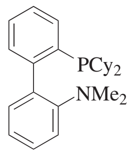


1-Phenyl-2-arylpropan-1-one [α-Arylation of a Ketone Using an *N*-Heterocyclic Carbene-Based Catalytic System].[51] In a drybox, 1.5 mmol of base (typically NaO*t*-Bu) was added to a screw-cap vial charged with 1 mol % of [*N*,*N*′-(2,6-diisopropyl phenyl)imidazol-2-ylidene]Pd$(OAc)_2$ complex. Dioxane (1.5 mL) was added and the vial sealed with a rubber septum. Outside the drybox, propiophenone (1.2 mmol) followed by the aryl halide (1 mmol) were injected into the vial with a syringe. The reaction mixture was shaken on a Lab-Line Orbit Shaker at 60° (J-Kem Scientific, Kem-Lab Controller) or stirred over a magnetic plate in an oil bath set at 60° for the indicated time. The reactions were monitored by gas chromatography. After reaching maximum conversion, the reaction mixture was allowed to cool to rt and it was then quenched with water. The water layer was extracted with methyl *tert*-butyl ether or Et_2O and dried over magnesium sulfate. The solvent was then evaporated in vacuo. When necessary the product was purified by flash chromatography on silica gel.



1-Vinyl-3-*tert*-butyl-1*H*-isochromene [Palladium-Catalyzed α-Arylation of a Ketone].[63] A solution of LiHMDS (1 M in THF, 3 equiv) was treated slowly with a solution of 3,3-dimethylbutan-2-one (2 equiv) at 5°. A solution of $Pd_2(dba)_3$ (5 mol %) and dppf (**1**) (10 mol %) in solvent was added at rt, followed by a solution of (*E*/*Z*)-*tert*-butyldimethyl[3-(2-bromophenyl)allyloxy]silane (1 equiv). The reaction mixture was heated at 100° overnight and quenched with 1 M HCl solution at rt. The mixture was twice extracted with CH_2Cl_2, the combined organic layers were dried, and the solvent was evaporated under reduced pressure yielding the crude product, which was purified by chromatography (details not reported) to give the title compound in 71% yield: IR (NaCl) 2954, 1638, 1085, 914, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–6.90 (m, 4H), 6.15 (ddd, J = 17.1, 10.4, 6.6 Hz, 1H), 5.67 (s, 1H), 5.46 (d, J = 6.6 Hz, 1H), 5.16 (dt, J = 17.1, 1.3 Hz, 1H), 5.23 (dt, J = 10.4, 1.3 Hz, 1H), 1.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 136.7, 132.0, 129.4, 128.5, 126.2, 124.9, 123.8, 118.2, 97.7, 79.3, 35.5, 28.3; MS (EI) m/z: M^+ 214, 187, 129; HRMS (EI) m/z: calcd for $C_{15}H_{18}O$, 214.135765; found, 214.136173.





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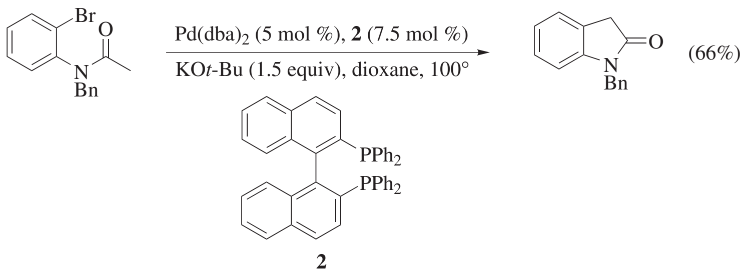
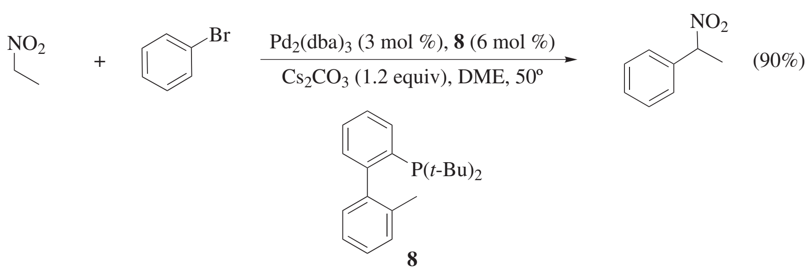
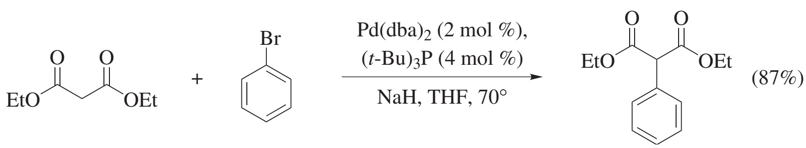
***tert*-Butyl 2-Phenyl-2,3-dihydro-1*H*-isoindole-1-carboxylate [Palladium-Catalyzed Intramolecular α-Arylation of an α-Amino Acid Ester].[78]** An oven-dried resealable Schlenk tube containing a magnetic stir bar was evacuated and purged with argon while cooling to ambient temperature. The Schlenk tube was charged with LiOt-Bu (2.0 equiv), $Pd_2(dba)_3$ (2.25 mol %), and 2-(dicyclohexylphosphino)-2′-(N,N-dimethylamino)biphenyl (5 mol %). The reaction vessel was evacuated, backfilled with argon, and dioxane (2 mL) was added via syringe under argon. The mixture was stirred for 5 min at rt, followed by addition of a solution of dodecane (0.045 mL, 0.2 mmol) and the substrate (0.188 g, 0.5 mmol) in dioxane (0.5 mL) via syringe. The solution was 0.2 M in dioxane as solvent. The Schlenk tube was sealed and placed in a preheated oil bath at 85° for 1 h. After complete conversion, as judged by either GC or TLC analysis, the reaction mixture was cooled to ambient temperature. The crude mixture was filtered through a silica gel plug, and the plug then washed thoroughly with ether. The filtrate was concentrated and further purified by flash column chromatography (hexanes/ether 15:1) to give 0.115 g (78% yield) of the title product: mp 72°; IR (CH_2Cl_2) 3043, 2979, 2933, 2875, 2840, 1740, 1603, 1505, 1468, 1368, 1146, 1094, 1036, 1003, 955, 839, 750, 690 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.47–7.41 (m, 1H), 7.32–7.26 (m, 2H), 7.10–7.03 (m, 2H), 6.97–6.91 (m, 1H), 6.86–6.81 (m, 1H), 6.70–6.55 (m, 2H), 5.36–5.33 (d, J = 3.5 Hz, 1H), 4.59–4.53 (dd, J = 3.5, 12.9 Hz, 1H), 4.36–4.31 (d, J = 12.9 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 171.2, 146.9, 139.1, 138.0, 130.0, 128.7, 127.8, 123.4, 123.0, 117.7, 112.8, 81.5, 68.3, 57.8, 54.3, 28.1. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17. Found: C, 77.12; H, 7.17.



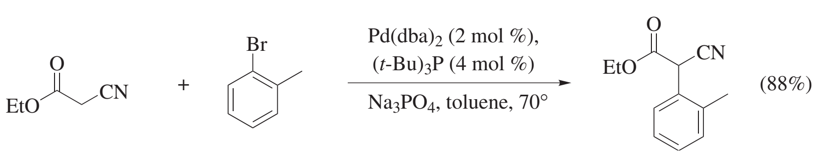
1-Benzyloxindole [Preparation of an Oxindole by Palladium-Catalyzed Intramolecular α-Arylation of an Amide].[67] In a drybox, $Pd(dba)_2$ (57.5 mg, 0.10 mmol), BINAP (**2**) (93.4 mg, 0.15 mmol), and potassium *tert*-butoxide (288 mg, 3.00 mmol) were combined in a round-bottom flask. Dioxane (18 mL) was added, and the flask was sealed with a septum. After removing the flask from the drybox, 2-bromo-*N*-benzylacetanilide (609 mg, 2.00 mmol) was added. The flask was placed in an oil bath at 100° for 3 h. The reaction mixture was poured into 50 mL of saturated NH_4Cl solution and extracted (3 × 30 mL) with ether. The combined ether extracts were washed with brine (50 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the resulting crude product was purified by flash chromatography on silica gel (hexanes/EtOAc 85:15); recrystallization from hexanes gave 0.297 g (66% yield) of the title product as pale yellow needles: mp 66.5–67°; FTIR (neat, NaCl plate) 1717 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.33 (m, 3H), 7.30–7.26 (m, 2H), 7.19 (t, J = 7.8 Hz, 1H), 7.03 (t, J = 7.3 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 4.94 (s, 2H), 3.65 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 144.4, 135.9, 128.8, 127.9, 127.7, 127.4, 124.5, 124.5, 122.5, 109.2, 43.8, 35.8. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.68; H, 5.87; N, 6.27. Found: C, 80.59; H, 5.92; N, 6.16.



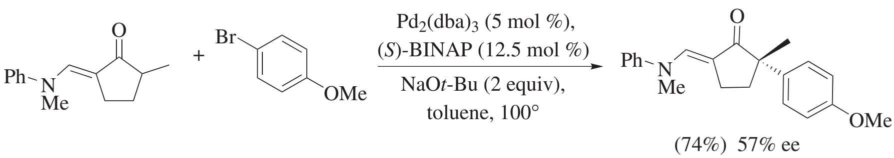
(1-Nitroethyl)benzene [Palladium-Catalyzed α-Arylation of Nitroethane].[147] A dried, resealable Schlenk tube containing a magnetic stir bar was charged with $Pd_2(dba)_3$ (27.4 mg, 0.03 mmol, 3 mol %), 2-(di-*tert*-butylphosphino)-2′-methylbiphenyl (**8**) (19.2 mg, 0.06 mmol, 6 mol %), and 1.2 equiv of Cs_2CO_3. The reaction vessel was capped with a rubber septum, evacuated, and backfilled three times with argon, and 1.0 mmol of bromobenzene, dimethoxyethane (5 mL), and 1.0–2.0 equiv of nitroethane were added sequentially via syringe under argon. The mixture was stirred vigorously for 1 min at rt, the Schlenk tube was sealed and placed in a preheated oil bath at 50° for 8–30 h. After completion of the reaction, as judged by either GC or TLC analysis, the reaction mixture was allowed to cool to ambient temperature. The crude mixture was quenched with a solution of saturated aqueous NH_4Cl (2 × 2 mL, two times), the aqueous phase was extracted with ether (2 mL), and the combined organic phases were washed with brine. The solvent was removed, and the remaining oil was purified by flash silica gel column chromatography (hexanes/Et_2O 20:1) to provide 0.136 g (90% yield) of the title product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.40 (m, 5H), 5.62 (q, J = 6.9 Hz, 1H), 1.89 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 129.9, 129.1, 127.5, 86.3, 19.5.



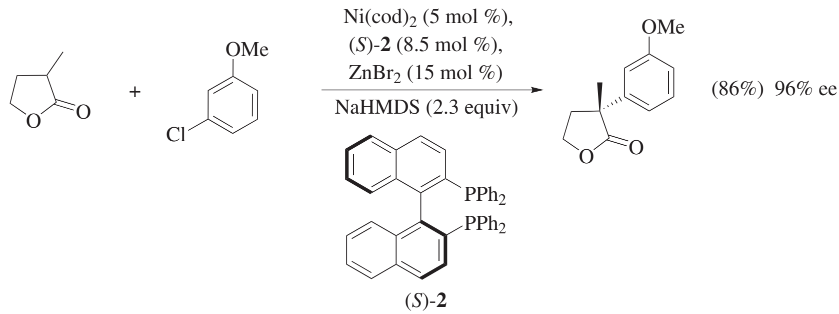
Diethyl 2-Phenylmalonate [Palladium-Catalyzed α-Arylation of a Malonate with an Aryl Bromide].[53,82] To a screw-capped vial in a dry box containing diethyl malonate (176 mg, 1.1 mmol) was added tetrahydrofuran (1.0 mL) followed by NaH (1.1 mmol). Upon completion of hydrogen evolution (ca. 2 min), bromobenzene (157 mg, 1.00 mmol), (t-Bu)$_3$P (0.040 mmol), Pd(dba)$_2$ (0.020 mmol), and THF (2.0 mL) were added. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The homogeneous reaction mixture was stirred at 70° and monitored by GC. After complete conversion of the aryl halide, the crude reaction mixture was filtered through a plug of Celite and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes/CH_2Cl_2 2:1) to give 0.204 g (87% yield) of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.43–7.34 (m, 5H), 4.62 (s, 1H), 4.27–4.18 (m, 4H), 1.27 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 168.17, 132.81, 129.27, 128.59, 128.20, 61.80, 57.96, 14.01.



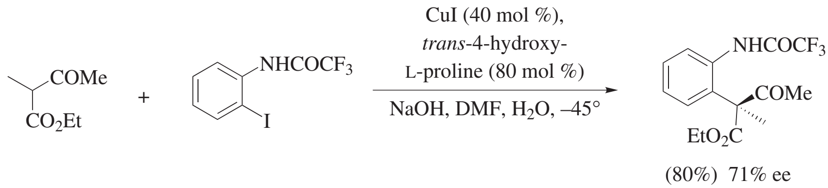
Ethyl 2-(2-Methylphenyl)cyanoacetate [Palladium-Catalyzed α-Arylation of Ethyl Cyanoacetate].[82] Into a screw-capped vial containing ethyl cyanoacetate (125 mg, 1.10 mmol) and 2-bromotoluene (172 mg, 1.00 mmol), were added $(t\text{-Bu})_3P$ (40 µL, 1.0 M in toluene, 0.040 mmol), $Pd(dba)_2$ (3.7 mg, 0.010 mmol), and Na_3PO_4 (3.0 mmol), followed by toluene (3.0 mL). The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The heterogeneous reaction mixture was stirred at 70° and monitored by GC. After complete conversion of the aryl bromide, the reaction mixture was filtered through a plug of Celite and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexanes/CH_2Cl_2, 3:1) to give the title product (88% yield): ^{1}H NMR ($CDCl_3$) δ 7.47–7.45 (m, 1 H), 7.32–7.22 (m, 3H), 4.89 (s, 1H), 4.31–4.19 (m, 2H), 2.40 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.03, 136.23, 131.24, 129.34, 128.93, 128.62, 127.05, 115.90, 63.25, 41.06, 19.42, 13.92.



(*R*)-(+)-2-Methyl-2-(4-anisyl)-5-(*N*-methylanilinomethylene)cyclopentanone [Palladium-Catalyzed Asymmetric α-Arylation of a Ketone Enolate].[41] An oven-dried Schlenk tube equipped with a rubber septum was evacuated and backfilled with argon. The tube was charged with tris(dibenzylideneacetone) dipalladium (0.005 mmol), (*S*)-BINAP (0.125 mmol), and (*E*)-2-methyl-5-((methyl(phenyl)amino)methylene)cyclopentanone (0.50 mmol). The tube was evacuated and backfilled three times with argon. Toluene (2 mL) was added and the mixture was stirred for 15 min at rt. 4-Bromoanisole (1.00 mmol) and sodium *tert*-butoxide (96 mg, 1.00 mmol) were added to the tube. The tube was capped with a septum, purged with argon, and additional toluene (1 mL) was added through the septum. The mixture was stirred at rt until the starting ketone had been completely consumed as judged by GC analysis. The reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) and diluted with ether (20 mL). The aqueous layer was extracted with ether (20 mL) and the combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography (10–20% EtOAc/hexanes) to give the title product (74% yield, 57% ee): $[\alpha]^{20}+1.53$ (*c* 10.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (t, $J = 1.5$ Hz, 1H), 7.33–7.29 (m, 4H), 7.13–7.08 (m, 3H), 6.85–6.80 (m, 2H), 3.75 (s, 3H), 3.45 (s, 3H), 2.56–2.32 (m, 3H), 1.89–1.79 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 157.8, 146.1, 142.4, 136.1, 129.1, 127.4, 124.6, 121.1, 113.6, 108.0, 55.3, 51.9, 40.1, 36.6, 25.4, 24.9; MS (EI) m/z: M^+ 321. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59. Found: C, 82.53; H, 7.68.



(−)-3-(3-Methoxyphenyl)-3-methyldihydrofuran-2-one [Nickel-Catalyzed Asymmetric α-Arylation of a Lactone].[33] An oven-dried, resealable Schlenk tube containing a magnetic stir bar was allowed to cool to rt and was then charged with (*S*)-BINAP (**2**) (13.2 mg, 21.3 μmol). The tube was sealed, evacuated, and backfilled with argon. From a freshly prepared, yellow, homogeneous stock solution of $Ni(cod)_2$ (0.05 M, toluene), 250 μL (12.5 μmol) was added by syringe while purging with argon. The tube was sealed and heated to 60° for 5 min during which time the solution turned dark red. The reaction vessel was removed from the oil bath, and sequentially α-methyl-γ-butyrolactone (47.0 μL, 0.5 mmol), dodecane (50 μL, internal standard) and NaHMDS (105.4 mg, 0.575 mmol) were added under argon. From a stock solution, $ZnBr_2$ (0.51 M in THF, 250 μL 37.5 μmol) was added by syringe while purging with argon; the mixture was then stirred for 5 min at rt. 3-Chloroanisole (0.25 mmol) was added by syringe followed by toluene (500 μL) while purging with argon. The tube was sealed and heated at 60° for 20 h. After complete conversion had been accomplished, as judged by GC analysis, the reaction mixture was allowed to cool to rt and was then filtered through a pad of silica gel, eluting with EtOAc. The eluate was concentrated under reduced pressure, followed by chromatography of the residue on silica gel (1.5 × 30 cm, EtOAc/hexanes), to give 42.6 mg of the title compound (86% yield, 96% ee) as a colorless oil: HPLC (OD-col., 10% *i*-PrOH/hexanes, 0.7 mL/min) t_r (major) = 13.7 min, t_r (minor) = 17.0 min; $[\alpha]^{20}$ −7.3 (*c* 2.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 18.30 (m, 1H), 6.99 (m, 2H), 6.84 (m, 1H), 4.34 (ddd, J = 9.0, 7.8, 3.9 Hz, 1H), 4.16 (ddd, J = 8.9, 8.9, 6.5 Hz, 1H), 3.82 (s, 3H), 2.69 (ddd, J = 12.9, 6.5, 3.9 Hz, 1H), 2.41 (ddd, J = 12.9, 8.7, 7.8 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 160.3, 143.0, 130.3, 118.5, 112.8, 112.6, 66.7, 65.5, 55.7, 47.9, 38.5, 25.9. Anal. Calcd. for $C_{12}H_{14}O_2$: C, 69.88; H, 6.84. Found: C, 69.58; H, 6.91.



(*S*)-Ethyl 2-Methyl-3-oxo-2-[2-(2,2,2-trifluoroacetamido)phenyl]butanoate [Copper-Catalyzed Enantioselective α-Arylation of an Acetoacetate].[36] A Schlenk tube was charged with 2-(2,2,2-trifluoroacetamido)phenyliodide (0.5 mmol), CuI (19 mg, 0.2 mmol), *trans*-4-hydroxy-L-proline (26 mg, 0.4 mmol), and NaOH (80 mg, 2 mmol), evacuated and backfilled with argon. After injection of H_2O (5 μL) and DMF (1 mL), the tube was immersed in a cooling bath and ethyl 2-methylacetoacetate (0.75 mmol) was injected. The reaction mixture was stirred at −45° until the conversion was complete as monitored by TLC. The mixture was partitioned between EtOAc and saturated NH_4Cl; the organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 50:1 to 20:1) to provide the title product (80% yield, 71% ee): HPLC (Chiralpak AD, 95:5 hexanes/*i*-PrOH, 0.7 mL/min) t_r (major) = 10.2 min, t_r (minor) = 9.7 min; $[\alpha]^{20}$+191 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (br s, 1H), 7.71−7.34 (m, 4H), 4.32−4.20 (m, 2H), 1.95 (s, 3H), 1.88 (s, 3H), 1.31 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 173.0, 155.8, 134.2, 131.8, 129.6, 127.5, 127.5, 127.0, 114.5, 63.9, 63.1, 24.5, 20.3, 13.9; ESI-MS m/z: $[M + Na]^+$ 354; HRMS: $[M + Na]^+$ calcd for $C_{15}H_{16}NO_4F_3Na$, 354.0924; found, 354.0920.

TABULAR SURVEY

The tabular survey includes all examples found in the literature through mid-2008. The literature survey was conducted by computer search of Beilstein and SciFinder and by direct inspection of the literature.

Table 1 compiles the arylation of ketones, aldehydes, and enol ethers. Table 2 lists the arylation of esters, amides, lactones, lactams, nitriles, ketene acetals, and preformed enolates. Table 3 compiles the arylation of 1,3-dicarbonyl compounds and cyanoacetates; other types of active methylene compounds can be found in Tables 1 and 2.

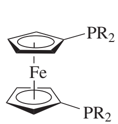
In all the tables, the examples are listed according to the nucleophiles involved, in order of increasing total number of carbon atoms. Protecting groups are included in the carbon count. Intramolecular couplings are included in the tables and are given after intermolecular reactions for the same carbon count. Aryl compounds are ordered according to the class of the structure in the following order: phenyl- > naphthyl- > heteroaromatic compounds. Within the same aryl class, the entries are ordered according to the nature of the leaving group in order of, Cl > Br > I > OTf. Entries of the same aryl halide are further ordered by increasing number of substituents and then by the position of those substituents (2 > 3 > 4). Finally, if all other functionalization of the aryl compound is the same, the entries are arranged by the substituent attached to the aryl ring, heteroatom-substituted (by increasing atomic number) > carbon-substituted. A sub-table contains examples where a comparison between halides was possible, following the same ordering rules as previously stated. The entry containing the sub-table is placed within the aryl compound ordering based on the first entry in the subtable.

Unreported yields are indicated using "(—) ". There are a number of entries where ee or de values are reported but for which the authors did not report the absolute configuration of the created center. In several entries substituents ("R") or halide ("X") functions were not reported. All these entries are faithful to the original literature data.

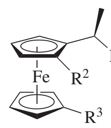
The following abbreviations are used in the tables:

Ad	adamantyl
All	allyl
biPh	biphenyl
p-cresol	4-methylphenol
Cy	cyclohexyl
dba	dibenzylideneacetone
diglyme	diethylene glycol dimethyl ether
dioxane	1,4-dioxane
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
eq	equivalents
ether	diethyl ether
LiHMDS	lithium bis(trimethylsilyl)amide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
monoglyme	ethylene glycol dimethyl ether
MS	molecular sieves
Nap	naphthyl
TBDPS	*tert*-butyldiphenylsilyl
tol	methylphenyl
xyl	dimethylphenyl

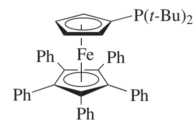
CHART 1. STRUCTURES OF LIGANDS USED IN TABLES



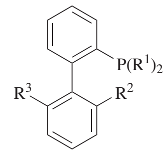
R	Ligand
Ph	**L1**
o-tol	**L2**
t-Bu	**L3**
Cy	**L4**



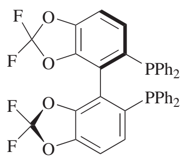
R^1	R^2	R^3	Ligand
OMe	PPh$_2$	H	**L5**
NMe$_2$	P(*t*-Bu)$_2$	H	**L6**
PPh$_2$	PCy$_2$	H	**L7**
PCy$_2$	PPh$_2$	H	**L8**
PCy$_2$	PCy$_2$	H	**L9**
P(*t*-Bu)$_2$	P(*o*-tol)$_2$	H	**L10**
NMe$_2$	PPh$_2$	PPh$_2$	**L11**



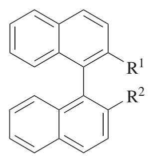
L12



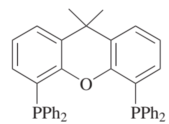
R^1	R^2	R^3	Ligand
Ph	NMe$_2$	H	**L13**
t-Bu	NMe$_2$	H	**L14**
t-Bu	H	H	**L15**
t-Bu	Me	H	**L16**
Cy	NMe$_2$	H	**L17**
Cy	H	H	**L18**
Cy	Me	H	**L19**
Cy	OMe	OMe	**L20**
Cy	*i*-Pr	*i*-Pr	**L21**



L22



R^1	R^2	Ligand
PPh$_2$	PPh$_2$	**L23**
P(*o*-tol)$_2$	P(*o*-tol)$_2$	**L24**
P(*p*-tol)$_2$	P(*p*-tol)$_2$	**L25**
NMe$_2$	P(*t*-Bu)$_2$	**L26**
NMe$_2$	PPh(*t*-Bu)	**L27**
NMe$_2$	PCy$_2$	**L28**
OH	PPh$_2$	**L29**
OMe	PPh$_2$	**L30**
—OP(NEt$_2$)O—		**L31**



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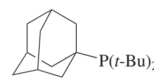

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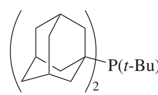

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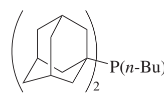
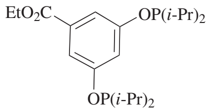


L35



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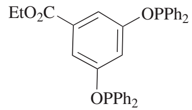
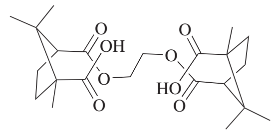
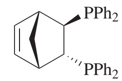


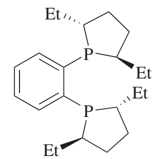
L37



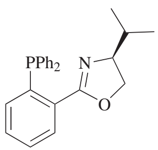
L38



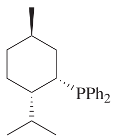
L39



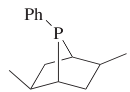
L40



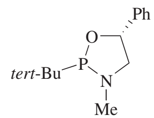
L41



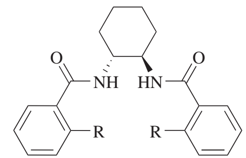
L42



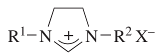
L43



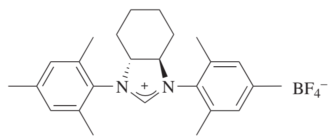
L44



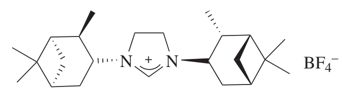
L45 R = PPh_2



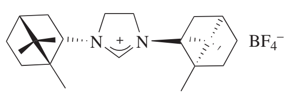
R^1	R^2	X	Ligand
Bu	Bu	PF_6	**L46**
2,6-(i-Pr)$_2C_6H_3$	2,6-(i-Pr)$_2C_6H_3$	BF_4	**L47**



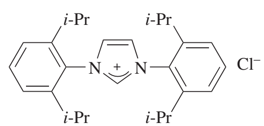
L48



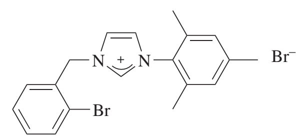
L49



L50

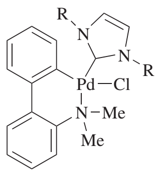


L51



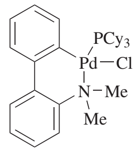
L52

CHART 2. STRUCTURES OF PALLADACYCLES AND PALLADIUM COMPLEXES USED IN TABLES

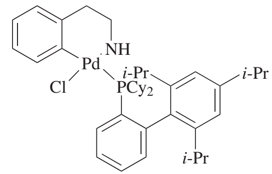


Pd cat **1**

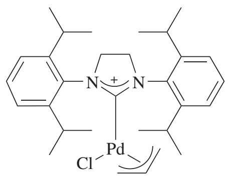
R = 2,6-(i-Pr)$_2$C$_6$H$_3$



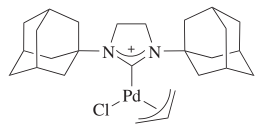
Pd cat **2**



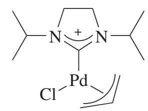
Pd cat **3**



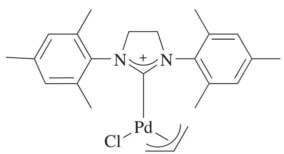
Pd cat **4**



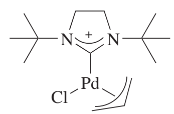
Pd cat **5**



Pd cat **6**

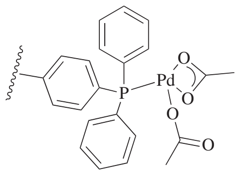


Pd cat **7**

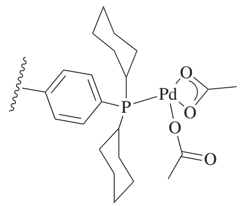


Pd cat **8**

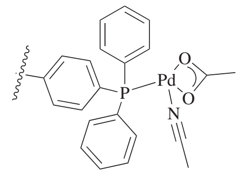
CHART 3. STRUCTURES OF POLYMER-SUPPORTED CATALYSTS USED IN TABLES



Pd cat **9**

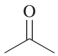
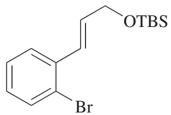
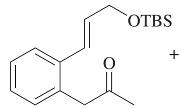
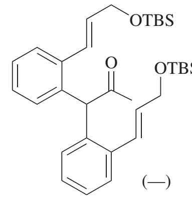
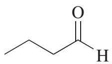
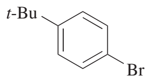
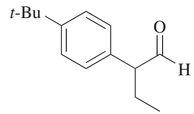
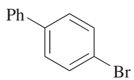
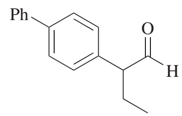
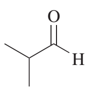
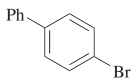
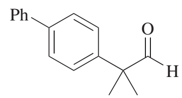


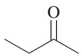
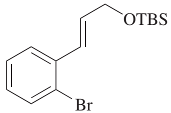
Pd cat **10**



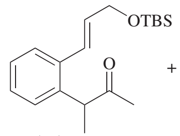
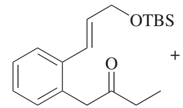
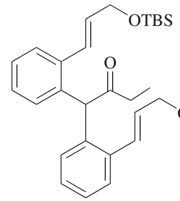
Pd cat **11**

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_3				
		$Pd_2(dba)_3$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h	 (—) +  (—)	63
C_4				
		$Pd(OAc)_2$ (2 mol %), **L23** (3 mol %), Cs_2CO_3 (1.2 eq), dioxane, 24 h	 (55)	148
		$Pd(OAc)_2$ (0.05 mol %), $P(t\text{-}Bu)_3$ (10 mol %), Cs_2CO_3 (1.2 eq), dioxane, 4 h	 (54)	65
		$Pd(OAc)_2$ (0.05 mol %), $P(t\text{-}Bu)_3$ (10 mol %), Cs_2CO_3 (1.2 eq), dioxane, 4 h	 (43)	65

$Pd_2(dba)_3$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h

 (—) +  (—) +  (—)

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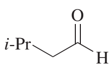
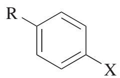
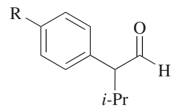
C_5

Catalyst, ligand, Cs_2CO_3 (1.2 eq), dioxane, 80–100°



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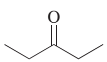
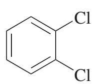
X	R	Catalyst	Ligand	
Cl	MeO	Pd cat **3**	none	(51)
Cl	MeS	Pd cat **3**	none	(50)
Cl	*t*-Bu	Pd cat **3**	none	(61)
Br	MeO	$[Pd(allyl)Cl]_2$	**L32**	(64)
Br	MeS	$Pd(OAc)_2$	**L32**	(58)
Br	*t*-Bu	$Pd(OAc)_2$	**L32**	(65)

$Pd(OAc)_2$ (1 mol %), **L35** (2 mol %), K_3PO_4 (2.2 eq), dioxane, 100°, 20 h

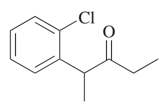
 (58)

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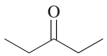
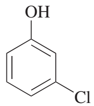
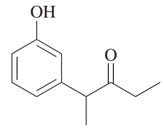
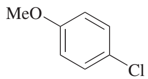
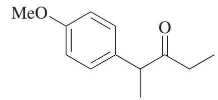
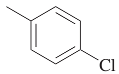
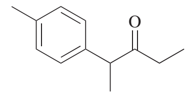
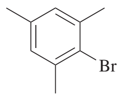
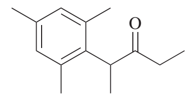
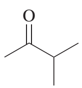
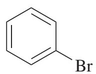
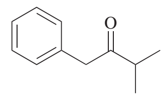
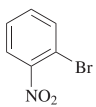
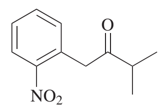
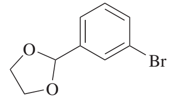
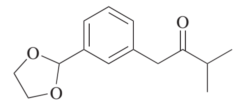
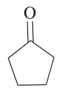
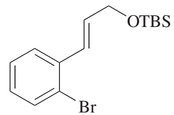
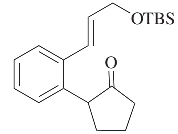
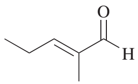
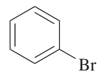
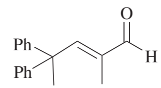
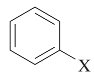
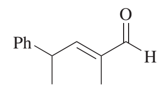
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5 		$Pd(OAc)_2$ (0.1 mol %), **L19** (0.2 mol %), NaO*t*-Bu (2 eq), THF, 70°, 24 h	 (88)	43
		$Pd(OAc)_2$ (0.1 mol %), **L19** (0.2 mol %), NaO*t*-Bu (1.3 eq), toluene, 70°, 24 h	 (74)	43
		$Pd(OAc)_2$ (1 mol %), **L35** (2 mol %), K_3PO_4 (2.2 eq), dioxane, 100°, 20 h	 (55)	48
		Pd cat **4** (1 mol %), NaO*t*-Bu (1.05 eq), THF, 60°, 0.5 h	 (68)	50
		1. CH_2=C=O 2. Bu_3SnOMe (1 eq), $PdCl_2[P(o\text{-tol})_3]_2$ (0.7 mol %), toluene, 100°, 5 h	 (60)	149
		$Pd_2(dba)_3$, **L17**, K_3PO_4 (2.2 eq), PhOH or PhOK (0.2 eq), toluene, 50°, 14 h	 (—)	45

		$Pd_2(dba)_3$ (1.5 mol %), **L25** (3.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°	 (76)	16
		$Pd_2(dba)_3$ (5 mol %), P(*t*-Bu)$_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h	 (—)	63
C_6 		$Pd(OAc)_2$ (5 mol %), P(*t*-Bu)$_3$ (20 mol %), Cs_2CO_3 (1.2 eq), DMF, 60°, 7 h	 (—)	47
x eq		$Pd(OAc)_2$ (5 mol %), PPh_3 (0.1 eq), base (*y* eq), DMF		92

X	*x*	Base	*y*	Temp (°)	Time (h)	
Br	1.0	Cs_2CO_3	1.2	120	1	(84)
Br	1.0	Cs_2CO_3	1.2	60	4	(80)
Br	2.0	Cs_2CO_3	2.0	120	1	(96)
Br	2.0	K_2CO_3	2.0	120	4	(69)
Br	2.0	Na_2CO_3	2.0	120	5	(12)
I	1.0	Cs_2CO_3	1.2	60	4	(34)

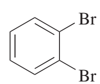
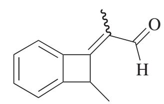
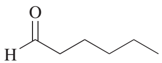
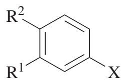
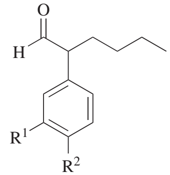
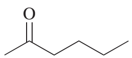
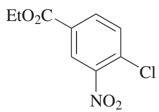
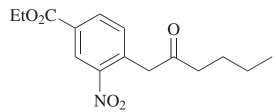
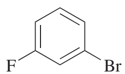
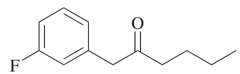
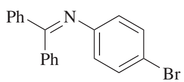
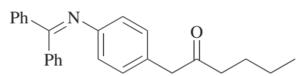
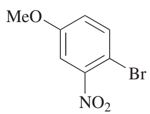
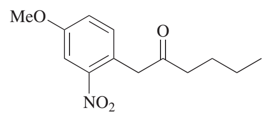
		$Pd(OAc)_2$ (5 mol %), P(*t*-Bu)$_3$ (10 mol %), Cs_2CO_3 (2 eq), DMF	 (45)	60

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6				
		Catalyst, ligand, Cs_2CO_3 (1.2 eq), dioxane, 80–100°		148

X	R^1	R^2	Catalyst	Ligand	Yield (%)
Cl	H	OCH_2CO_2Et	Pd cat **3**	none	(45)
Cl	Me	NMe_2	Pd cat **3**	none	(62)
Br	Me	NMe_2	$Pd(OAc)_2$	**L32**	(65)
Br	Me	OCH_2CO_2Et	$[Pd(allyl)Cl]_2$	**L32**	(84)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd_2(dba)_3$, **L17**, K_3PO_4 (2.5 eq), PhOH (0.2 eq), toluene, 50°, 24 h	 (65)	45
		$Pd_2(dba)_3$ (1 mol %), **L32** (1.2 mol %), NaO*t*-Bu (1.3 eq), THF, 70°, 12 h	 (74)	43
		$Pd_2(dba)_3$ (1.5 mol %), **L23** (3.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°	 (64)	16
		$Pd_2(dba)_3$, **L17**, K_3PO_4 (2.5 eq), PhOH (0.2 eq), toluene, 50°, 24 h	 (67)	45

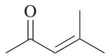
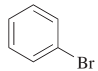
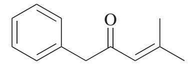
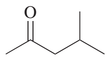
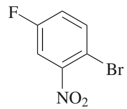
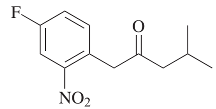
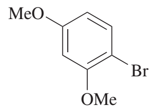
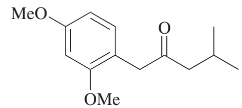
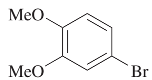
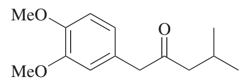
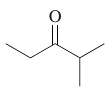
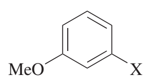
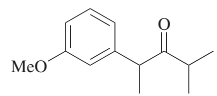
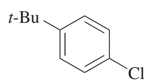
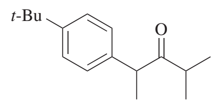
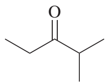
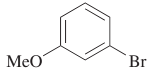
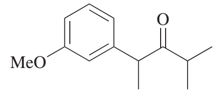
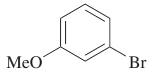
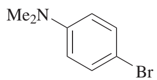
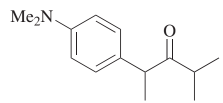
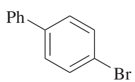
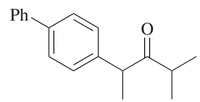
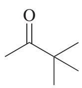
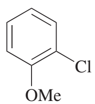
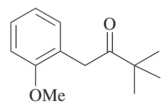
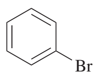
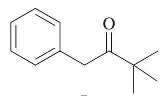
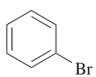
		1. CH_2=C=O 2. Bu_3SnOMe (1 eq), $PdCl_2[P(o\text{-tol})_3]_2$ (0.7 mol %), toluene, 100°, 5 h		(64)	149
		$Pd_2(dba)_3$, **L17** (4 mol %), PhOH (0.2 eq), K_3PO_4 (2.5 eq), toluene, 50°, 24 h		(63)	45
		$Pd_2(dba)_3$ (3 mol %), **L23** (3.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°, 16 h		(72)	43
		$Pd_2(dba)_3$ (0.5 mol %), **L32** (0.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°, 17.5 h		(72)	43
		$Pd(dba)_2$, $P(t\text{-Bu})_3$, NaO*t*-Bu, Rt to70°			23
	X	Solvent			
	Cl	toluene	(82)		
	Br	THF	(83)		
		$Pd(OAc)_2$ (0.1 mol %), **L17** (0.2 mol %), NaO*t*-Bu (1.3 eq), toluene, 90°, 16 h		(79)	43

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		$Pd(dba)_2$ (2 mol %), **L3** (2.5 mol %), 70°, 12 h	 **I** (92)	40
		$Pd(OAc)_2$ (1 mol %), $P(t\text{-}Bu)_3$ (2.5 mol %), 50°, 12 h	**I** (83)	40
		$Pd(OAc)_2$ (0.1 mol %), **L17** (0.2 mol %), NaO*t*-Bu (1.3 eq), toluene, 85°, 24 h	 (70)	43
		$Pd_2(dba)_3$ (1.5 mol %), **L25** (3.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°	 (93)	16
		Pd cat **4** (1 mol %), NaO*t*-Bu (1.05 eq), THF, 60°, 1 h	 (91)	50
		$Pd(dba)_2$ (7.5 mol %), **L2** (9 mol %), KHMDS (2.2 eq), THF, reflux, 0.75 h	 **I** (51)	17
		1. CH_2=C=O 2. Bu_3SnOMe (1 eq), $PdCl_2[P(o\text{-}tol)_3]_2$ (0.7 mol %), toluene, 100°, 5 h	**I** (86)	149

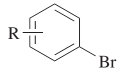
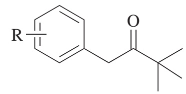
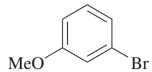
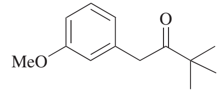
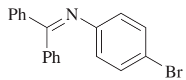
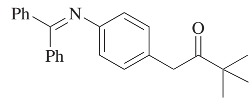
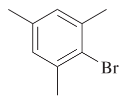
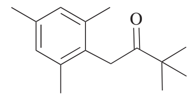
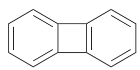
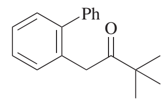
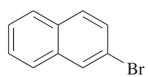
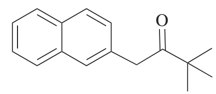
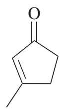
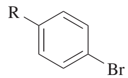
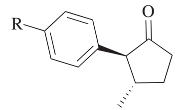
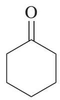
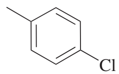
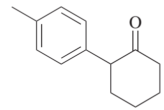
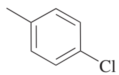
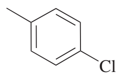
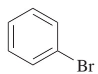
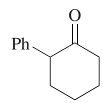
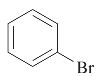
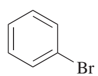
	Pd(dba)$_2$, P(t-Bu)$_3$ or **L47**, LiHMDS or NaHMDS, rt		R: 2-MeO (87); 3-MeO (88); 4-t-Bu (92); 4-Ph (92)	23
	Pd(OAc)$_2$ (1 mol %), NaOt-Bu (1.3 eq), toluene, 80°, 6 h		(68)	43
	Pd$_2$(dba)$_3$ (1.5 mol %), **L25** (3.6 mol %), NaOt-Bu (1.3 eq), THF, 70°		(78)	16
	Pd(dba)$_2$, P(t-Bu)$_3$ or **L47**, LiHMDS or NaHMDS, rt		(98)	23
	Pd(PPh$_3$)$_4$ (5 mol %), p-cresol (10 mol %), C$_6$D$_6$, 120°		(65)	59
	Pd(dba)$_2$, P(t-Bu)$_3$ or **L47**, LiHMDS or NaHMDS, rt		(90)	23

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		1. CuCl (1 mol %), (*S*)-**L25** (1 mol %), NaO*t*-Bu (1 mol %), Ph_2SiH_2 (0.51 eq), THF/pentane (1:1), –78° 2. $Pd(OAc)_2$ (5 mol %), **L15** (10 mol %), CsF (1.1 eq), THF, rt, 18 h	 R — dr[a] H (72) 96.5:3.5 MeO (71) 97:3 EtO_2C (54) 97.5:2.5 *t*-Bu (75) 96.5:3.5	44
		Pd cat **2** (1 mol %), NaO*t*-Bu, dioxane, 70°, 2 h	 **I** (97)	52
		$Pd(OAc)_2$ (1 mol %), **L35** (2 mol %), K_3PO_4, dioxane, 100°, 20 h	**I** (59)	48
		$Pd(OAc)_2$ (1 mol %), **L51** (1 mol %), NaO*t*-Bu (1.5 eq), dioxane, 60°, 2 h	**I** (67)	51
		$Pd(dba)_2$ (2 mol %), **L3** (2.5 mol %), NaO*t*-Bu, THF, 70°, 12 h	 **I** (70)	40
		$Pd(OAc)_2$ (1 mol %), $P(t\text{-}Bu)_3$ (1.25 mol %), NaO*t*-Bu, THF, 50°, 3 h	**I** (73)	40
		$Pd(dba)_2$, **L3**, NaO*t*-Bu, rt to 70°	**I** (70)	23

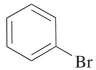
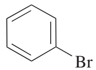
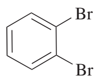
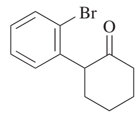
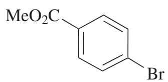
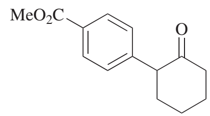
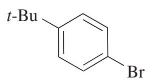
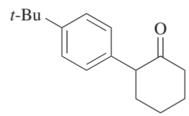
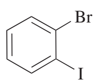
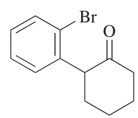
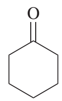
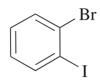
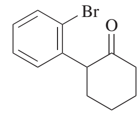
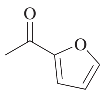
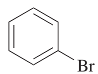
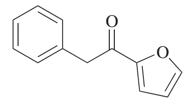
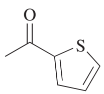
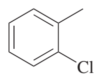
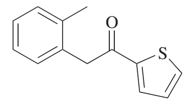
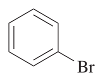
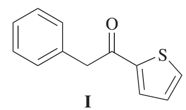
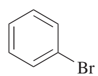
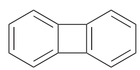
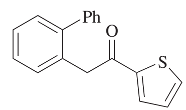
	$PdCl_2$(cod), ligand, Cs_2CO_3, DMF, 153°, 1 h	**I** Ligand: **L36** (88); **L37** (83)	56
	1. CH_2=C=O 2. Bu_3SnOMe (1 eq), $PdCl_2[P(o\text{-tol})_3]_2$ (0.7 mol %), toluene, 100°, 5 h	**I** (54)	149
	$Pd_2(dba)_3$ (0.5 mol %), **L24** (1 mol %), Cs_2CO_3, toluene, 80°, 24 h	 (—)	62
	$Pd_2(dba)_3$ (1 mol %), ligand (1.1 mol %), K_3PO_4, toluene, 80°, 15 h	 Ligand: **L19** (70); **L23** (74)	43
	$Pd_2(dba)_3$ (1.5 mol %), **L25** (3.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°	 (83)	16
	$Pd(dba)_2$ (0.5 mol %), **L32** (1.2 mol %), Cs_2CO_3, toluene, 80°	 (78)	61

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		$Pd_2(dba)_3$ (0.5 mol %), ligand (1 mol %), Cs_2CO_3, toluene, 80°, 24 h	 Ligand **L1** (—) **L3** (25) **L9** (—) **L15** (—) **L16** (—) **L17** (9) **L23** (78) **L24** (—)	62
		$Pd(dba)_2$ (7.5 mol %), **L2** (9 mol %), KHMDS (2.2 eq), THF, reflux, 0.75 h	 (57)	17
		$Pd(OAc)_2$ (1 mol %), **L51** (1 mol %), NaO*t*-Bu (1.5 eq), dioxane, 60°, 12 h	 (13)	51
		$Pd(dba)_2$ (7.5 mol %), **L2** (9 mol %), KHMDS (2.2 eq), THF, reflux, 0.75 h	 **I** (68)	17
		$Pd(dba)_2$, **L1** or **L3**, KHMDS, 70°	**I** (68)	23
		$Pd(PPh_3)_4$ (5 mol %), *p*-cresol (10 mol %), C_6D_6, 120°	 (75)	59

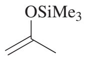
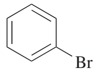
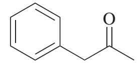
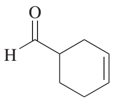
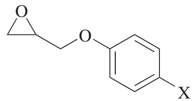
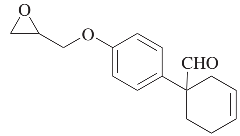
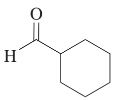
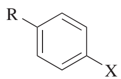
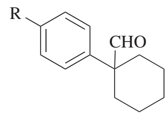
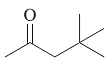
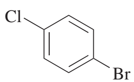
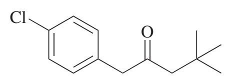
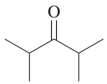
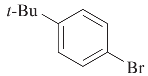
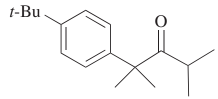
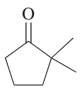
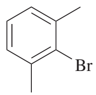
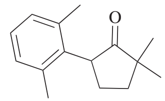
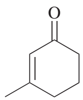
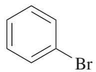
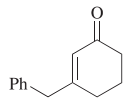
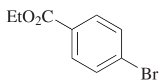
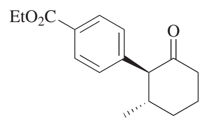
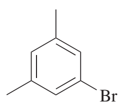
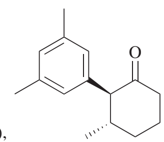
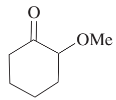
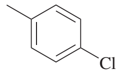
			$Pd(dba)_2$ (3 mol %), $P(t\text{-}Bu)_3$ (5.4 mol %), ZnF_2 (1.4 eq), MnF_2 (1.4 eq), DMF, 70°	 (68)	150
C_7			Catalyst, ligand, Cs_2CO_3 (1.2 eq), dioxane, 80–100°		148
		X	**Catalyst** / **Ligand**		
		Cl	Pd cat **3** / none	(51)	
		Br	$Pd(OAc)_2$ / **L22**	(54)	
			Catalyst, ligand, Cs_2CO_3 (1.2 eq), dioxane, 80–100°		148
		X / **R**	**Catalyst** / **Ligand**		
		Cl / Me_2N	Pd cat **3** / none	(54)	
		Cl / MeO	Pd cat **3** / none	(60)	
		Cl / MeS	Pd cat **3** / none	(63)	
		Br / Me_2N	$Pd(OAc)_2$ / **L20**	(68)	
		Br / MeO	$Pd(OAc)_2$ / **L20**	(65)	
		Br / MeS	$Pd(OAc)_2$ / **L20**	(59)	
			$Pd_2(dba)_3$ (1.5 mol %), **L25** (3.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°	 (88)	16

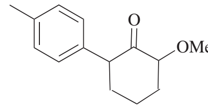
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		$Pd(OAc)_2$ (0.5 mol %), **L19** (0.2 mol %), NaO*t*-Bu (1.3 eq), toluene, 85°, 24 h	 (61)	43
		$Pd(OAc)_2$ (0.5 mol %), **L19** (0.2 mol %), NaO*t*-Bu (1.3 eq), toluene, 70°, 23 h	 (61)	43
		$Pd(OAc)_2$ (0.05 eq), PPh_3 (0.1 eq), Cs_2CO_3 (1.2–4 eq), DMF, 60°, 2 h	 (50)	92
		1. CuCl (1 mol %), (*S*)-**L25** (1 mol %), NaO*t*-Bu (0.01 eq), Ph_2SiH_2 (0.51 eq), THF/pentane (1:1), –78° 2. $Pd(OAc)_2$ (5 mol %), **L15** (10 mol %), CsF (1.1 eq), THF, rt, 18 h	 (42), 96:4 dr[b]	44
		1. CuCl (1 mol %), (*S*)-**L25** (1 mol %), NaO*t*-Bu (0.01 eq), Ph_2SiH_2 (0.51 eq), THF/pentane (1:1), –78° 2. $Pd(OAc)_2$ (5 mol %), **L15** (10 mol %), CsF (1.1 eq), THF, rt, 18 h	 (52), 97:3 dr[b]	44

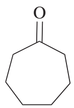


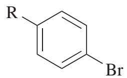


Pd(OAc)$_2$ (1 mol %), **L51** (1 mol %), NaO*t*-Bu (1.5 eq), dioxane, 60°, 12 h

 (—)

51

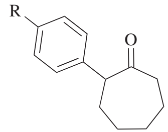




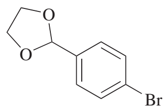
R
NC
t-Bu

Pd$_2$(dba)$_3$, ligand, THF, 80°

Ligand	Time (h)	
L32	16	(72)
L19	17	(81)

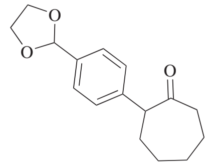


43

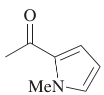


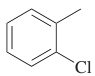
Pd(OAc)$_2$, ligand, NaO*t*-Bu (1.3 eq), toluene

Ligand	Temp (°)	Time (h)	
L18	60	18.5	(66)
L19	45	20	(80)

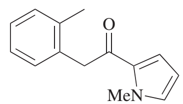


43

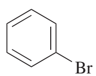




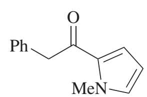
Pd(OAc)$_2$ (1 mol %), **L51** (1 mol %), NaO*t*-Bu (1.5 eq), dioxane, 60°, 6 h

 (46)

51

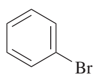


Pd(dba)$_2$, **L1** or **L3**, KHMDS, 70°



I (79)

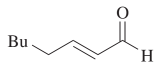
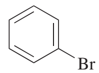
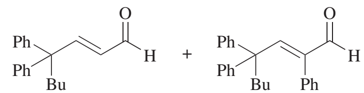
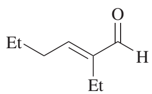
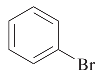
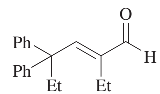
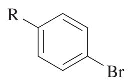
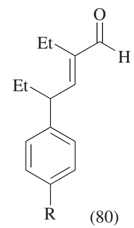
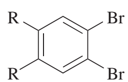
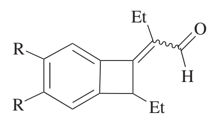
23

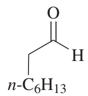


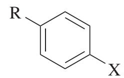
Pd(dba)$_2$ (7.5 mol %), **L3** (9 mol %), KHMDS (2.2 eq), THF, reflux, 0.75 h

I (79)

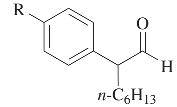
17

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8				
		$Pd(OAc)_2$, PPh_3, Cs_2CO_3	 (—) + (—)	47
		$Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (0.2 eq), Cs_2CO_3 (1.2 eq), DMF, 7 h, 60°	 (—)	47
		$Pd(OAc)_2$ (0.05 eq), PPh_3 (0.1 eq), Cs_2CO_3 (1.2–4 eq), DMF		92
	R	Temp (°) / Time (h)		
	H	120 / 1	(80)	
	MeO	60 / 2	(60)	
	Cl	60 / 4	(64)	
	Me	60 / 5	(69)	
		$Pd(OAc)_2$ (5 mol %), ligand, Cs_2CO_3 (2 eq), DMF, 80°, 4 h		60
	R	Ligand		
	H	PPh_3	(12)	
	H	$P(o\text{-}tol)_3$	(—)	
	H	$P(t\text{-}Bu)_3$	(77)	
	Me	$P(t\text{-}Bu)_3$	(50)	





Catalyst, ligand, Cs_2CO_3 (1.2 eq), dioxane, 80–100°



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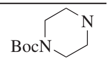
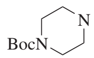
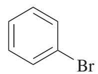
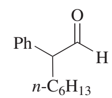
X	R	Catalyst	Ligand	
Cl		Pd cat **3**	none	(50)
Cl	MeO	Pd cat **3**	none	(65)
Br		$[Pd(cinnamyl)Cl]_2$	**L32**	(56)
Br	MeO	$[Pd(allyl)Cl]_2$	**L32**	(70)

x eq

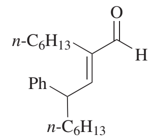


$Pd(OAc)_2$ (0.05 mol %), ligand (10 mol %), base (1.2 eq), 110°



I

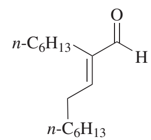
+



II

+

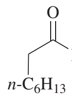
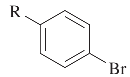
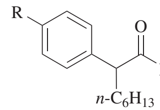
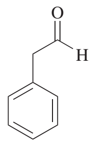
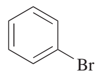
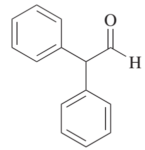
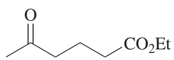
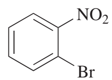
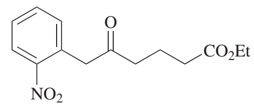
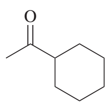
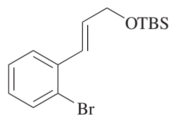
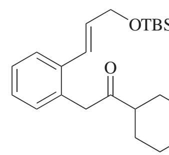
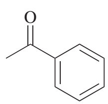
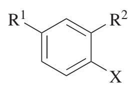
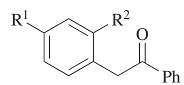
65



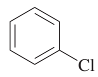
III

x	Ligand	Base	Solvent	Time (h)	**I**	**II**	**III**
2.0	$P(t\text{-}Bu)_3$	Cs_2CO_3	DMF	2	(49)	(20)	(31)
1.0	$P(t\text{-}Bu)_3$	Cs_2CO_3	dioxane	2	(53)	(1)	(2)
2.0	$P(t\text{-}Bu)_3$	Cs_2CO_3	dioxane	2	(77)	(1)	(5)
2.0	$P(t\text{-}Bu)_3$	K_2CO_3	dioxane	24	(70)	(2)	(12)
2.0	PPh_3	Cs_2CO_3	DMF	2	(0)	(45)	(22)
2.0	PPh_3	Cs_2CO_3	dioxane	2	(0)	(6)	(15)
2.0	PPh_3	Cs_2CO_3	dioxane	23	(0)	(32)	(11)
2.0	PCy_3	Cs_2CO_3	dioxane	2	(0)	(4)	(18)
2.0	PCy_3	Cs_2CO_3	dioxane	21	(0)	(46)	(10)

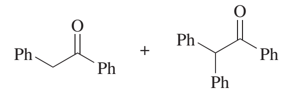
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8 		$Pd(OAc)_2$ (0.05 mol %), $P(t\text{-}Bu)_3$ (10 mol %), Cs_2CO_3 (1.2 eq), dioxane, 4 h	 R: OMe (61); Me (67); Ph (59)	65
		$Pd(OAc)_2$ (0.05 mol %), $P(t\text{-}Bu)_3$ (10 mol %), Cs_2CO_3 (1.2 eq), dioxane, 2 h	 (56)	65
		$Pd_2(dba)_3$, **L17** (4 mol %), K_3PO_4 (2.5 eq), PhOH (0.2 eq), toluene, 50°, 23 h	 (65)	45
		$Pd_2(dba)_3$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h	 (—)	63
		Pd cat **4** (1 mol %), NaO*t*-Bu (1.05 eq), THF, 0.5 h		50

X	R^1	R^2	
Cl	H	H	(93)
Cl	H	Me	(90)
Cl	MeO	H	(78)
Cl	Me	H	(88)
OTf	H	MeO	(80)



Pd(dba)$_2$, ligand, base, 20 h



I **II**

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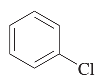
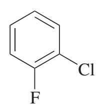
Ligand	Base	Solvent	Temp (°)	**I**	**II**
L35	NaO*t*-Bu	toluene	120	(70)	(—)
L35	Na_2CO_3	dioxane	100	(0)	(0)
L35	K_2CO_3	dioxane	100	(40)	(25)
L35	K_3PO_4	dioxane	100	(16)	(51)
L35	Cs_2CO_3	dioxane	100	(22)	(62)
L35	CaO	dioxane	100	(0)	(0)
L35	K_3PO_4	dioxane	100	(16)	(51)
L35	K_3PO_4	dioxane	100	(59)	(31)
P(*t*-Bu)$_2$(*n*-Bu)	K_3PO_4	dioxane	100	(9)	(20)
P(*t*-Bu)$_3$	K_3PO_4	dioxane	100	(0)	(19)
PCy$_3$	K_3PO_4	dioxane	100	(33)	(32)
PCy$_2$(*n*-Bu)	K_3PO_4	dioxane	100	(17)	(3)
PCy$_2$Ph	K_3PO_4	dioxane	100	(31)	(31)
PCy$_2$(biPh)	K_3PO_4	dioxane	100	(17)	(19)



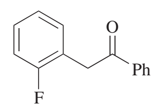
Pd(dba)$_2$ (0.1 mol %), **L35**, NaO*t*-Bu, toluene, 120°, 20 h

I (70)

48



Pd(OAc)$_2$, **L35**, K_3PO_4, dioxane, 100°, 20 h



(57)

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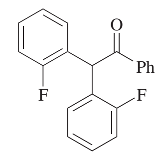

(23)

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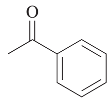
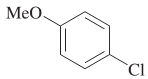
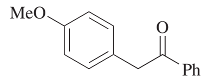
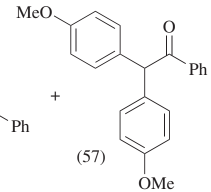
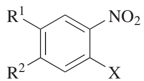
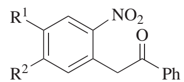
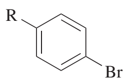
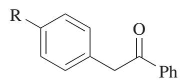
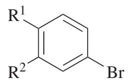
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

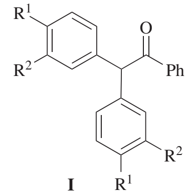
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8 		$Pd(OAc)_2$, **L35**, K_3PO_4, dioxane, 100°, 20 h	 (25) +  (57)	48
		$Pd_2(dba)_3$ (1 mol %), **L17** (4 mol %), K_3PO_4 (2.5 eq), *p*-methoxyphenol (20%), toluene, 35–50°, 22 h		45
		Catalyst, ligand, base, toluene, 130°		56

X	R^1	R^2	Yield (%)
Cl	EtO_2C	H	(61)
Br	Me	H	(90)
Br	MeO	MeO	(65)

R	Catalyst	Ligand	Base	Yield (%)
H	$PdCl_2$(cod)	**L36**	K_3PO_4	(>99)
H	$Pd(OCOCF_3)_2$	**L37**	K_3PO_4	(94)
H	$PdCl_2$(cod)	**L36**	Cs_2CO_3	(>99)
H	$Pd(OCOCF_3)_2$	**L37**	Cs_2CO_3	(88)
MeO	$PdCl_2$(cod)	**L36**	K_3PO_4	(>99)
MeO	$Pd(OCOCF_3)_2$	**L37**	K_3PO_4	(93)
F	$PdCl_2$(cod)	**L36**	K_3PO_4	(>99)
F	$Pd(OCOCF_3)_2$	**L37**	K_3PO_4	(94)



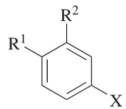
Pd(OAc)$_2$ (1 mol %), PPh$_3$ (8 mol %), Cs$_2$CO$_3$ (2.5 eq), DMF, 150°, 0.5–1 h



I

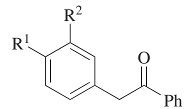
R^1	R^2	
H	H	(96)
MeO	MeO	(85)

53



See table

I +

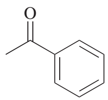
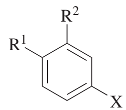
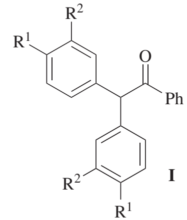
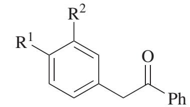


II

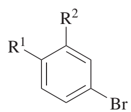
54, 55

X	R^1	R^2	Catalyst	Ligand	Base	Solvent	Temp (°)	**I**	**II**
Br	H	H	Pd/C (5 mol %)	none	Na$_2$CO$_3$	DMF	150	(2)^c	(3)^c
Br	H	H	PdCl$_2$ (3 mol %)	PPh$_3$	K$_2$CO$_3$	DMF	130	(11)^c	(—)^c
Br	H	H	Pd(OAc)$_2$	PPh$_3$	Cs$_2$CO$_3$	DMF	153	(91)	(—)
Br	H	H	Pd(OCOCF$_3$)$_2$ (5 mol %)	PPh$_3$	Cs$_2$CO$_3$	DMF	150	(82)^c	(4)^c
Br	H	H	Pd(PPh$_3$)$_4$ (1 mol %)	none	Cs$_2$CO$_3$	xylene	153	(71)^c	(2)^c
Br	H	H	Pd cat **9** (5 mol %)	none	K$_2$CO$_3$	toluene	130	(8)^c	(43)^c
Br	H	H	Pd cat **10** (1 mol %)	none	K$_2$CO$_3$	toluene	130	(45)^c	(16)^c
Br	H	H	Pd cat **10** (2 mol %)	none	K$_2$CO$_3$	xylene	153	(15)^c	(44)^c
Br	H	H	Pd cat **10** (2 mol %)	none	Cs$_2$CO$_3$	DMF	153	(—)^c	(3)^c
Br	H	H	Pd cat **11**	none	Cs$_2$CO$_3$	DMF	153	(89)	(—)
Br	H	MeO	Pd cat **11** (5 mol %)	none	Cs$_2$CO$_3$	DMF	153	(85)^c	(2)^c
Br	H	MeO	Pd(OAc)$_2$	P(t-Bu)$_3$	NaOt-Bu	THF	80	(5)^c	(70)^c
Br	H	MeO	Pd(OAc)$_2$	PPh$_3$	Cs$_2$CO$_3$	DMF	153	(71)	(—)

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8 		See table *(cont. from previous page)*	 **I** +  **II**	54, 55

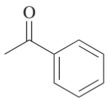
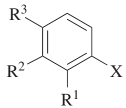
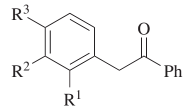
X	R^1	R^2	Catalyst	Ligand	Base	Solvent	Temp (°)	**I**	**II**
Br	H	MeO	$Pd(OCOCF_3)_2$ (5 mol %)	PPh_3	Cs_2CO_3	DMF	150	(54)[c]	(11)[c]
Br	H	MeO	$Pd(PPh_3)_4$ (1 mol %)	none	Cs_2CO_3	xylene	150	(25)[c]	(—)[c]
Br	H	MeO	Pd cat **11**	none	Cs_2CO_3	DMF	153	(79)	(—)
Br	F	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(63)	(—)
Br	F	H	Pd cat **11**	none	Cs_2CO_3	DMF	153	(73)	(—)
Br	MeO	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(61)	(—)
Br	MeO	MeO	Pd cat **11**	none	Cs_2CO_3	DMF	153	(80)	(—)
I	H	H	Pd cat **11** (7 mol %)	PPh_3	Cs_2CO_3	DMF	100	(49)[c]	(—)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		See table	**I** + **II**	55

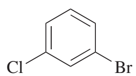
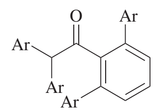
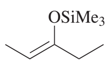
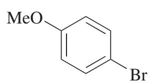
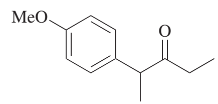
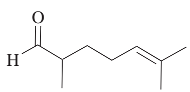
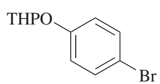
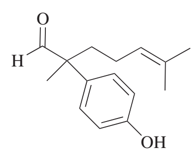
R^1	R^2	Catalyst	Ligand	Base	Solvent	Temp (°)	**I**	**II**
H	H	$Pd(PPh_3)_4$ (0.5 mol %)	none	Cs_2CO_3	DMF	150	(18)[c]	(1)[c]
H	H	$Pd(OAc)_2$ (5 mol %)	PEt_3	Cs_2CO_3	DMF	150	(27)[c]	(—)[c]
H	H	$Pd(OAc)_2$ (5 mol %)	$P(o\text{-tol})_3$	Cs_2CO_3	DMF	153	(8)[c]	(22)[c]
H	H	$Pd(OAc)_2$ (5 mol %)	$P(o\text{-tol})_3$	NaO*t*-Bu	THF	80	(80)	(—)

H	H	Pd cat **9** (1 mol %)	none	K_2CO_3	toluene	130	(4)[c]	(13)[c]
H	H	Pd cat **10** (5 mol %)	none	NaO*t*-Bu	toluene	85	(—)	(87)
H	H	Pd cat **10** (1 mol %)	none	K_2CO_3	xylene	130	(32)[c]	(17)[c]
H	MeO	Pd cat **9** (5 mol %)	none	K_2CO_3	toluene	130	(6)[c]	(32)[c]
H	MeO	Pd cat **10**	none	NaO*t*-Bu	THF	85	(—)	(92)
F	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(63)	(—)
F	H	Pd cat **10**	none	NaO*t*-Bu	THF	85	(—)	(80)
MeO	MeO	Pd cat **10**	none	NaO*t*-Bu	THF	85	(—)	(91)

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

	Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8			$Pd(dba)_2$ (7.5 mol %), ligand, KHMDS (2.2 eq), THF, reflux, 0.75 h		17

X	R^1	R^2	R^3	Ligand	Yield (%)
Br	H	H	H	**L2**	(84)
Br	H	H	H	**L1**	(76)
Br	Me	H	H	**L2**	(94)
Br	H	NC	H	**L2**	(73)
Br	H	H	*t*-Bu	**L2**	(85)
Br	H	H	MeO	**L2**	(69)
I	H	H	H	**L2**	(79)

	Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
			$Pd(PPh_3)_4$ (0.5 mol %), Cs_2CO_3 (3–5 eq), *o*-xylene, 23 h	 (61) Ar = *m*-ClC_6H_4	46
			$Pd_2(dba)_3$ (2.5 mol %), $P(t\text{-}Bu)_3$ (6 mol %), Bu_3SnF (2 eq), benzene, reflux, 26 h	 (70)	151
C_9			$Pd(OAc)_2$ (2 mol %), **L20** (3 mol %), Cs_2CO_3 (1.2 eq), dioxane, 100°	 (—)	148

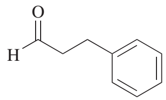
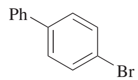
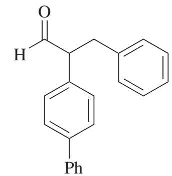
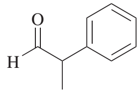
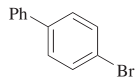
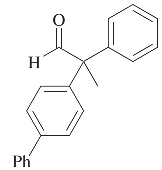
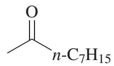
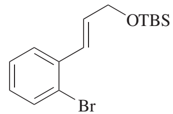
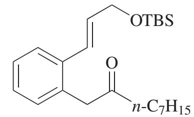
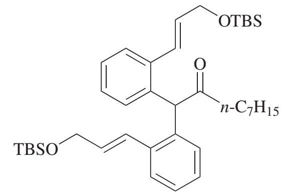
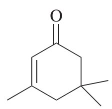
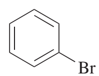
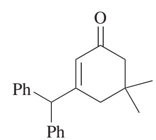
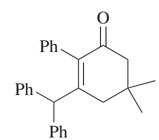
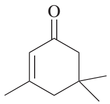
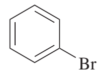
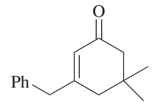
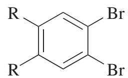
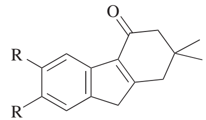
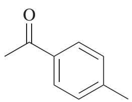
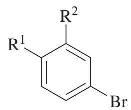
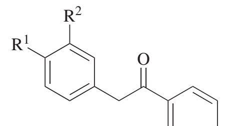
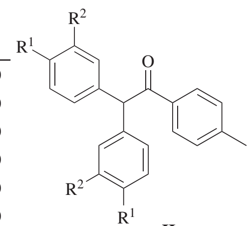
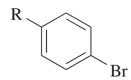
		$Pd(OAc)_2$ (0.05 mol %), P(*t*-Bu)$_3$ (10 mol %), Cs_2CO_3 (1.2 eq), dioxane, 3 h	 (45)	65
		$Pd(OAc)_2$ (0.05 mol %), P(*t*-Bu)$_3$ (10 mol %), Cs_2CO_3 (1.2 eq), dioxane, 3 h	 (43)	65
		$Pd_2(dba)_3$ (5 mol %), P(*t*-Bu)$_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h	 (—) +  (—)	63
		$Pd(OAc)_2$, PPh_3 or P(*t*-Bu)$_3$, Cs_2CO_3	 (—) +  (—)	47

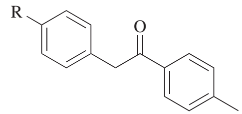
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 		$Pd(OAc)_2$ (0.05 eq), PPh_3 (10 mol %), Cs_2CO_3, DMF	 Temp (°) / Time (h): 60 / 6 / (56) 80 / 5 / (56)	92
		$Pd(OAc)_2$, PPh_3 (5 mol %), Cs_2CO_3 (4 eq), DMF, 80°, 5–6 h	 R: H (94) Me (80)	60
		See table	 **I** +  **II**	55

R^1	R^2	Catalyst	Ligand	Base	Solvent	Temp (°)	**I**	**II**
H	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(—)	(91)
H	H	Pd cat **10**	none	NaO*t*-Bu	THF	85	(86)	(—)
H	H	Pd cat **11**	none	Cs_2CO_3	DMF	153	(—)	(93)
H	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(—)	(71)
H	MeO	Pd cat **10**	none	NaO*t*-Bu	THF	85	(86)	(—)
H	MeO	Pd cat **11**	none	Cs_2CO_3	DMF	153	(—)	(75)
F	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(—)	(63)
F	H	Pd cat **10**	none	NaO*t*-Bu	THF	85	(74)	(—)
F	H	Pd cat **11**	none	Cs_2CO_3	DMF	153	(—)	(80)
MeO	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(—)	(61)
MeO	MeO	Pd cat **10**	none	NaO*t*-Bu	THF	85	(82)	(—)
MeO	MeO	Pd cat **11**	none	Cs_2CO_3	DMF	153	(—)	(92)



Catalyst, ligand, K_3PO_4, toluene, 130°



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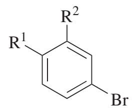
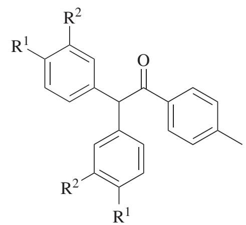
R	Catalyst	Ligand	
H	$PdCl_2$(cod)	**L36**	(>99)
H	$Pd(OCOCF_3)_2$	**L37**	(90)
MeO	$PdCl_2$(cod)	**L36**	(>99)
MeO	$Pd(OCOCF_3)_2$	**L37**	(90)
F	$PdCl_2$(cod)	**L36**	(>99)
F	$Pd(OCOCF_3)_2$	**L37**	(91)



Catalyst, ligand, Cs_2CO_3, DMF, 153°



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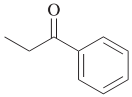
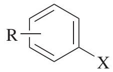
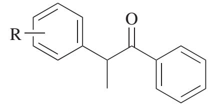
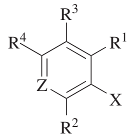
R^1	R^2	Catalyst	Ligand	
H	H	$Pd(OAc)_2$	PPh_3	(87)
H	H	Pd cat **11**	none	(93)
H	MeO	$Pd(OAc)_2$	PPh_3	(69)
H	MeO	Pd cat **11**	none	(75)
F	H	$Pd(OAc)_2$	PPh_3	(68)
F	H	Pd cat **11**	none	(80)
MeO	MeO	$Pd(OAc)_2$	PPh_3	(60)
MeO	MeO	Pd cat **11**	none	(92)

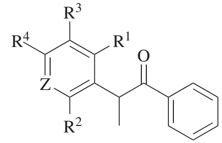
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 		$Pd(OAc)_2$ (1 mol %), **L51** (1 mol %), base, 60°		51

X	R	Base	Solvent	Time (h)	Yield (%)
Cl	H	NaO*t*-Bu	dioxane	6	(71)
Cl	2-MeO	NaO*t*-Bu	dioxane	1	(94)
Cl	2-Me	NaO*t*-Bu	dioxane	2	(90)
Cl	2-CF_3	NaO*t*-Bu	dioxane	12	(71)
Cl	3-MeO	NaO*t*-Bu	dioxane	1	(81)
Cl	4-MeO	NaO*t*-Bu	dioxane	3	(90)
Cl	4-Me	NaO*t*-Bu	toluene	1	(77)
Cl	4-Me	NaO*t*-Bu	DME	2	(85)
Cl	4-Me	NaO*t*-Bu	dioxane	1	(87)
Cl	4-Me	NaO*t*-Bu	THF	1	(84)
Cl	4-Me	NaO*t*-Bu	MTBE	1	(82)
Cl	4-Me	NaO*t*-Bu	dioxane	3	(96)
Cl	4-Me	KO*t*-Bu	dioxane	4	(85)
Cl	4-Me	KOMe	dioxane	5	(60)
Cl	4-Me	NaH	dioxane	2	(85)
Cl	4-Me	KH	dioxane	12	(78)
Cl	4-Me	Cs_2CO_3	dioxane	3	(10)
Cl	4-Me	K_3PO_4	dioxane	3	(27)
Cl	4-CF_3	NaO*t*-Bu	dioxane	12	(69)
Br	4-Me	NaO*t*-Bu	dioxane	1	(88)
I	4-Me	NaO*t*-Bu	dioxane	1	(83)



Catalyst (1 mol %), NaO*t*-Bu, THF



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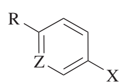
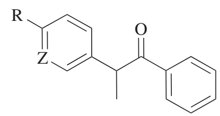
X	R^1	R^2	R^3	R^4	Z	Catalyst	Temp (°)	
Cl	H	H	H	H	CH	Pd cat **4**	70	(100)
Cl	H	H	H	H	CH	Pd cat **4**	50	(91)
Cl	H	H	H	H	CH	Pd cat **5**	70	(95)
Cl	H	H	H	H	CH	Pd cat **6**	70	(95)
Cl	H	H	H	H	CH	Pd cat **7**	70	(93)
Cl	H	H	H	H	CH	Pd cat **8**	70	(99)
Cl	H	MeO	H	H	CH	Pd cat **4**	60	(80)
Cl	H	Me	H	H	CH	Pd cat **4**	60	(87)
Cl	H	H	MeO	H	CH	Pd cat **4**	70	(88)
Cl	H	H	H	CF_3	CH	Pd cat **4**	70	(81)
Cl	H	H	H	PhC(O)	CH	Pd cat **4**	70	(71)
Br	Me	Me	H	Me	CH	Pd cat **4**	60	(72)
OTf	H	H	H	H	CH	none	60	(91)
OTf	H	H	H	Me	CH	none	60	(93)
Cl	H	H	H	H	N	Pd cat **4**	50	(60)



Pd cat **1** (1 mol %), NaO*t*-Bu, dioxane, 70°, 2 h



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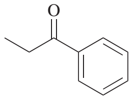
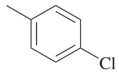
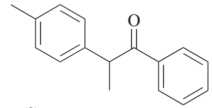
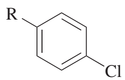
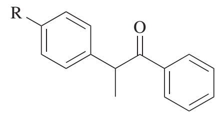
X	Z	R	
Cl	CH	Me	(89)
OTf	CH	Me	(78)
Cl	N	H	(90)

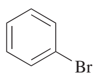
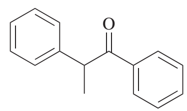
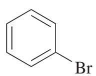
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 		$Pd(dba)_2$ (*x* mol %), **L35**, base, 20 h		48

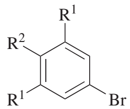
x	Base	Solvent	Temp (°)	
0.01	NaO*t*-Bu	toluene	80	(40)
0.01	NaO*t*-Bu	toluene	120	(41)
0.05	NaO*t*-Bu	toluene	80	(97)
0.1	NaO*t*-Bu	toluene	80	(100)
1	K_3PO_4	dioxane	100	(90)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$ (0.5 mol %), **L19** (0.2 mol %), NaO*t*-Bu (1.3 eq), 80°, toluene		43

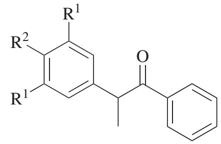
R	Time (h)	
CN	18	(78)
CO_2Me	16	(76)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(dba)_2$, **L1** or **L3**, KHMDS, 70°	 **I** (71)	23
		$Pd(dba)_2$ (7.5 mol %), ligand, KHMDS (2.2 eq), THF, reflux, 0.75 h	**I**	17

Ligand	
L2	(71)
L1	(47)



Catalyst (x mol %),
NaOt-Bu (1.3 eq), toluene



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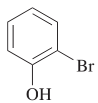
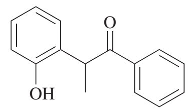
R^1	R^2	Catalyst	x	Temp (°)	Time (h)	
H	H	$Pd(OAc)_2$	0.001	120	24	(74)
H	MeO	$Pd(OAc)_2$	1.0	80	3	(84)
Me	H	$Pd(OAc)_2$	1.0	80	2.3	(76)
Me	H	$Pd_2(dba)_3$	1.0	80	14	(93)



$Pd(OAc)_2$ (5 mol %),
ligand (10 mol %),
NaOt-Bu (2.3 eq), 80°



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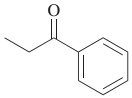
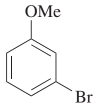
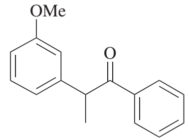
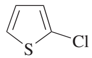
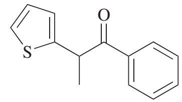
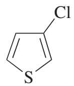
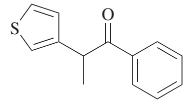
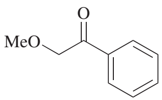
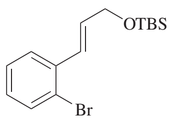
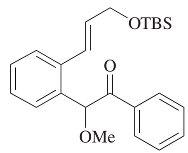
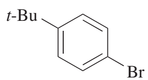
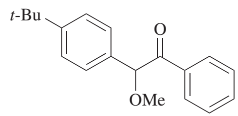
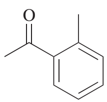
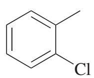
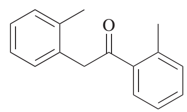
Ligand	Solvent	
L9	THF	(85)
L9	DME	(78)
L9	dioxane	(84)
L9	DMF	(54)
L9	DMA	(37)
L9	*t*-BuOH	(45)
L9	DCE	(0)
L9	toluene	(64)
L9	toluene	(97)
L14	toluene	(42)
L15	toluene	(30)
L16	toluene	(0)
L18	toluene	(0)
L19	toluene	(62)

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

	Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9			$Pd_2(dba)_3$ (1.5 mol %), **L25** (3.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°	 (91)	16
			$Pd(OAc)_2$ (1 mol %), **L51** (1 mol %), NaO*t*-Bu, dioxane, 60°, 12 h	 (42)	51
			$Pd(OAc)_2$ (1 mol %), **L51** (1 mol %), NaO*t*-Bu, dioxane, 60°, 24 h	 (36)	51
			$Pd_2(dba)_3$ (5 mol %), LiHMDS, $P(t\text{-}Bu)_3$ (10 mol %), dioxane, 90°, 3 h	 (—)	63
			$Pd(OAc)_2$ (0.5 mol %), **L19** (0.2 mol %), NaO*t*-Bu (1.3 eq), toluene, 70°, 17 h	 (83)	43
			$Pd(OAc)_2$ (1 mol %), **L51** (1 mol %), NaO*t*-Bu (1.5 eq), dioxane, 60°, 24 h	 (75)	51

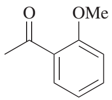
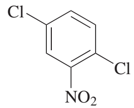
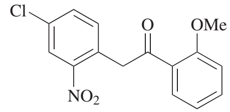
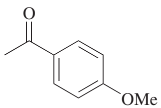
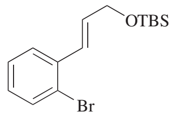
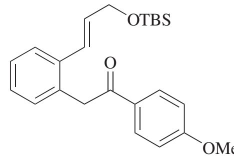
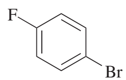
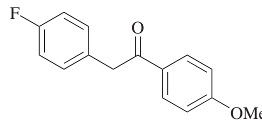
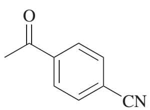
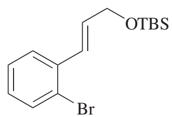
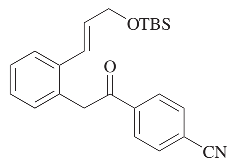
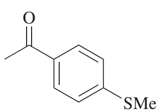
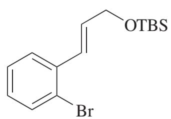
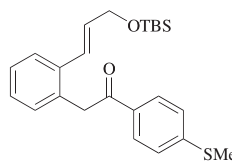
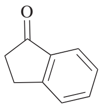
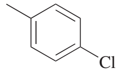
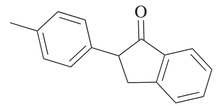
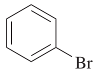
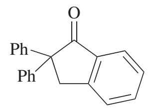
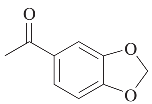
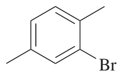
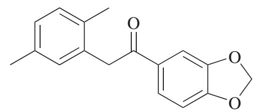
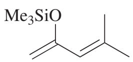
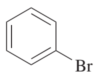
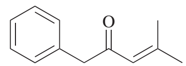
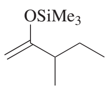
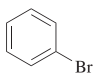
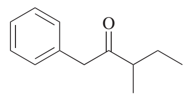
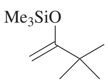
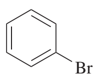
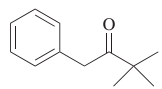
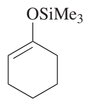
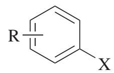
		$Pd_2(dba)_3$ (1 mol %), **L17** (4 mol %), K_3PO_4 (2.5 eq), *p*-methoxyphenol (20 mol %), toluene, 30–80°	 (—)	45
		$Pd_2(dba)_3$ (5 mol %), P(*t*-Bu)$_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h	 (—)	63
		Catalyst, Cs_2CO_3, DMF, 153°		54
		Catalyst: $Pd(OAc)_2$; Ligand: PPh_3	(52)	
		Catalyst: Pd cat **11**; Ligand: none	(70)	
		$Pd_2(dba)_3$ (5 mol %), P(*t*-Bu)$_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h	 (—)	63
		$Pd_2(dba)_3$ (5 mol %), P(*t*-Bu)$_3$ (10 mol %), LiHMDS (3 eq), dioxane, 90°, 3 h	 (—)	63

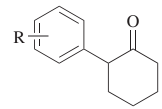
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 		$Pd(OAc)_2$, **L35**, base, dioxane, 100°, 20 h	 Base K_3PO_4 (42) Cs_2CO_3 (26)	48
		Catalyst, ligand, K_3PO_4, xylene, 153°, 22 h Catalyst / Ligand $PdCl_2$(cod) / **L36** $Pd(OCOCF_3)_2$ / **L37**	 (89) (89)	56
		$Pd_2(dba)_3$ (5 mol %), **L23** (6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°	 (84)	16
		$PdCl_2[P(o\text{-tol})_3]_2$ (3 mol %), Bu_3SnF, benzene	 (56)	13
		$PdCl_2[P(o\text{-tol})_3]_2$ (3 mol %), Bu_3SnF, benzene	 (47)	13
		$PdCl_2[P(o\text{-tol})_3]_2$ (3 mol %), Bu_3SnF, benzene	 (29)	13





$Pd_2(dba)_3$ (2.5 mol %), P(*t*-Bu)$_3$ (6 mol %), Bu_3SnF, benzene



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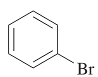
X	R	Time (h)	Yield
Cl	2-Me	3.5	(25)
Cl	2-Me	20	(55)
Cl	4-O_2N	5	(61)
Cl	4-O_2N	20	(64)
Br	2-Me	21	(70)
Br	4-O_2N	8	(71)
Br	4-Me_2N	9	(54)
Br	4-MeO	9	(78)
Br	4-MeO	19	(64)
Br	4-MeO_2C	20	(62)
I	H	21	(75)
I	2-MeO	21	(71)
I	3-MeO	20	(53)
I	4-O_2N	8	(70)
I	4-MeO	19	(82)



$PdCl_2[P(o\text{-tol})_3]_2$ (3 mol %), Bu_3SnF, benzene

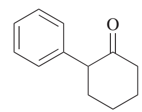


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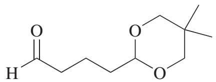
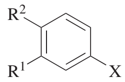
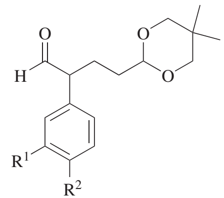
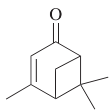
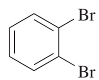
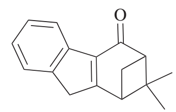
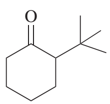
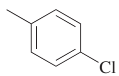
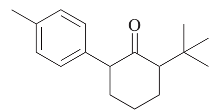
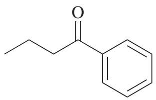
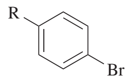
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

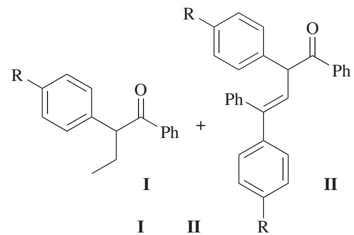
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}				
		Catalyst, ligand, Cs_2CO_3 (1.2 eq), dioxane, 80–100°		148

X	R^1	R^2	Catalyst	Ligand	
Cl	H	$MeOCH_2CH_2O$	Pd cat **3**	none	(60)
Cl	Me	MeO	Pd cat **3**	none	(58)
Br	H	$MeOCH_2CH_2O$	$[Pd(cinnamyl)Cl]_2$	**L32**	(66)
Br	Me	MeO	$[Pd(cinnamyl)Cl]_2$	**L32**	(74)

		$Pd(OAc)_2$, PPh_3 (5 mol %), Cs_2CO_3 (4 eq), DMF, 80°, 21 h	 (62)	60
		$Pd(OAc)_2$ (1 mol %), **L51** (1 mol %), NaO*t*-Bu, dioxane, 60°, 12 h	 (20)	51

Pd(OAc)$_2$ (x mol %), phosphine, Cs_2CO_3, xylene, 140°



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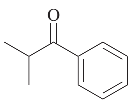
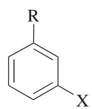
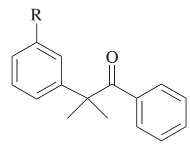
R	x	Phosphine	Time (h)	I	II
H	0.1	PPh_3	2	(20)	(23)
H	0.1	P(o-tol)$_3$	2	(14)	(78)
H	0.1	P(t-Bu)$_3$	2	(78)	(19)
H	0.075	P(o-tol)$_3$	4.5	(12)	(81)
F	0.075	P(o-tol)$_3$	2	(—)	(64)
Me	0.075	P(o-tol)$_3$	2	(—)	(50)

Pd(dba)$_2$, ligand, NaOt-Bu, rt to 70°



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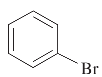
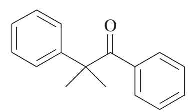
X	R	Ligand	Yield
Cl	MeO	**L3**	(82)
Cl	MeO	P(t-Bu)$_3$	(92)
Br	H	**L3**	(78)
Br	H	P(t-Bu)$_3$	(87)



Pd(dba)$_2$ (2 mol %), **L2** (15 mol %), KHMDS (1.2 eq), THF, reflux, 5 h



(55)

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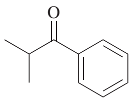
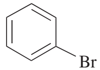
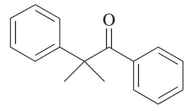
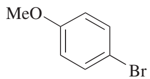
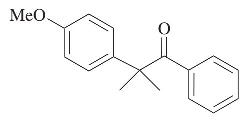
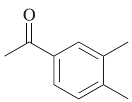
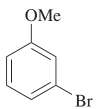
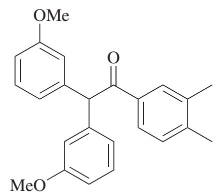
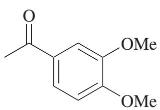
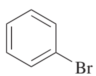
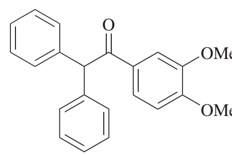
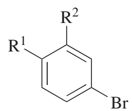
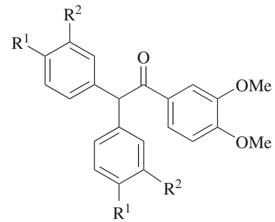
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

	Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}			Catalyst (2 mol %), ligand (2.5 mol %), NaO*t*-Bu, THF, 50°		40
			Catalyst / **Ligand** / **Time (h)**		
			$Pd(dba)_2$ / **L3** / 6	(87)	
			$Pd(OAc)_2$ / P(*t*-Bu)$_3$ / 12	(92)	
			$Pd(OAc)_2$ (0.5 mol %), **L15** (0.2 mol %), NaO*t*-Bu (1.3 eq), toluene, 80°, 1 h	 (72)	43
			$Pd(OAc)_2$ (1 mol %), PPh_3 (8 mol %), Cs_2CO_3 (2.5 eq), DMF, 150°, 0.5–1 h	 (74)	53
			$Pd(OAc)_2$ (1 mol %), PPh_3 (8 mol %), Cs_2CO_3 (2.5 eq), DMF, 150°, 0.5–1 h	 (85)	53



See table



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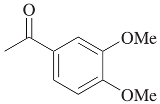
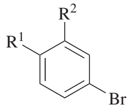
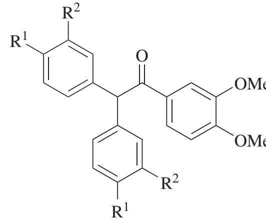
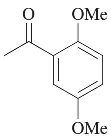
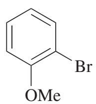
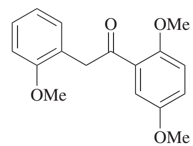
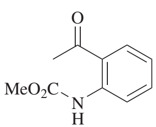
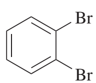
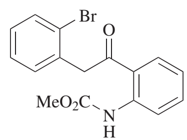
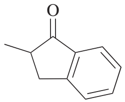
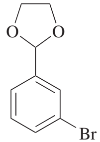
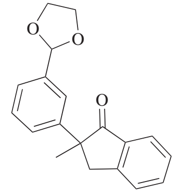
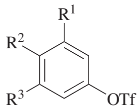
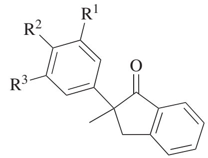
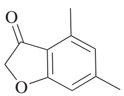
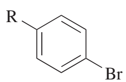
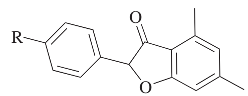
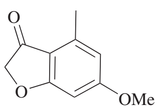
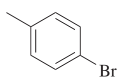
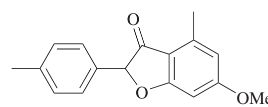
R^1	R^2	Catalyst	Ligand	Base	Solvent	Temp (°)	
H	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(62)
H	H	Pd cat **10**	none	NaO*t*-Bu	THF	85	(90)
H	H	Pd cat **11**	none	Cs_2CO_3	DMF	153	(57)
H	MeO	Pd cat **10**	none	NaO*t*-Bu	THF	85	(82)
H	MeO	Pd cat **11**	none	Cs_2CO_3	DMF	153	(47)
H	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(64)
O_2N	H	Pd cat **11**	none	Cs_2CO_3	DMF	153	(70)
O_2N	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(72)
F	H	Pd cat **10**	none	NaO*t*-Bu	THF	85	(35)
F	H	Pd cat **11**	none	Cs_2CO_3	DMF	153	(20)
F	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(52)
MeO	MeO	Pd cat **10**	none	NaO*t*-Bu	THF	85	(90)
MeO	MeO	Pd cat **11**	none	Cs_2CO_3	DMF	153	(88)
MeO	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(74)

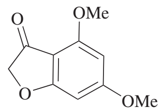
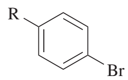
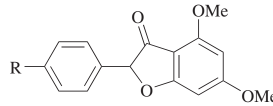
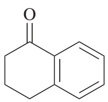
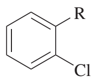
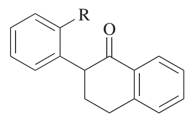
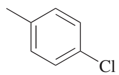
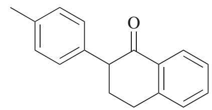
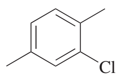
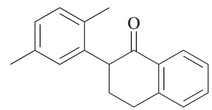
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

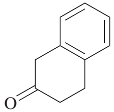
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}				
		Catalyst, ligand, Cs_2CO_3, DMF, 153°		54
	R^1 / R^2	Catalyst / Ligand		
	H / H	$Pd(OAc)_2$ / PPh_3	(62)	
	H / H	Pd cat **11** / none	(90)	
	H / MeO	$Pd(OAc)_2$ / PPh_3	(57)	
	H / MeO	Pd cat **11** / none	(82)	
	O_2N / H	$Pd(OAc)_2$ / PPh_3	(35)	
	O_2N / H	Pd cat **11** / none	(20)	
	MeO / MeO	$Pd(OAc)_2$ / PPh_3	(47)	
	MeO / MeO	Pd cat **11** / none	(64)	
		$Pd(OAc)_2$ (1 mol %), **L19** (2 mol %), NaO*t*-Bu, toluene, 80°	 (91)	43
		$Pd(OAc)_2$ (4.9 mol %), **L32** (2 eq), Cs_2CO_3, toluene, 130°, 20 h	 (17)	114

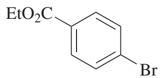
		Pd(0), **L23**, NaO*t*-Bu, toluene, 100°		(79), 70% ee	30
		Catalyst, **L22**, NaO*t*-Bu (2 eq), toluene			34

R^1	R^2	R^3	Catalyst	Temp (°)		% ee
H	H	H	$Pd(dba)_2$	60	(77)	70
H	H	CF_3	$Ni(cod)_2$	80	(70)	86
H	Me	H	$Pd(dba)_2$	60	(79)	78
H	NC	H	$Ni(cod)_2$	80	(84)	95
H	CF_3	H	$Ni(cod)_2$	80	(69)	96
MeO	MeO	H	$Pd(dba)_2$	60	(78)	82
t-Bu	H	*t*-Bu	$Pd(dba)_2$	60	(84)	89

		$Pd(OAc)_2$, **L19**, NaO*t*-Bu, toluene or THF, 60–80°		R H (15) MeO (22) Me (51)	153
		$Pd(OAc)_2$, **L19**, NaO*t*-Bu, toluene or THF, 60–80°		(39)	153

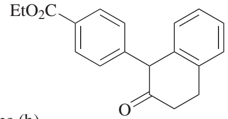
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} 		$Pd(OAc)_2$, **L19**, NaO*t*-Bu, toluene or THF, 60–80°	 R: H (21); MeO (35); Me (50)	153
		Pd cat **4** (1 mol %), NaO*t*-Bu (1.05 eq), THF		50
	R	Temp (°) / Time (h)		
	OMe	70 / 6	(35)	
	Me	60 / 1	(50)	
		$Pd(OAc)_2$ (1 mol %), **L51** (1 mol %), NaO*t*-Bu, dioxane, 60°, 6 h	 (90)	51
		$Pd(OAc)_2$, ligand, NaO*t*-Bu, toluene, 80°		43
		Ligand / Time (h)		
		L17 / 22	(76)	
		L19 / 5	(93)	



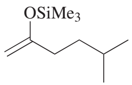


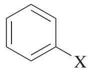
$Pd(OAc)_2$, **L19**, base

Base	Solvent	Temp (°)	Time (h)	
NaO*t*-Bu	THF	80	22	(85)
K_3PO_4	toluene	100	23	(91)

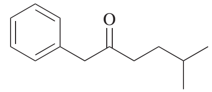


43



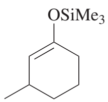


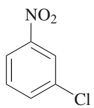
$PdCl_2[P(o\text{-tol})_3]_2$ (3 mol %), Bu_3SnF, benzene



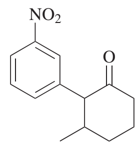
13

X	Time (h)	
Br	3	(85)
Br	4	(65)
I	3.5	(22)



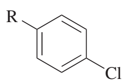


$Pd(dba)_2$ (3 mol %), $P(Bu\text{-}t)_3$ (5.4 mol %), ZnF_2 (1.4 eq), MnF_2 (1.4 eq), DMF, 90°

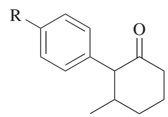


(77)

150



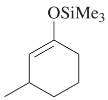
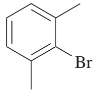
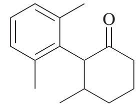
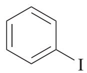
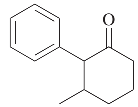
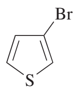
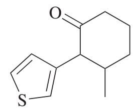
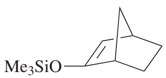
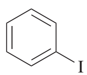
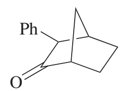
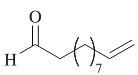
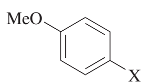
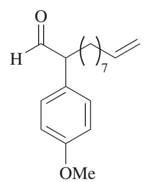
$Pd(OAc)_2$ (3 mol %), $P(t\text{-Bu})_3$ (5.4 mol %), Bu_3SnF (1.4 eq), CsF (1.4 eq), toluene



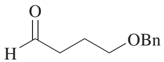
150

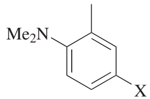
R	Temp (°)	
O_2N	85	(84)
Me(O)C	90	(70)
MeO_2C	90	(80)

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

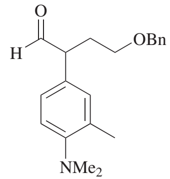
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} 		$Pd(OAc)_2$ (3 mol %), $P(t\text{-}Bu)_3$ (5.4 mol %), Bu_3SnF (1.4 eq), CsF (1.4 eq), toluene	 (85)	150
		$Pd_2(dba)_3$ (2.5 mol %), $P(t\text{-}Bu)_3$ (6 mol %), Bu_3SnF, benzene, 21 h	 (85)	151
		$Pd(OAc)_2$ (3 mol %), $P(t\text{-}Bu)_3$ (5.4 mol %), Bu_3SnF (1.4 eq), CsF (1.4 eq), toluene	 (78)	150
		$Pd_2(dba)_3$ (2.5 mol %), $P(t\text{-}Bu)_3$ (6 mol %), Bu_3SnF, benzene, 21 h	 (58)	151
C_{11} 		Catalyst, ligand, Cs_2CO_3 (1.2 eq), dioxane, 80–100°		148

X	Catalyst	Ligand	Yield (%)
Cl	Pd cat **3**	none	(58)
Br	$[Pd(allyl)Cl]_2$	**L32**	(70)





Catalyst, ligand, Cs_2CO_3 (1.2 eq), dioxane, 80–100°



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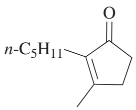
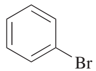
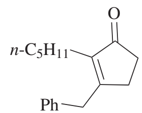
X	Catalyst	Ligand	Yield
Cl	Pd cat **3**	none	(57)
Br	$Pd(OAc)_2$	**L32**	(73)



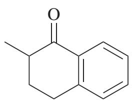


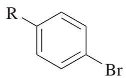
$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Cs_2CO_3, DMF, 60°, 21 h



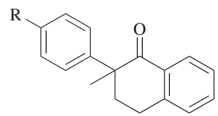
(58)

92

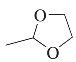


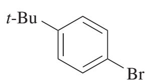


Pd(0), (*S*)-**L23**, NaO*t*-Bu, toluene, 100°

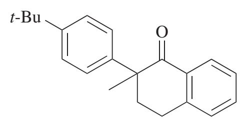


30

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



Pd(0), (*S*)-**L23**, NaO*t*-Bu, toluene, 100°



(56), 77% ee

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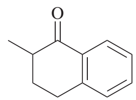
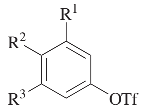
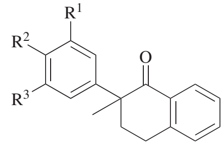
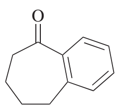
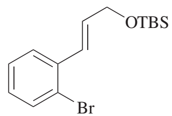
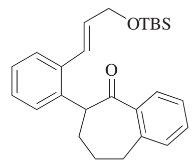
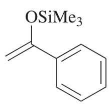
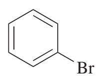
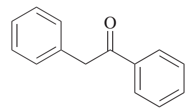
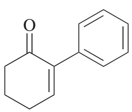
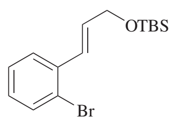
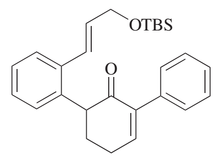
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

	Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}			Catalyst, **L22**, NaO*t*-Bu (2 eq), toluene		34

R^1	R^2	R^3	Catalyst	Temp (°)		% ee
H	H	H	$Pd(dba)_2$	60	(81)	90
H	Me	H	$Pd(dba)_2$	60	(79)	92
H	NC	H	$Ni(cod)_2$	100	(55)	97
H	CF_3	H	$Ni(cod)_2$	100	(40)	98
H	*t*-Bu	H	$Ni(cod)_2$	60	(85)	92
MeO	MeO	H	$Pd(dba)_2$	60	(79)	91
t-Bu	H	*t*-Bu	$Pd(dba)_2$	60	(83)	95

	Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
			$Pd_2(dba)_3$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h	 (—)	63
			$PdCl_2[P(o\text{-}tol)_3]_2$ (3 mol %), Bu_3SnF, benzene	 (35)	13
C_{12}			$Pd_2(dba)_3$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h	 (—)	63

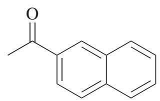
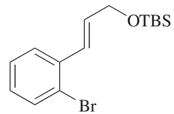
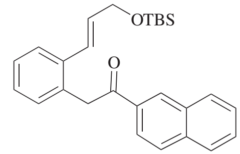
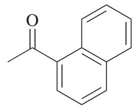
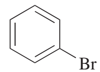
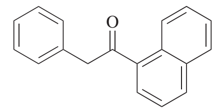
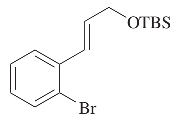
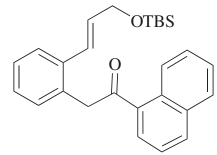
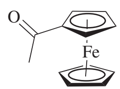
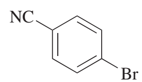
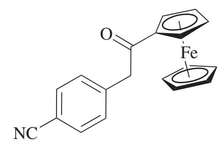
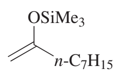
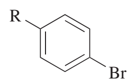
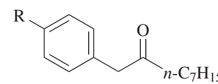
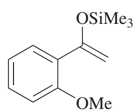
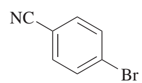
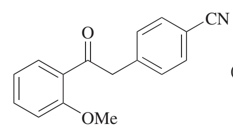
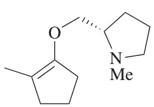
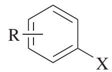
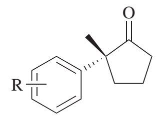
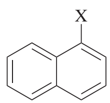
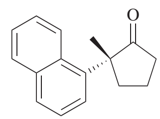
		$Pd_2(dba)_3$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h		(—)	63
		Pd cat **4** (1 mol %), NaO*t*-Bu (1.05 eq), THF, 70°, 1 h		(35)	50
		$Pd_2(dba)_3$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h		(—)	63
		$Pd_2(dba)_3$ (1.5 mol %), **L25** (3.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°		(75)	16
		$PdCl_2[P(o\text{-tol})_3]_2$ (3 mol %), Bu_3SnF, benzene		R: H (65); MeO (62)	13
		$Pd(dba)_2$ (3 mol %), $P(t\text{-}Bu)_3$ (5.4 mol %), ZnF_2 (1.4 eq), MnF_2 (1.4 eq), DMF, 90°		(78)	154

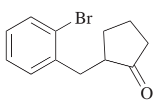
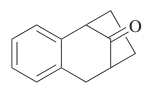
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

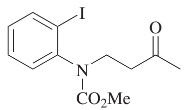
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12} 		1. $Pd(OAc)_2$, DMF, H_2O 2. H_3O^+		154

R	X	Temp (°)	Time (h)		% ee
4-PhCO	Br	80	24	(47)	97
H	I	70	68	(61)	94
2-MeO	I	70	24	(67)	98
2-MeO	I	80	30	(50)	94
3-MeO	I	70	18	(68)	93
4-MeO	I	70	18	(54)	93
4-PhCO	I	100	24	(78)	94

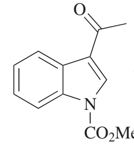
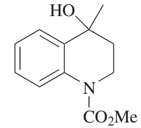
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		1. $Pd(OAc)_2$, DMF, H_2O, 48 h 2. H_3O^+		154

X	Temp (°)		% ee
Br	100	(49)	91
I	80	(45)	90

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$PdCl_2(Ph_3P)_2$ (10 mol %), $CsCO_3$ (3 eq), THF, 100°, 16 h	 (26)	20



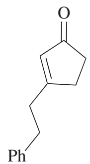
Et$_3$N, toluene, 110°, 24 h

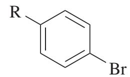
 + 

(29) (44)

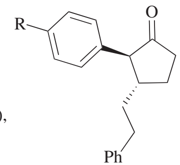
155, 113

C_{13}





1. CuCl (1 mol %), (*S*)-**L25** (1 mol %), NaO*t*-Bu (1 mol %), Ph$_2$SiH$_2$ (0.51 eq), 0°
2. Pd(OAc)$_2$ (5 mol %), **L15** (10 mol %), CsF (1.1 eq), THF, rt, 18 h



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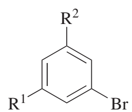
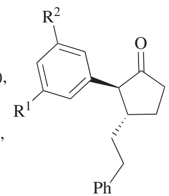
R	Solvent		% ee, dr
H	THF	(75)	95, 98:2
MeO	toluene	(55)	95, 99:1
t-Bu	THF	(80)	76, —
t-Bu	THF/pentane	(75)	95, —
t-Bu	toluene	(—)	95, —



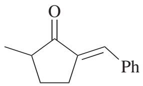
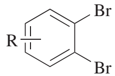
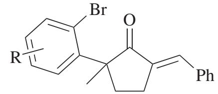
1. CuCl (1 mol %), (*S*)-**L25** (1 mol %), P(*t*-Bu)$_3$ (1 mol %), Ph$_2$SiH$_2$ (0.51 eq), THF/pentane, 0°
2. Pd(OAc)$_2$ (5 mol %), **L15** (10 mol %), CsF (1.1 eq), THF, rt, 18 h

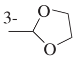


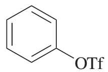
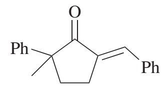
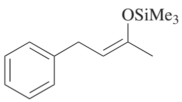
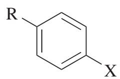
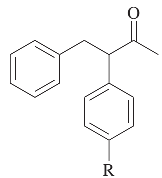
44

R^1	R^2		% ee, dr
EtO$_2$C	H	(44)	95, 98.5:1.5
Me	Me	(58)	95, 99:1

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

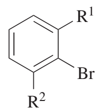
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13} 		Catalyst, (*S*)-**L23**, base		30

R	Catalyst	Base		% ee
3-Me	$Pd(OAc)_2$	NaO*t*-Bu	(86)	95
3- 	$Pd_2(dba)_3$	NaHMDS	(80)	94
4-*t*-Bu	$Pd(OAc)_2$	NaO*t*-Bu	(75)	98

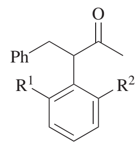
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$, **L22**, NaO*t*-Bu (2 eq), toluene, 100°	 (70), 95% ee	34
		$Pd(OAc)_2$ (3 mol %), $P(t\text{-}Bu)_3$, additive, toluene, 85°		150

X	R	Additive	
Cl	CN	Bu_3SnF (1.4 eq), CsF (1.4 eq)	(80)
Cl	CO_2Me	Bu_3SnF (1.4 eq), CsF (1.4 eq)	(89)
Br	NO_2	Bu_3SnF (1.4 eq), CsF (1.4 eq)	(84)
Br	NMe_2	Bu_3SnF (1.4 eq), CsF (1.4 eq)	(96)
Br	OH	Bu_3SnF (1.4 eq), CsF (1.4 eq)	(55)
Br	CF_3	Bu_3SnF (1.4 eq), CsF (1.4 eq)	(91)
Br	C(O)Me	Bu_3SnF (1.4 eq), CsF (1.4 eq)	(97)
Br	*t*-Bu	none	(0)
Br	*t*-Bu	Me_4NF (1.2 eq)	(0)

Br	*t*-Bu	CsF (1.2 eq)	(18)
Br	*t*-Bu	CsF (1.4 eq)	(81)
Br	*t*-Bu	ZnF_2 (1.2 eq)	(38)
Br	*t*-Bu	Bu_3SnF (1.2 eq)	(34)
Br	*t*-Bu	Bu_3SnF (1.4 eq), CsF (1.4 eq)	(67)
Br	*t*-Bu	Bu_3SnF (1.2 eq), CsF (1.2 eq)	(65)

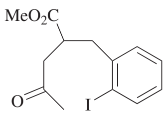


$Pd(OAc)_2$ (3 mol %), P(*t*-Bu)$_3$, Bu_3SnF (1.4 eq), CsF (1.4 eq), toluene, 85°

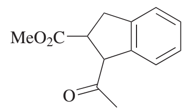


R^1	R^2	
H	OMe	(97)
Me	Me	(93)

150



$Pd(PPh_3)_4$ (20 mol %), KO*t*-Bu



(6)

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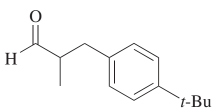
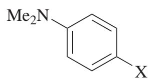
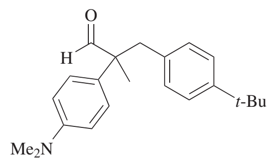
C_{14}





Catalyst, ligand, Cs_2CO_3 (1.2 eq), dioxane, 80–100°



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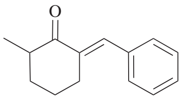
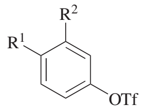
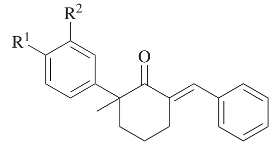
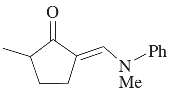
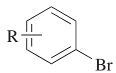
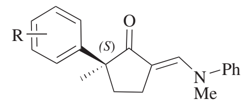
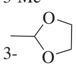
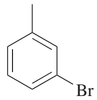
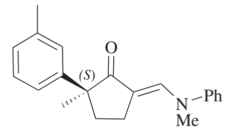
X	Catalyst	Ligand	
Cl	Pd cat **3**	none	(55)
Br	$Pd(OAc)_2$	**L20**	(68)

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound		Conditions		Product(s) and Yield(s) (%)		Refs.
C_{14} 			Pd(dba)$_2$, **L22**, NaO*t*-Bu (2 eq), toluene, 60°				34
	R^1	R^2				% ee	
	H	H			(80)	78	
	MeO	MeO			(70)	77	
			Catalyst (*x* mol %), (*S*)-**L23**, NaO*t*-Bu, toluene, 100°				41
	R		Catalyst	*x*		% ee	
	2-Me		Pd$_2$(dba)$_3$	2.5	(45)	8	
	2-Me		Pd(OAc)$_2$	5	(52)	10	
	3-MeO		Pd$_2$(dba)$_3$	5	(87)	85	
	3-Me		Pd$_2$(dba)$_3$	2.5	(70)	80	
	3- 		Pd$_2$(dba)$_3$	5	(96)	86	
	4-MeO		Pd$_2$(dba)$_3$	5	(74)	57	
	4-Me		Pd$_2$(dba)$_3$	5	(65)	63	
	4-CF$_3$		Pd$_2$(dba)$_3$	5	(93)	53	
	4-*t*-Bu		Pd$_2$(dba)$_3$	5	(65)	88	
	4-*t*-Bu		Pd(OAc)$_2$	10	(70)	89	



Pd$_2$(dba)$_3$, ligand, NaO*t*-Bu, toluene



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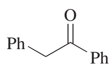
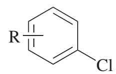
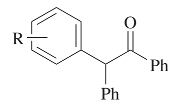
Ligand		% ee
(*R*,*R*$_p$)-**L27**	(57)	5
(*R*,*S*$_p$)-**L27**	(83)	10
(*R*)-**L28**	(72)	58





Pd(dba)$_2$ (10 mol %), **L35** (10 mol %), base (2.2 eq), toluene, 20 h



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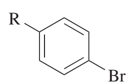
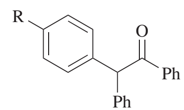
R	Base	
2-F	K_3PO_4	(72)
4-MeO	K_3PO_4	(76)
4-Me	K_3PO_4	(90)
4-Me	Cs_2CO_3	(99)



Catalyst, ligand, Cs_2CO_3, toluene, 130°



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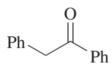
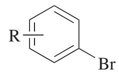
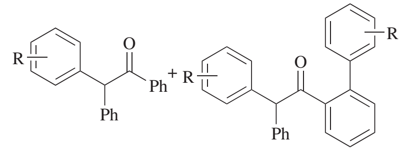
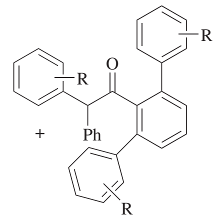
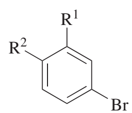
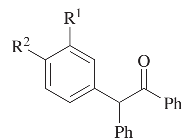
R	Catalyst	Ligand	
H	PdCl$_2$(cod)	**L36**	(78)
H	Pd(OCOCF$_3$)$_2$	**L37**	(84)
MeO	PdCl$_2$(cod)	**L36**	(95)
MeO	Pd(OCOCF$_3$)$_2$	**L37**	(96)
Me	PdCl$_2$(cod)	**L36**	(88)
Me	Pd(OCOCF$_3$)$_2$	**L37**	(96)

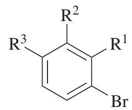
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}				
		Catalyst (0.5 mol %), ligand, base	 **I** + **II** +  **III**	46

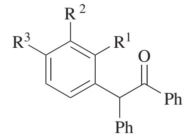
R	Catalyst	Ligand	Base	Solvent	Time (h)	**I**	**II**	**III**
H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	xylene	5	(47)	(35)	(9)
H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	xylene	22	(1)	(5)	(54)
H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	2	(79)	(5)	(0)
H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	22	(3)	(1)	(0)
H	$Pd(PPh_3)_4$	none	Cs_2CO_3	xylene	20	(6)	(7)	(61)
H	$Pd(OAc)_2$	P(*o*-tol)$_3$	Cs_2CO_3	xylene	22	(91)	(7)	(0)
H	$Pd(PPh_3)_4$	none	K_2CO_3	xylene	24	(96)	(3)	(0)
3-Cl	$Pd(PPh_3)_4$	none	Cs_2CO_3	xylene	20	(—)	(—)	(54)
3-CF_3	$Pd(PPh_3)_4$	none	Cs_2CO_3	xylene	44	(—)	(—)	(41)
4-Cl	$Pd(PPh_3)_4$	none	Cs_2CO_3	xylene	20	(—)	(—)	(25)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$ (1 mol %), PPh_3 (8 mol %), Cs_2CO_3 (2.5 eq), DMF, 150°, 0.5–1 h		53

R^1	R^2	
H	H	(80)
OMe	H	(73)
—OCH_2O—		(70)

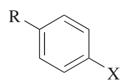


Catalyst, ligand, Cs_2CO_3, DMF

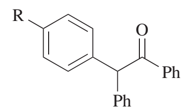


55

R^1	R^2	R^3	Catalyst	Ligand	Temp (°)	
H	H	H	$Pd(OAc)_2$	PPh_3	150	(80)
H	H	H	Pd cat **10**	none	153	(57)
H	OMe	H	$Pd(OAc)_2$	PPh_3	150	(73)
H	OMe	H	Pd cat **10**	none	153	(54)
H	H	NO_2	$Pd(OAc)_2$	PPh_3	150	(54)
H	H	OMe	$Pd(OAc)_2$	PPh_3	150	(71)
H	H	OMe	Pd cat **10**	none	153	(60)
H	—OCH_2O—		$Pd(OAc)_2$	PPh_3	150	(70)
H	—OCH_2O—		Pd cat **10**	none	153	(45)
H	OMe	OMe	Pd cat **10**	none	153	(37)
F	OMe	OMe	$Pd(OAc)_2$	PPh_3	150	(57)



$PdCl_2$, Cs_2CO_3, DMF, 2 h



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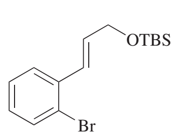
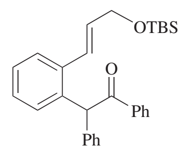
X	R	Temp (°)	
Br	H	130	(96)
I	H	100	(90)
I	MeO	100	(93)
I	Cl	100	(82)



$Pd_2(dba)_3$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h



(—)

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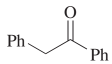
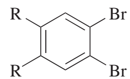
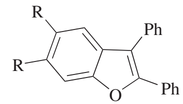
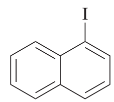
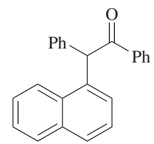
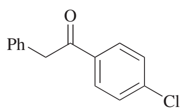
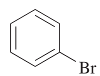
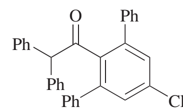
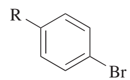
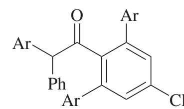
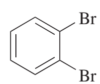
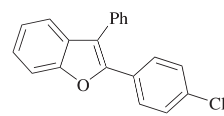
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14} 		$Pd(OAc)_2$ (0.5 mol %), PPh_3 (20 mol %), Cs_2CO_3 (2 eq), xylene, 160°	 R / Time (h) / yield: F 2 (40) Me 4 (69)	60
		$PdCl_2$, PPh_3, K_2CO_3, DMF, 100°, 2 h	 (75)	73
		$Pd(PPh_3)_4$ (0.5 mol %), Cs_2CO_3, xylene, 160°	 Time (h) / yield: 6 (59) 20 (40)	47
		$Pd(PPh_3)_4$ (0.5 mol %), $CsCO_3$ (3–5 eq), xylene	 Ar = 4-RC_6H_4 R / Time (h) / yield: H 6 (59) Ph 21 (30)	46
		$Pd(OAc)_2$ (0.5 mol %), PPh_3 (0.2 eq), Cs_2CO_3 (2 eq), xylene, 160°, 2 h	 (49)	60

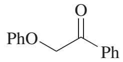
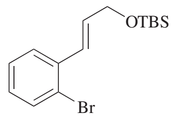
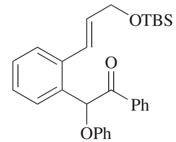
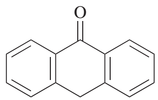
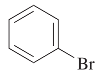
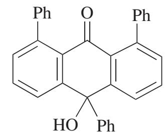
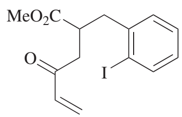
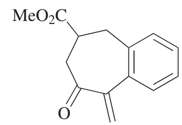
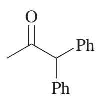
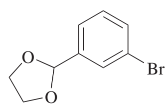
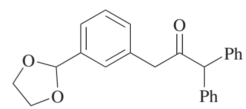
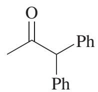
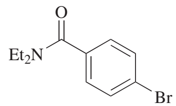
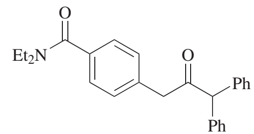
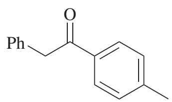
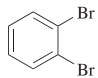
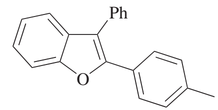
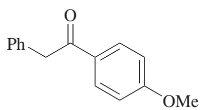
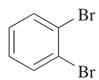
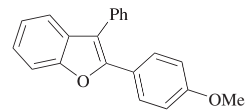
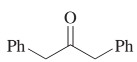
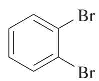
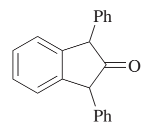
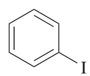
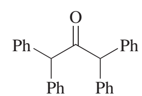
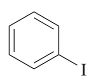
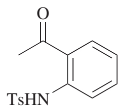
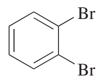
			$Pd_2(dba)_3$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), LiHMDS, dioxane, 90°, 3 h	 (—)	63
			$Pd(OAc)_2$ (2.5 mol %), PPh_3 (10 mol %), Cs_2CO_3 (1 eq), xylene, 160°, 5 h	 (47)	47
			$Pd(OAc)_2$, PPh_3, additive, Et_3N, MeCN, 82°		58
			Additive — Time (h)		
			none — 4	(22)	
			Bu_4NCl — 3	(23)	
			none — 0.8	(24)	
C_{15}			$Pd_2(dba)_3$ (1.5 mol %), **L25** (3.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°	 (72)	16

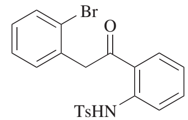
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15}				
		$Pd_2(dba)_3$ (1.5 mol %), **L25** (3.6 mol %), NaO*t*-Bu (1.3 eq), THF, 70°	 (69)	16
		$Pd(OAc)_2$ (0.5 mol %), PPh_3 (20 mol %), Cs_2CO_3 (2 eq), xylene, 160°, 2 h	 (74)	60
		$Pd(OAc)_2$ (0.5 mol %), PPh_3 (20 mol %), Cs_2CO_3 (2 eq), xylene, 160°, 2 h	 (75)	60
		$Pd(OAc)_2$ (0.5 mol %), PPh_3 (20 mol %), K_2CO_3 (2 eq), xylene, 160°, 4 h	 (64)	60
		$PdCl_2$, LiCl (4 mol %), Cs_2CO_3	 **I** (48)	18
		$PdCl_2$, Cs_2CO_3, DMF, 100°, 2 h	**I** (59)	73





Catalyst, ligand, base



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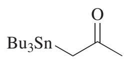
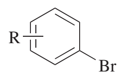
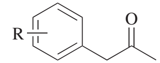
Catalyst	Ligand	Base	Solvent	Temp (°)	Time (h)	
$Pd(dba)_2$	$P(t\text{-}Bu)_3$	K_3PO_4	toluene	80	24	(0)
$Pd(dba)_2$	**L1**	NaO*t*-Bu	THF	80	8	(0)
$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	80	22	(0)
$Pd_2(dba)_3$	**L23**	NaO*t*-Bu	THF	80	22	(0)
$Pd(OAc)_2$	**L32**	K_3PO_4	toluene	130	5	(76)
$Pd(OAc)_2$	**L32**	K_3PO_4	toluene	130	29	(72)
$Pd(OAc)_2$	**L32**	Cs_2CO_3	toluene	120	48	(86)
$Pd(OAc)_2$	**L32**	Cs_2CO_3	THF	130	5	(61)
$Pd(OAc)_2$	**L51**	NaO*t*-Bu	dioxane	130	5	(0)





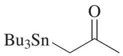
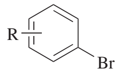
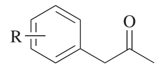
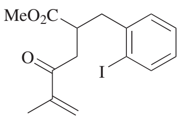
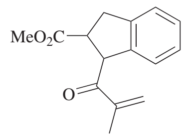
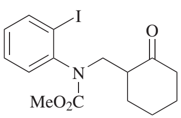
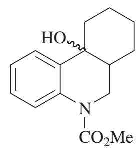
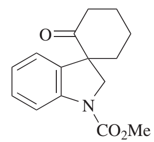
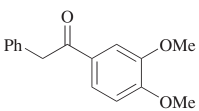
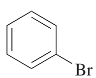
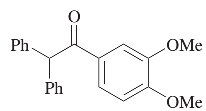
Catalyst, toluene, 100°, 5 h



149

R	Catalyst	
H	$Pd(PPh_3)_4$	(22)
H	$PdCl_2(PPh_3)_2$	(15)
H	$PdCl_2[P(o\text{-tol})_3]_2$	(78)
H	$PdCl_2[P(p\text{-tol})_3]_2$	(16)
H	$PdCl_2[P(2,4,6\text{-}Me_3C_6H_2)_3]_2$	(0)
2-Cl	$PdCl_2[P(o\text{-tol})_3]_2$	(80)
2-Me	$PdCl_2[P(o\text{-tol})_3]_2$	(91)
3-Me	$PdCl_2[P(o\text{-tol})_3]_2$	(88)
4-Me_2N	$PdCl_2[P(o\text{-tol})_3]_2$	(71)
4-MeO	$PdCl_2[P(o\text{-tol})_3]_2$	(51)

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15}				
		Catalyst, toluene, 100°, 5 h		149
	R	Catalyst		
	4-Cl	$PdCl_2[P(o\text{-tol})_3]_2$	(73)	
	4-Me	$PdCl_2[P(o\text{-tol})_3]_2$	(80)	
	4-Ac	$PdCl_2[P(o\text{-tol})_3]_2$	(64)	
	2,4,6-Me_3	$PdCl_2[P(o\text{-tol})_3]_2$	(94)	
		$Pd(PPh_3)_4$ (10–12 mol %), base	 Base: Et_3N (6); K_2CO_3 (23)	58
		$PdCl_2(PPh_3)_2$ (0.2 eq), Et_3N	 I +  II	155, 113
		Solvent / Time (h)	I / II	
		THF / 65	(32) / (24)	
		toluene / 24	(45) / (31)	
C_{16}				
		$Pd(OAc)_2$ (1 mol %), PPh_3 (8 mol %), Cs_2CO_3 (2.5 eq), DMF, 150°, 0.5–1 h	 I (74)	53, 55

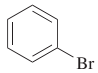
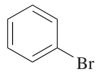
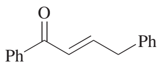
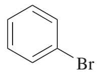
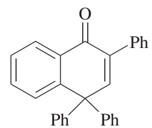
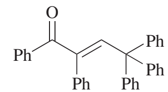
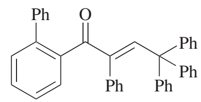
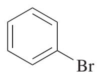
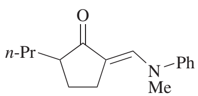
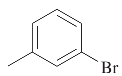
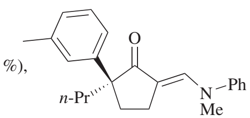
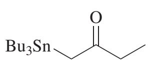
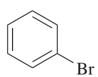
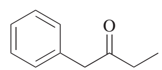
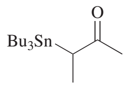
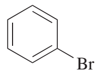
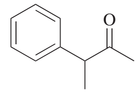
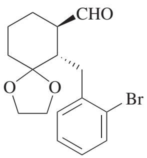
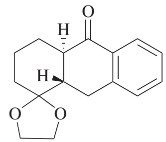
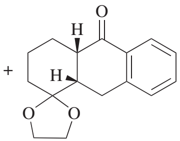
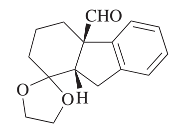
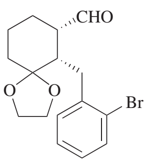
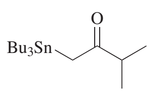
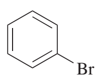
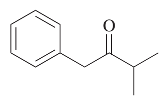
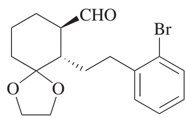
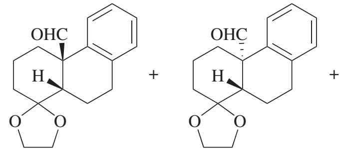
<table>
<tr><td></td><td></td><td>Pd cat 11, Cs_2CO_3, DMF, 153°, 0–8 h</td><td>I (51)</td><td>55</td></tr>
<tr><td></td><td></td><td>Catalyst, ligand, Cs_2CO_3,
toluene, 130°, 75 min</td><td>I<table><tr><th>Catalyst</th><th>Ligand</th><th>I</th></tr><tr><td>$PdCl_2$(cod)</td><td>L36</td><td>(92)</td></tr><tr><td>$Pd(OCOCF_3)_2$</td><td>L37</td><td>(95)</td></tr></table></td><td>56</td></tr>
<tr><td></td><td></td><td>$Pd(OAc)_2$ (1.7 mol %),
PPh_3 (6.8 mol %), Cs_2CO_3 (1 eq),
xylene, 160°, 2 h</td><td>
I (8)
+

II (12)
+

III (34)</td><td>47</td></tr>
<tr><td></td><td></td><td>$Pd(OAc)_2$ (1 mol %),
$P(t\text{-}Bu)_3$ (4 mol %), Cs_2CO_3 (1 eq),
xylene, 160°, 2 h</td><td>II (85)</td><td>47</td></tr>
<tr><td></td><td></td><td>$Pd_2(dba)_3$ (1 mol %), (S)-L23 (2.5 mol %),
NaOt-Bu (2 eq), toluene</td><td> (74), 91% ee</td><td>41</td></tr>
<tr><td></td><td></td><td>$PdCl_2[P(o\text{-}tol)_3]_2$ (10 mol %),
toluene, 100°, 5 h</td><td> (67)</td><td>149</td></tr>
</table>

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16} 		$PdCl_2[P(o\text{-tol})_3]_2$ (10 mol %), toluene, 100°, 5 h	 (60)	149
		$PdCl_2(PPh_3)_2$ (10 mol %), Cs_2CO_3 (3 eq)	 I +  II +	64
		Solvent | Temp | Time (h) toluene | reflux | 5 THF | 100° | 24	I | II | III (76) | (11) | — (29) | (9) | (17)  III	
		$PdCl_2(PPh_3)_2$ (10 mol %), Cs_2CO_3 (3 eq)	**I + II + III**	64
		Solvent | Temp | Time (h) toluene | reflux | 6 THF | 100° | 22	I | II | III (32) | (17) | (13) (31) | (10) | (19)	
C_{17} 		$PdCl_2[P(o\text{-tol})_3]_2$ (10 mol %), toluene, 100°, 5 h	 (87)	149



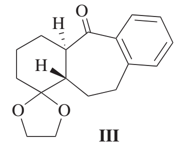
$PdCl_2(PPh_3)_2$ (10 mol %), Cs_2CO_3 (3 eq), 3 h



II **I**

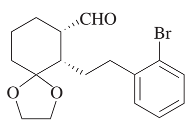
Solvent	Temp
toluene	reflux
THF	100°

I	II	III
(49)	(4)	(22)
(52)	(9)	(—)



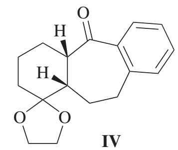
III

64



$PdCl_2(PPh_3)_2$ (10 mol %), Cs_2CO_3 (3 eq), 3 h

I + **II** +

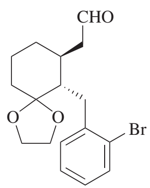


IV

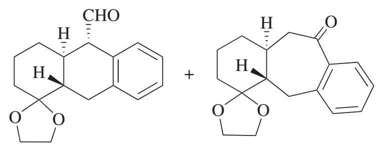
64

Solvent	Temp
toluene	reflux
THF	100°

I	II	IV
(52)	(22)	(6)
(48)	(6)	(—)



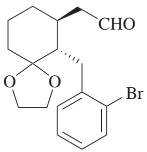
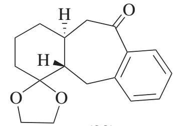
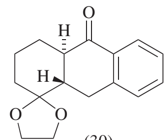
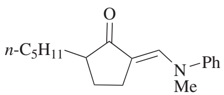
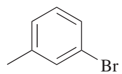
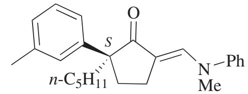
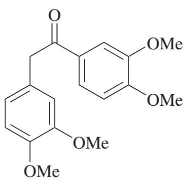
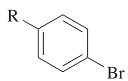
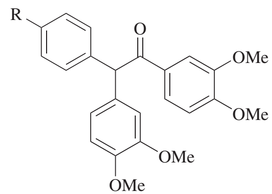
$PdCl_2(PPh_3)_2$ (10 mol %), Cs_2CO_3 (3 eq), toluene, reflux, 1.5 h



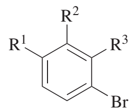
(32) (23)

64

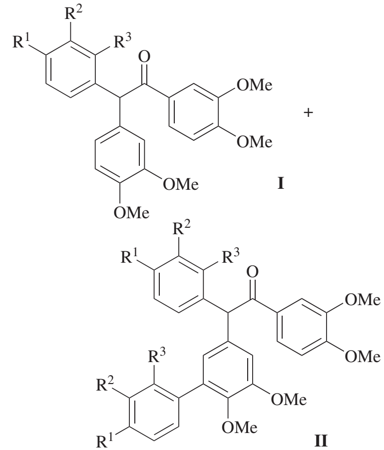
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

	Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{17}			$PdCl_2(PPh_3)_2$ (10 mol %), Cs_2CO_3 (3 eq), THF, 100°, 14 h	 (23) +  (30)	64
C_{18}			$Pd_2(dba)_3$ (1 mol %), (*S*)-**L23** (2.5 mol %), NaO*t*-Bu (2 eq), toluene	 (75), 93% ee	41
			Catalyst, ligand, Cs_2CO_3, toluene, 130°		56

R	Catalyst	Ligand	
H	$PdCl_2$(cod)	**L36**	(93)
H	$Pd(OCOCF_3)_2$	**L37**	(92)
MeO	$PdCl_2$(cod)	**L36**	(95)
MeO	$Pd(OCOCF_3)_2$	**L37**	(91)



See table

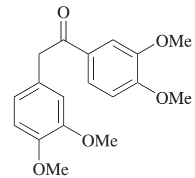
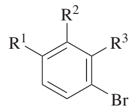
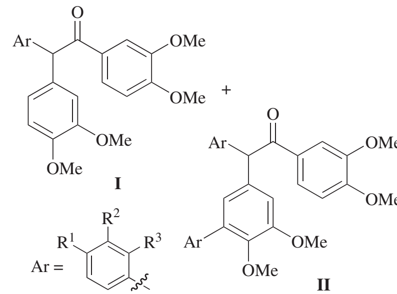


I + II

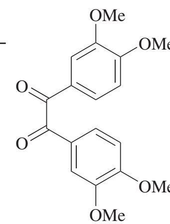
53

R^1	R^2	R^3	Catalyst	Ligand	Base	Solvent	Temp (°)	**I**	**II**
H	H	H	$PdCl_2$	none	Cs_2CO_3	DMF	100	(20)	(—)
H	H	H	$PdCl_2$	PPh_3	K_2CO_3	DMF	170	(24)	(—)
H	H	H	$Pd(OAc)_2$	PPh_3	K_2CO_3	xylene	170	(55)	(29)
H	H	H	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	170	(83)	(—)
H	H	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	xylene	150	(85)	(—)
H	H	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	150	(85)	(—)
H	H	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	170	(52)	(35)
H	H	O_2N	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	150	(44)	(—)
H	H	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	150	(46)	(—)
H	MeO	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	150	(51)	(—)
H	MeO	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	150	(47)	(—)
—OCH_2O—		H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	150	(55)	(—)
MeO	MeO	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	150	(12)	(—)

TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

	Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18}			See table		55

R^1	R^2	R^3	Catalyst	Ligand	Base	Solvent	Temp (°)	**I**	**II**	**III**
H	H	H	$Pd(OAc)_2$	PPh_3	K_2CO_3	xylene	150	(86)	(—)	(—)
H	H	H	$Pd(OAc)_2$	PPh_3	K_2CO_3	xylene	170	(58)	(31)	(6)
H	H	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	xylene	170	(23)	(32)	(25)
H	H	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	150	(89)	(—)	(—)
H	H	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	170	(56)	(38)	(—)
H	H	H	$Pd(OAc)_2$	PEt_3	Cs_2CO_3	DMF	150	(32)	(29)	(—)
H	H	O_2N	Pd cat **11**	none	Cs_2CO_3	DMF	150	(53)	(—)	(—)
H	H	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	150	(51)	(—)	(—)
H	MeO	H	Pd cat **11**	none	Cs_2CO_3	DMF	150	(40)	(—)	(—)
H	MeO	H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(47)	(—)	(—)
H	MeO	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	150	(44)	(—)	(—)
MeO	MeO	H	Pd cat **11**	none	Cs_2CO_3	DMF	150	(53)	(—)	(—)
—OCH_2O—		H	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(55)	(—)	(—)
—OCH_2O—		H	Pd cat **11**	none	Cs_2CO_3	DMF	150	(38)	(—)	(—)
MeO	MeO	MeO	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	153	(12)	(—)	(—)



III

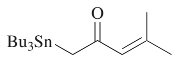
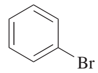
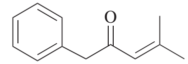
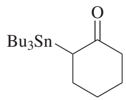
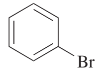
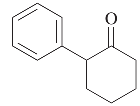
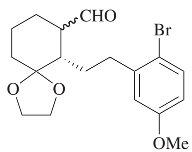
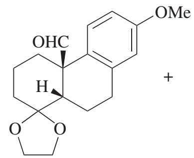
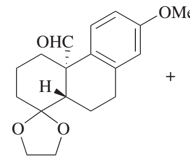
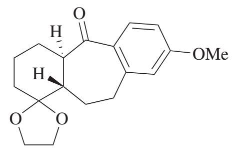
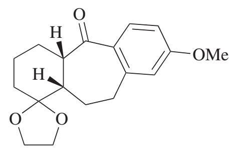
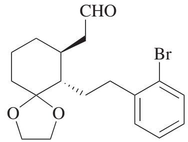
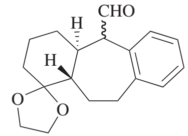
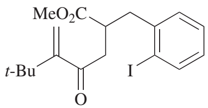
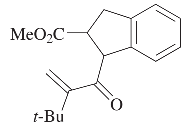
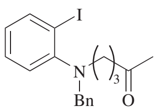
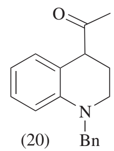
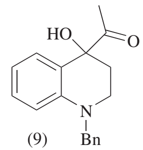
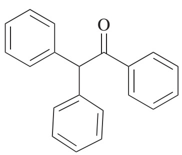
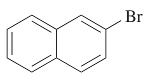
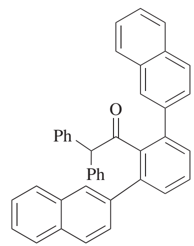
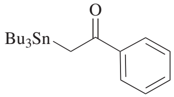
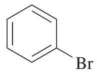
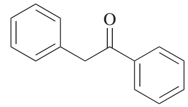
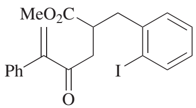
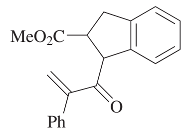
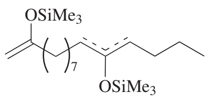
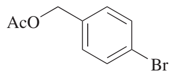
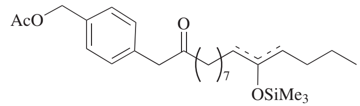
		$PdCl_2[P(o\text{-tol})_3]_2$ (10 mol %), toluene, 100°, 5 h	 (64)	149
		$PdCl_2[P(o\text{-tol})_3]_2$ (10 mol %), toluene, 100°, 5 h	 (54)	149
		$PdCl_2(PPh_3)_2$ (10 mol %), Cs_2CO_3 (3 eq), toluene, reflux, 3.5 h	 **I** (2) +  **II** (12) +  **III** (34) +  **IV** (10)	64
		$PdCl_2(PPh_3)_2$ (10 mol %), Cs_2CO_3 (3 eq), THF, 100°, 14 h	**I** (12.5) + **II** (52.5) + **III** (11) + **IV** (6)	64

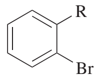
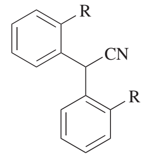
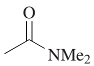
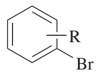
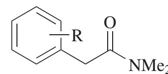
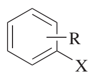
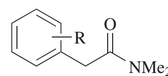
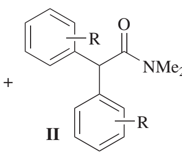
TABLE 1. ARYLATION OF ALDEHYDES, KETONES, AND ENOL ETHERS (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18} 		$PdCl_2(PPh_3)_2$ (10 mol %), Cs_2CO_3 (3 eq), THF, 100°, 14 h	 (40)	64
		$Pd(PPh_3)_4$ (20 mol %), Bu_4NF (3 eq), THF, rt, 15 h	 (68)	58
		$PdCl_2(PPh_3)_2$ (0.2 eq), Cs_2CO_3 (3 eq), THF, 100–110°, 48 h	 (20) +  (9)	155, 113
C_{20} 		$Pd(PPh_3)_4$ (0.5 mol %), Cs_2CO_3 (3–5 eq), xylene, 23 h	 (43)	46

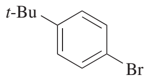
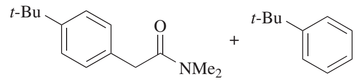
		$PdCl_2[P(o\text{-tol})_3]_2$ (10 mol %), toluene, 100°, 5 h	 (90)	149
		$Pd(PPh_3)_4$, KO*t*-Bu, THF, rt, 5 h	 (42)	58
C_{21}				
		Bu_3SnF (1.5 eq), $PdCl_2[P(o\text{-tol})_3]_2$ (0.045 eq), benzene, 3 h	 (56)	13

[a] The intermediate dimeric silyl enol ether was formed with 97% ee.
[b] The intermediate dimeric silyl enol ether was formed with 84% ee.
[c] These yields were determined by GC-MS.

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_2				
CH_3CN		$Pd(OAc)_2$ (5 mol %), **L23** (5 mol %), NaHMDS (1.3 eq), toluene, 100°, 16 h	 R: H (62); Me (60)	26
C_4				
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (1 mol %), **L12** (1 mol %), rt, 24 h	 R: 2-MeO (91); 4-NC (89); $4\text{-}MeO_2C$ (95)	68
		$Pd(dba)_2$ (5 mol %), **L23** (7.5 mol %), KHMDS (2 eq), dioxane, 100°	 **I** +  **II**	67

X	R	Time (h)	**I**	**II**
Br	2-Me	1.5	(72)	(4)
Br	4-MeO	4	(48)	(18)
Br	4-Me	1.5	(72)	(10)
Br	4-Me	1.5[a]	(24)	(74)
Br	4-Ph	2	(66)	(13)
I	4-Me	1	(70)	(4)

		$Pd(OAc)_2$ (7.5 mol %), ligand (9 mol %), base (1.2 eq), 85°, 2 h	 **I** + **II**	67

Ligand	Base	Solvent	I	II
L1	KHMDS	THF	(22)	(22)
L1	KHMDS	dioxane	(48)	(2)
L1	LTMP	THF	(5)	(4)
L1	LTMP	dioxane	(38)	(5)
L23	KHMDS	THF	(32)	(8)

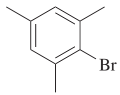
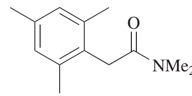
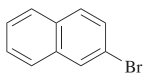
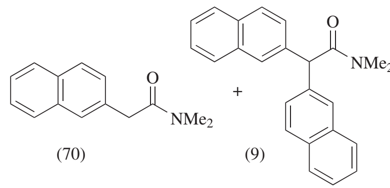
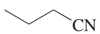
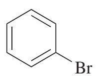
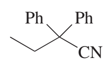
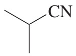
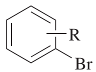
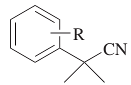
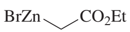
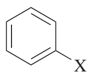
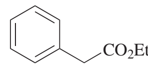
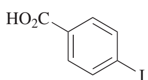
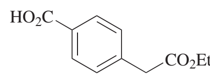
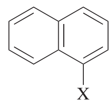
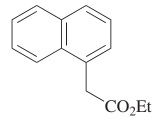
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (1 mol %), **L12** (1 mol %), rt, 24 h	 (96)	68
		$Pd(dba)_2$ (5 mol %), **L23** (7.5 mol %), KHMDS (2 eq), dioxane, 100°, 2 h	 (70) + (9)	67
		$Pd_2(dba)_3$•$CHCl_3$ (1 mol %), $P(t\text{-}Bu)_3$ (2 mol %), LiHMDS (2.2 eq), toluene, 70°, 6 h	 (69)	26

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

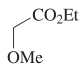
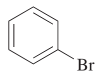
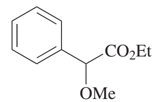
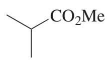
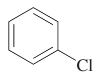
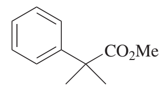
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_4				
		$Pd(OAc)_2$ (*x* mol %), **L23** (*x* mol %), NaHMDS (1.3 eq), toluene, 100°		26
		Catalyst (10 mol %)		109
		$Pd(PPh_3)_4$ (10 mol %), $CH_2(OMe)_2$/HMPA (1:1), reflux, 3 h	 (85)	109

R	*x*	Time (h)	
2-Me	1	6	(70)
4-MeO	1	8	(83)
4-NC	0.5	1	(99)
4-*t*-Bu	1	2	(87)

X	Catalyst	Solvent	Temp	Time (h)	
Cl	$Pd(PPh_3)_4$	$CH_2(OMe)_2$/HMPA (1:1)	reflux	3	(0)
Cl	$Ni(PPh_3)_4$	$CH_2(OMe)_2$/HMPA (1:1)	reflux	3	(65)
Br	$Pd(PPh_3)_4$	benzene/HMPA (1:1)	reflux	7	(15)
Br	$Ni(PPh_3)_4$	$CH_2(OMe)_2$/HMPA (1:1)	reflux	3	(67)
I	$Pd(PPh_3)_4$	$CH_2(OMe)_2$/HMPA (1:1)	reflux	6	(47)
I	$Ni(PPh_3)_4$	$CH_2(OMe)_2$/HMPA (1:1)	rt	3	(55)

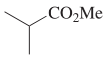
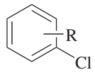
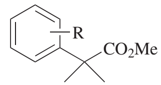
		Catalyst (10 mol %), $CH_2(OMe)_2$/HMPA (1:1), reflux, 3 h			109

X	Catalyst	
Br	$Pd(PPh_3)_4$	(0)
Br	$Ni(PPh_3)_4$	(69)
I	$Pd(PPh_3)_4$	(47)

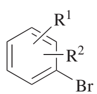
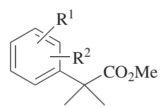
C_5 		$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), $LiNCy_2$, toluene, rt or $Pd(dba)_2$, carbene,[b] NaHMDS, toluene, rt		(<5)	99
		1. Base (1.3 eq), toluene, rt, 10 min 2. $[PdP(t\text{-}Bu)_3Br]_2$ (0.1 mol %), 4 h			156

Base	Temp	
NaHMDS	rt	(0)
NaHMDS	60°	trace
NaHMDS	100°	(90)
$LiNCy_2$	rt	(0)
$LiNCy_2$	100°	trace

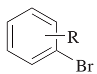
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5 		1. NaHMDS (1.2 eq), toluene, rt, 10 min 2. Catalyst (*x* mol %), ligand (*y* mol %), 100°, 4 h		156

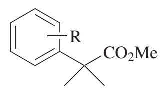
R	Catalyst	*x*	Ligand	*y*	Yield (%)
H	$Pd(dba)_2$	0.2	$P(t\text{-}Bu)_3$	0.2	(89)
H	$[PdP(t\text{-}Bu)_3Br]_2$	0.1	none	—	(92)
3-MeO	$Pd(dba)_2$	0.4	$P(t\text{-}Bu)_3$	0.4	(77)
3-MeO	$[PdP(t\text{-}Bu)_3Br]_2$	0.2	none	—	(74)
3-F	$Pd(dba)_2$	0.4	$P(t\text{-}Bu)_3$	0.4	(77)
3-F	$[PdP(t\text{-}Bu)_3Br]_2$	0.2	none	—	(81)
3-CF_3	$Pd(dba)_2$	0.4	$P(t\text{-}Bu)_3$	0.4	(81)
3-CF_3	$[PdP(t\text{-}Bu)_3Br]_2$	0.2	none	—	(75)
4-MeO	$Pd(dba)_2$	0.4	$P(t\text{-}Bu)_3$	0.4	(67)
4-MeO	$[PdP(t\text{-}Bu)_3Br]_2$	0.2	none	—	(71)
4-F	$Pd(dba)_2$	0.4	$P(t\text{-}Bu)_3$	0.4	(90)
4-F	$[PdP(t\text{-}Bu)_3Br]_2$	0.2	none	—	(87)
4-CF_3	$Pd(dba)_2$	0.4	$P(t\text{-}Bu)_3$	0.4	(67)
4-CF_3	$[PdP(t\text{-}Bu)_3Br]_2$	0.2	none	—	(71)
4-Me	$Pd(dba)_2$	0.4	$P(t\text{-}Bu)_3$	0.4	(79)
4-Me	$[PdP(t\text{-}Bu)_3Br]_2$	0.2	none	—	(84)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(dba)_2$ (*x* mol %), $P(t\text{-}Bu)_3$ (0.1–5.0 mol %), $LiNCy_2$ (1.3 eq), toluene, rt		75

R^1	R^2	x	Time (h)	
H	H	0.1	18	(87)
3-MeO	H	0.1	24	(97)
3-F	H	0.1	16	(93)
3-Cl	H	0.1	12	(71)
3-Me	H	0.1	24	(97)
3-CF_3	H	0.1	24	(89)
4-Me_2N	H	0.05	18	(88)
4-MeO	H	0.1	24	(90)
4-PhO	H	0.1	12	(95)
4-F	H	0.1	16	(90)
4-Cl	H	0.1	14	(72)
4-Me	H	0.1	24	(90)
4-CF_3	H	0.1	24	(86)
4-*t*-Bu	H	0.1	12	(91)
4-Ph	H	0.05	18	(96)
4-PhCO	H	3.0	16	(73)
3-F	4-Ph	0.2	14	(91)



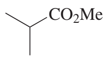
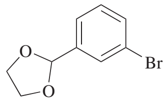
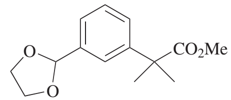
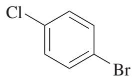
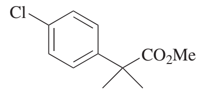
1. $LiNCy_2$ (1.3 eq), toluene, rt, 10 min
2. $[PdP(t\text{-}Bu)_3Br]_2$ (x mol %), rt, 4 h



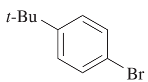
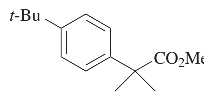
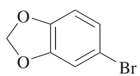
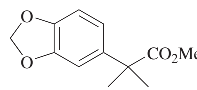
157

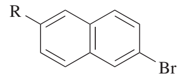
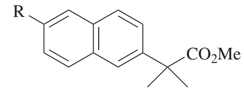
R	x	
3-MeO	0.5	(88)
3-F	0.5	(72)
4-Me_2N	0.05	(88)
4-MeO	0.5	(85)
4-F	0.5	(85)
4-Cl	0.5	(89)
4-CF_3	0.5	(60)
4-*t*-Bu	0.05	(72)

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

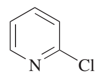
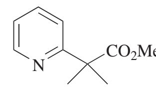
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5 		$Pd(dba)_2$ (2.0 mol %), $P(t\text{-}Bu)_3$ (2.0 mol %), $LiNCy_2$ (1.3 eq), toluene, rt, 16 h	 (77)	75
		1. NaHMDS (1.2 eq), toluene, rt, 10 min 2. Catalyst (*x* mol %), ligand (*y* mol %), 100°, 4 h		156

Catalyst	*x*	Ligand	*y*	
$Pd(dba)_2$	0.4	$P(t\text{-}Bu)_3$	0.4	(69)
$[PdP(t\text{-}Bu)_3Br]_2$	0.2	none	—	(82)

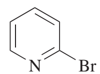
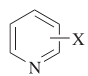
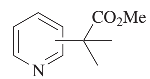
		$Pd(dba)_2$ (0.5 mol %), $P(t\text{-}Bu)_3$ (0.5 mol %), LiHMDS (2.3 eq), rt, 12 h	 (92) **I**	77
		1. $LiNCy_2$ (1.3 eq), toluene, 0°, 20 min 2. $[PdP(t\text{-}Bu)_3Br]_2$ (0.05 mol %), rt, 4 h	**I** (86)	157
		$Pd(dba)_2$ (0.1 mol %), $P(t\text{-}Bu)_3$ (0.1 mol %), $LiNCy_2$ (1.3 eq), toluene, rt, 20 h	 (95)	75

	Pd(dba)$_2$ (x mol %), P(t-Bu)$_3$ (0.1–0.2 mol %), LiNCy$_2$ (1.3 eq), toluene, rt		75

R	x	Time (h)	
H	0.1	8	(94)
MeO	0.2	24	(93)

	1. NaHMDS (1.2 eq), toluene, rt, 10 min 2. Catalyst (x mol %), ligand (y mol %), 100°, 4 h	 **I**	156

Catalyst	x	Ligand	y	
Pd(dba)$_2$	0.4	P(t-Bu)$_3$	0.4	(66)
[PdP(t-Bu)$_3$Br]$_2$	0.2	none	—	(71)

	1. LiNCy$_2$ (1.3 eq), toluene, rt, 10 min 2. [PdP(t-Bu)$_3$Br]$_2$ (0.5 mol %), rt, 4 h	**I** (71)	156
	Pd(dba)$_2$ (5.0 mol %), P(t-Bu)$_3$ (5.0 mol %), LiNCy$_2$ (1.3 eq), toluene, rt		75

X	Time (h)	
2-Br	7	(94)
3-Br	12	(80)
4-Br	16	(51)

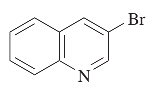
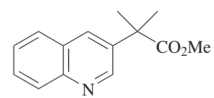
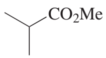
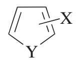
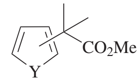
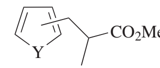
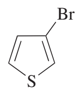
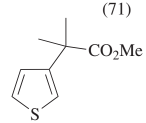
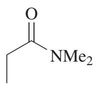
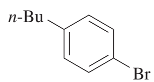
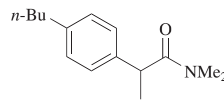
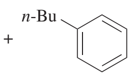
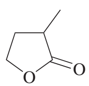
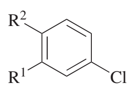
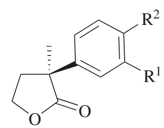
	Pd(dba)$_2$ (5.0 mol %), P(t-Bu)$_3$ (5.0 mol %), LiNCy$_2$ (1.3 eq), toluene, rt, 12 h	 (70)	75

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5 		$Pd(dba)_2$ (5.0 mol %), $P(t\text{-}Bu)_3$ (5.0 mol %), $LiNCy_2$ (1.3 eq), toluene, rt	 **I** +  **II**	75
	Y X	Time (h)	**I** **II**	
	O 2-Br	7	(72) (—)	
	O 3-Br	9	(71) (—)	
	S 2-Br	9	(48) (43)	
	S 3-Br	9	(71) (—)	
		1. $LiNCy_2$ (1.3 eq), toluene, rt, 10 min 2. $[PdP(t\text{-}Bu)_3Br]_2$ (0.5 mol %), rt, 4 h	 (75)	156
		$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (7.5 mol %), KHMDS (2 eq), dioxane, 100°, 3 h	 (16) +  (78)	67
		$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), $ZnBr_2$ (15 mol %), NaHMDS (2.3 eq), toluene/THF (3:1), 60°, 17–20 h		33
	R^1 R^2		% ee	
	H H		(86) >97	
	Me_2N H		(81) 97	
	MeO H		(86) 96	
	H TBSO		(67) 95	
	H MeO		(76) 94	

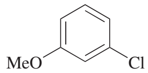
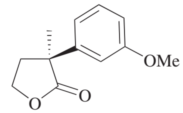
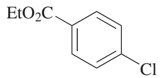
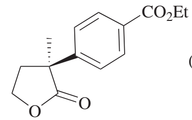
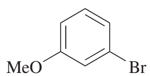
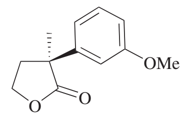
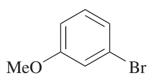
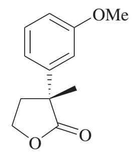
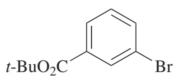
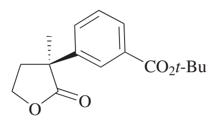
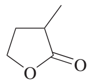
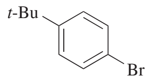
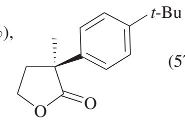
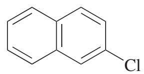
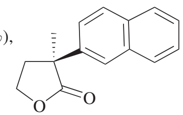
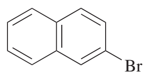
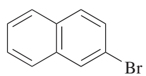
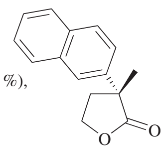
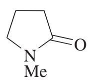
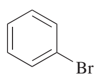
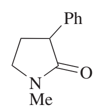
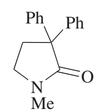
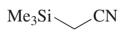
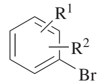
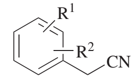
	$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), NaHMDS (*x* eq), toluene, 60°, 17–20 h	 *x* — % ee 1.3 (40) 95 2.3 (52) 95	33
	$Ni(cod)_2$ (5 mol %), (*S*)-**L20** (8.5 mol %), $ZnBr_2$ (15 mol %), NaHMDS (8 eq), toluene/THF (3:1), 60°, 17–20 h	 (73), 90% ee	33
	$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), NaHMDS (2.3 eq), toluene, 60°, 17–20 h	 (29), 99% ee	33
	$Pd_2(dba)_3$ (2.5 mol %), (*S*)-**L23** (15 mol %), NaHMDS, toluene, 50°	 (31), 59% ee	33
	$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), $ZnBr_2$ (15 mol %), NaHMDS (2.3 eq), toluene/THF (3:1), 60°, 17–20 h	 (58), 93% ee	33

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5				
		$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), $ZnBr_2$ (15 mol %), NaHMDS (2.3 eq), toluene/THF (3:1), 60°, 17–20 h	 (57), 94% ee	33
		$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), $ZnBr_2$ (15 mol %), NaHMDS (2.3 eq), toluene/THF (3:1), 60°, 17–20 h	 **I** (95), 94% ee	33
		$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), NaHMDS (2.3 eq), toluene, 60°, 17–20 h	**I** (33), 98% ee	33
		$Pd_2(dba)_3$ (2.5 mol %), (*S*)-**L23** (15 mol %), NaHMDS, toluene, 50°	 (62), 60% ee	33
		$Pd(dba)_2$ (5 mol %), **L23** (7.5 mol %), KHMDS (2 eq), dioxane, 100°, 3 h	 (49) +  (9)	67

Reagent	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd_2(dba)_3$ (2 mol %), ligand (x mol %), ZnF_2 (0.5 eq), DMF, 90°		80

R^1	R^2	Ligand	x	Time (h)	Yield (%)
2-Me	H	P(t-Bu)$_3$	4	24	(83)
2-i-Pr	H	P(t-Bu)$_3$	4	24	(69)
2-Cy	H	P(t-Bu)$_3$	4	24	(71)
4-O_2N	H	**L23**	2	8	(68)
4-Me_2N	H	PPh(t-Bu)$_2$	4	18	(83)
4-MeO	H	**L23**	2	18	(64)
4-F	H	**L23**	2	18	(79)
4-NC	H	**L23**	2	8	(81)
4-EtO_2C	H	**L23**	2	8	(84)
4-CF_3	H	**L23**	2	18	(78)
4-MeCO	H	**L23**	2	8	(78)
4-t-Bu	H	**L23**	2	18	(87)
4-PhCO	H	**L23**	2	8	(92)
2-Me	4-Me	P(t-Bu)$_3$	4	24	(78)
2-Me	6-Me	P(t-Bu)$_3$	4	24	(84)
3-Me	5-Me	**L23**	2	18	(74)

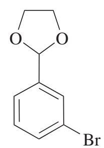
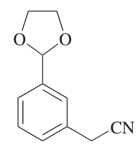
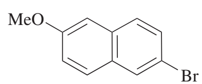
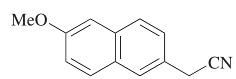
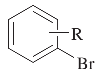
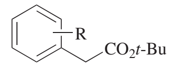
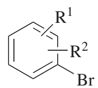
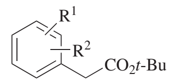
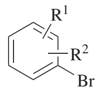
Substrate	Conditions	Product	Yield (%)	Refs.
	$Pd_2(dba)_3$ (2 mol %), **L23** (2 mol %), ZnF_2 (0.5 eq), DMF, 90°, 18 h		(78)	80
	$Pd_2(dba)_3$ (2 mol %), **L23** (2 mol %), ZnF_2 (0.5 eq), DMF, 90°, 18 h		(87)	80

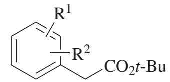
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6				
$MeCO_2t$-Bu		$Pd(dba)_2$ (x mol %), **L47** (x mol %), LiHMDS (2.3 eq), rt, 12 h		77
	R	x		
	H	1	(87)	
	2-MeO	2	(87)	
	3-MeO	0.5	(88)	
	4-MeO	1	(85)	
	4-*t*-Bu	0.5	(92)	
	4-Ph	0.5	(92)	
		$Pd(dba)_2$ (x mol %), P(*t*-Bu)$_3$ (0.2–1.0 mol %), $LiNCy_2$ (1.3 eq), toluene, rt		75

R^1	R^2	x	Time (h)	Yield (%)
H	H	0.2	24	(92)
2-F	H	1.0	15	(88)
2-CF_3	H	1.0	15	(82)
3-MeO	H	0.5	24	(94)
3-F	H	1.0	15	(95)
3-CF_3	H	0.5	24	(85)
4-MeO	H	0.5	24	(95)
4-F	H	1.0	15	(95)
4-CF_3	H	1.0	10	(94)
4-*t*-Bu	H	0.5	8	(87)
4-Ph	H	0.5	15	(96)
3-F	4-Ph	1.0	15	(93)

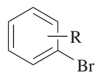


Pd(dba)$_2$ (x mol %), **L47** (0.5–2 mol %), LiHMDS (2.3 eq), toluene, rt

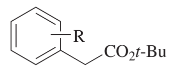


75

R^1	R^2	x	Time (h)	
H	H	1.0	12	(87)
2-MeO	H	2.0	12	(87)
3-MeO	H	0.5	12	(88)
3-F	H	1.0	12	(91)
3-CF_3	H	1.0	12	(88)
4-MeO	H	1.0	12	(85)
4-F	H	1.0	12	(90)
4-*t*-Bu	H	0.5	12	(92)
4-Ph	H	0.5	15	(93)
3-F	4-Ph	1.0	12	(80)



Pd(dba)$_2$ (3 mol %), **L17** (6.3 mol %), LiHMDS (2.5 eq), toluene



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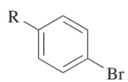
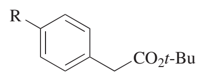
R	Temp	Time (h)	
2-Me	80°	0.2	(78)
4-F	rt	6	(71)
4-Me	rt	4	(81)



1. LiNCy$_2$ (1.3 eq), toluene, rt, 10 min
2. [PdP(*t*-Bu)$_3$Br]$_2$ (x mol %), rt, 4 h



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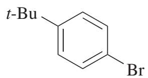
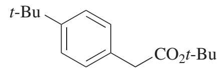
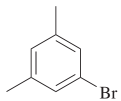
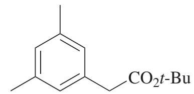
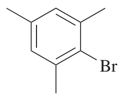
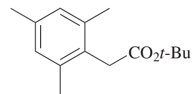
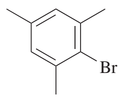
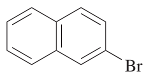
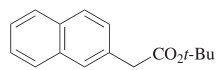
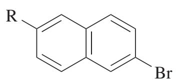
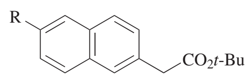
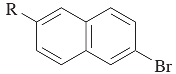
R	x	
MeO	0.2	(86)
F	0.4	(82)
CF_3	0.4	(73)
t-Bu	0.2	(83)

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6				
$MeCO_2t$-Bu		1. $LiNCy_2$ (1.3 eq), toluene, 0°, 20 min 2. $[PdP(t\text{-}Bu)_3Br]_2$ (0.04 mol %), rt, 4 h	 (87)	157
		$Pd(dba)_2$ (0.2 mol %), $P(t\text{-}Bu)_3$ (0.2 mol %), $LiNCy_2$ (1.3 eq), toluene, rt, 10 h	 (97)	75
		$Pd(dba)_2$ (0.5 mol %), **L47** (0.5 mol %), LiHMDS (2.3 eq), rt, 12 h	 (98) **I**	77
		$Pd(dba)_2$ (0.5 mol %), $P(t\text{-}Bu)_3$ (0.5 mol %), LiHMDS (2.3 eq), toluene, rt	**I** (98)	75
		$Pd(dba)_2$ (0.5 mol %), **L47** (0.5 mol %), LiHMDS (2.3 eq), rt, 12 h	 (90)	77
		$Pd(dba)_2$ (3 mol %), **L17** (6.3 mol %), LiHMDS (2.5 eq), toluene, rt	 **I**	74

R	Time (h)	
H	1	(84)
MeO	4	(90)

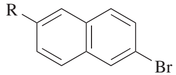


Pd(dba)$_2$ (x mol %),
L47 (0.2–0.5 mol %),
LiNCy$_2$ (1.3 eq), toluene, rt, 15 h

I

R	x	
H	0.2	(93)
MeO	0.5	(96)

75

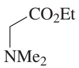


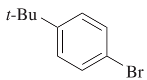
Pd(dba)$_2$ (x mol %),
L47 (0.5–1.0 mol %),
LiHMDS (2.3 eq), toluene, rt, 12 h

I

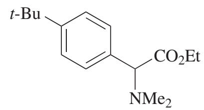
R	x	
H	0.5	(90)
MeO	1.0	(60)

75



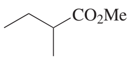


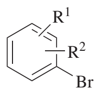
Pd(dba)$_2$ (2 mol %),
P(t-Bu)$_3$ (2 mol %),
K$_3$PO$_4$ (2.3 eq), 100°, 12 h



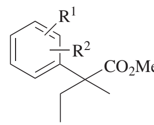
(84)

77





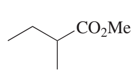
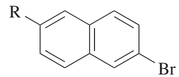
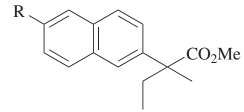
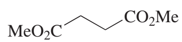
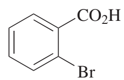
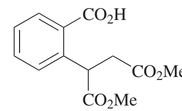
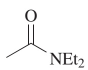
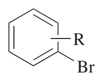
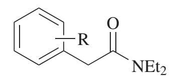
Pd(dba)$_2$ (x mol %),
P(t-Bu)$_3$ (0.1–0.2 mol %),
LiNCy$_2$ (1.3 eq), toluene, rt



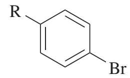
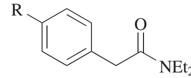
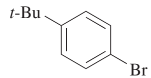
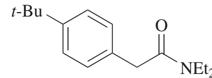
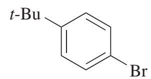
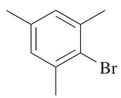
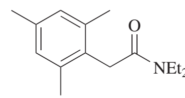
75

R^1	R^2	x	Time (h)	
3-MeO	H	0.1	16	(96)
3-F	H	0.2	12	(91)
3-Me	H	0.1	18	(87)
3-CF$_3$	H	0.1	10	(76)
4-MeO	H	0.2	10	(99)
4-F	H	0.2	12	(90)
4-Me	H	0.1	14	(81)
4-CF$_3$	H	0.1	10	(83)
4-Ph	H	0.1	10	(78)
3-F	4-Ph	0.1	10	(83)

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

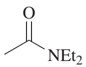
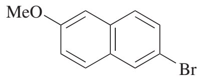
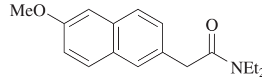
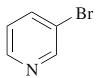
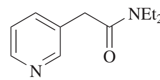
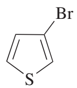
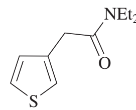
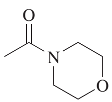
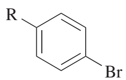
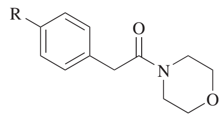
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6				
		$Pd(dba)_2$ (x mol %), $P(t\text{-}Bu)_3$ (0.1–0.2 mol %), $LiNCy_2$ (1.3 eq), toluene, rt		75
	R	x / Time (h)		
	H	0.1 / 12	(88)	
	MeO	0.2 / 10	(99)	
		CuBr (cat), NaH (2 eq), 0.5 h	 (60)	101
		1. s-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (x mol %), **L12** (x mol %), rt, 24 h		68

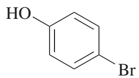
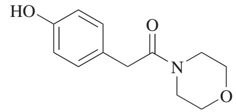
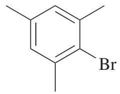
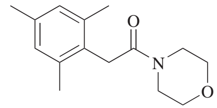
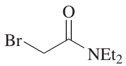
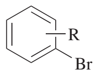
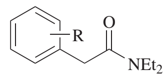
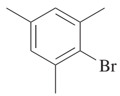
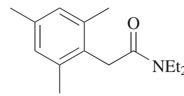
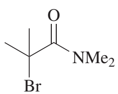
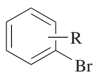
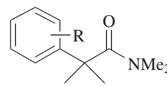
R	x	
2-F	3	(92)
2-NC	2	(84)
$4\text{-}Me_2N$	3	(90)[c]
$4\text{-}O_2N$	1	(90)
4-MeO	1	(93)
4-MeS	1	(91)
4-Cl	1	(94)
4-NC	1	(98)
$4\text{-}CF_3$	1	(90)
$4\text{-}MeO_2C$	1	(97)
4-MeCO	2	(92)
4-t-Bu	1	(93)
4-PhCO	1	(92)

	1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $[PdP(t\text{-}Bu)_3Br]_2$ (0.5 mol %), KH (1.05 eq), rt, 24 h	 R | H_2N (80) HO (91)	68
	1. Base, rt, 1 min 2. $ZnCl_2$, rt, 5 min 3. $Pd(dba)_2$ (1 mol %), **L12** (1 mol %), THF, rt, 4 h Base LDA (2 eq) $LiNCy_2$ (1.2 eq)	 **I** (20) (100)	68
	1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (1–5 mol %), ligand (*x* mol %), 24 h	**I**	68
	1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (1 mol %), **L12** (1 mol %), rt, 24 h	 (96)	68

Ligand	*x*	Temp	
$P(t\text{-}Bu)_3$	1	rt	(25)
$P(t\text{-}Bu)_3$	2	rt	(34)
PCy_3	1	rt	(0)
PCy_3	2	rt	(0)
L12	1	rt	(100)
L12	2	rt	(100)
L17	1	rt	(25)
L17	1	70°	(57)
L17	7.5	rt	(40)
L17	7.5	70°	(76)
L23	1	rt	(0)
L23	2	70°	(60)

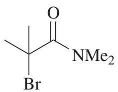
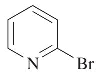
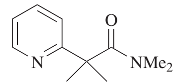
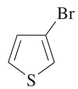
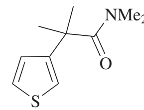
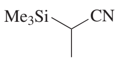
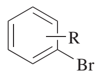
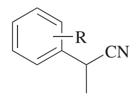
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6				
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (1 mol %), **L12** (1 mol %), rt, 24 h	 (95)	68
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (2 mol %), **L12** (2 mol %), 70°, 24 h	 (91)	68
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (2 mol %), **L12** (2 mol %), 70°, 24 h	 (89)	68
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (*x* mol %), **L12** (*x* mol %), rt, 12 h		68
	R	*x*		
	O_2N	2	(89)	
	MeO	2	(89)	
	MeS	1	(89)	
	CF_3S	1	(83)	
	NC	2	(89)	
	CF_3	3	(88)	
	MeO_2C	2	(89)	
	PhCO	2	(92)	

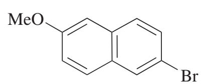
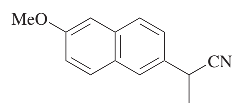
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $[PdP(t\text{-}Bu)_3Br]_2$ (1 mol %), KH (1.05 eq), 70°, 12 h	 (92)	68
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (2 mol %), **L12** (2 mol %), rt, 12 h	 (90)	68
		1. Zn (1.5 eq), THF, rt, 0.5 h 2. $Pd(dba)_2$ (1 mol %), **L12** (1 mol %), THF, rt, 6 h	 R 2-F (91) 4-O_2N (81) 4-NC (87) 4-MeO_2C (89) 4-*t*-Bu (90)	68
		1. Zn (1.5 eq), THF, rt, 0.5 h 2. $Pd(dba)_2$ (1 mol %), **L12** (1 mol %), THF, rt, 6 h	 (91)	68
		1. Zn (1.5 eq), THF, rt, 0.5 h 2. $[PdP(t\text{-}Bu)_3Br]_2$ (2.5 mol %), THF/toluene (2:8), 12 h		68

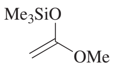
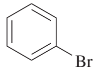
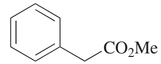
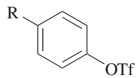
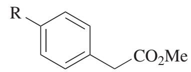
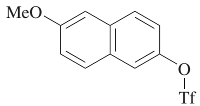
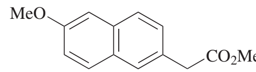
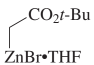
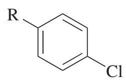
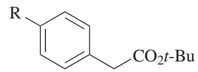
R	Temp	
3-F	rt	(91)
4-Me_2N	70°	(93)
4-MeO	rt	(94)
4-Cl	70°	(91)
4-CF_3	70°	(86)
4-*t*-Bu	rt	(94)
4-PhCO	rt	(88)

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

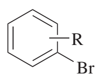
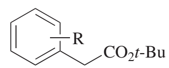
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		1. Zn (1.5 eq), THF, rt, 0.5 h 2. $[PdP(t\text{-}Bu)_3Br]_2$ (2.5 mol %), THF/toluene (2:8), 70°, 12 h	 (94)	68
		1. Zn (1.5 eq), THF, rt, 0.5 h 2. $[PdP(t\text{-}Bu)_3Br]_2$ (2.5 mol %), THF/toluene (2:8), rt, 12 h	 (82)	68
		$Pd_2(dba)_3$ (2 mol %), ligand, ZnF_2 (0.5 eq), DMF, 90°		80

R	Ligand	Time (h)	
2-Me	$P(t\text{-}Bu)_3$ (4 mol %)	24	(71)
2-*i*-Pr	$P(t\text{-}Bu)_3$ (4 mol %)	24	(60)
2-Cy	$P(t\text{-}Bu)_3$ (4 mol %)	24	(64)
4-MeO	**L23** (2 mol %)	18	(71)
4-NC	**L23** (2 mol %)	8	(82)
4-EtO_2C	**L23** (2 mol %)	8	(84)
4-*t*-Bu	**L23** (2 mol %)	18	(77)
4-PhCO	**L23** (2 mol %)	8	(87)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd_2(dba)_3$ (2 mol %), **L23** (2 mol %), ZnF_2 (0.5 eq), DMF, 90°, 18 h	 (98)	80

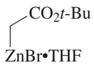
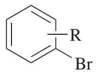
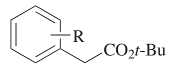
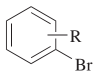
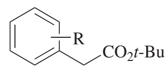
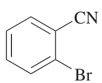
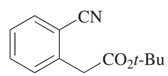
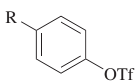
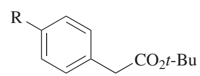
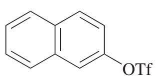
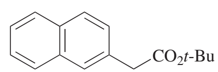
		$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (5 mol %), **L1** (20 mol %), TlOAc (1 eq)	 (56)	100
		$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (5 mol %), **L1** (20 mol %), LiOAc (2 eq), THF, reflux, 6 h	 R: H (53); MeO (50)	100
		$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (5 mol %), **L1** (20 mol %), LiOAc (2 eq), THF, reflux, 6 h	 (40)	100
		Catalyst (x mol %), ligand (1 mol %), THF, 70°, 12 h		156

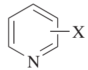
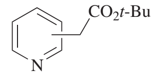
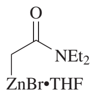
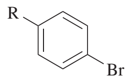
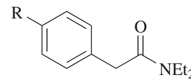
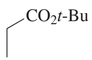
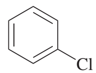
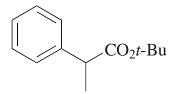
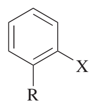
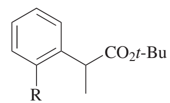
R	Catalyst	x	Ligand	Yield
H	$[PdP(t\text{-}Bu)_3Br]_2$	0.5	—	trace
H	$Pd(dba)_2$	1	**L12**	(95)
O_2N	$Pd(dba)_2$	1	**L12**	(83)
NC	$Pd(dba)_2$	1	**L12**	(86)
MeO_2C	$Pd(dba)_2$	1	**L12**	(85)

		$Pd(dba)_2$ (1 mol %), **L12** (1 mol %), THF, rt, 4 h		76

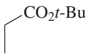
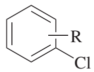
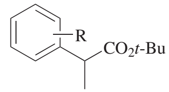
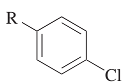
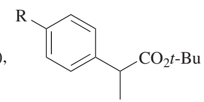
R	Yield
2-O_2N	(87)
2-NC	(91)
4-O_2N	(96)
4-EtCO	(94)
4-PhCO	(72)[d]

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		$Pd(dba)_2$ (1–2 mol %), **L12**, THF, rt	 R: 2-O_2N (87); 2-HO (83); 2-NC (91); 4-H_2N (80); 4-O_2N (96); 4-HO (91); 4-PhCO (75)	22
		$[PdP(t\text{-}Bu)_3Br]_2$ (0.5 mol %), KH (1.05 eq), THF, rt		76
	R	Time (h)		
	2-HO	4	(83)	
	4-H_2N	24	(85)	
	4-HO	4	(91)	
		$[PdP(t\text{-}Bu)_3Br]_2$ (0.5 mol %), THF, rt, 4 h	 (81)	76
		$PdCl_2(PPh_3)_2$ (20 mol %), DIBALH, THF/HMPA (2:1), overnight	 R: MeS (50); Cl (55)	22
		$PdCl_2(PPh_3)_2$ (20 mol %), DIBALH, THF/HMPA (2:1), overnight	 (60)	158

Reactant	Aryl halide	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(dba)_2$ (1 mol %), **L12** (1 mol %), THF, 70°, 4 h	 X: 3-Br (90); 4-Br (79)	76, 22
		$Pd(dba)_2$ (2 mol %), **L11** (2 mol %), dioxane, rt, 6 h	 R: MeO (91); NC (86); CF_3 (91); EtO_2C (94); *t*-Bu (92)	76, 68
C_7 		$Pd(dba)_2$ (1.0 mol %), **L47** (1.0 mol %), NaHMDS (2.2 eq), toluene, rt, 12 h	 **I** (71)	75
		1. Base (1.3 eq), toluene, rt, 10 min 2. $[PdP(t\text{-}Bu)_3Br]_2$ (0.2 mol %), rt	**I** Base: NaHMDS (100); $LiNCy_2$ (60)	156
		$Pd(dba)_2$ (*x* mol %), **L47** (*x* mol %), NaHMDS (2.3 eq), rt, 12 h		77

X	R	*x*	Yield
Cl	H	1	(71)
Br	H	0.5	(75)
Br	Me	0.5	(88)

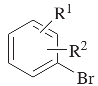
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7 		1. NaHMDS (1.2 eq), toluene, rt, 10 min 2. Catalyst (*x* mol %), ligand (*y* mol %), 4 h		156
		$Pd_2(dba)_3$ (1.5 mol %), **L14** (6.3 mol %), LiHMDS (2.5 eq), toluene, 80°		74

First entry (ref. 156):

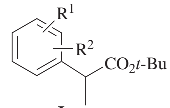
R	Catalyst	*x*	Ligand	*y*	Temp	
H	$Pd(dba)_2$	0.4	$P(t\text{-}Bu)_3$	0.4	rt	(91)
H	$[PdP(t\text{-}Bu)_3Br]_2$	0.2	none	—	rt	(94)
2-MeO	$Pd(dba)_2$	1	$P(t\text{-}Bu)_3$	1	rt	(62)
2-MeO	$[PdP(t\text{-}Bu)_3Br]_2$	0.4	none	—	rt	(77)
3-MeO	$Pd(dba)_2$	1	$P(t\text{-}Bu)_3$	1	rt	(41)
3-MeO	$[PdP(t\text{-}Bu)_3Br]_2$	0.4	none	—	rt	(75)
4-MeO	$Pd(dba)_2$	1	$P(t\text{-}Bu)_3$	1	rt	(69)
4-MeO	$[PdP(t\text{-}Bu)_3Br]_2$	0.4	none	—	rt	(88)
4-F	$[PdP(t\text{-}Bu)_3Br]_2$	0.15	none	—	60°	(73)
4-Br	$Pd(dba)_2$	0.3	$P(t\text{-}Bu)_3$	0.3	60°	(84)
4-Br	$[PdP(t\text{-}Bu)_3Br]_2$	0.15	none	—	60°	(81)
2,6-Me_2	$Pd(dba)_2$	0.4	$P(t\text{-}Bu)_3$	0.4	60°	(42)
2,6-Me_2	$[PdP(t\text{-}Bu)_3Br]_2$	0.2	none	—	60°	(81)

Second entry (ref. 74):

R	Time (h)	
MeO	5	(56)
PhO	3	(54)



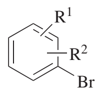
Pd(dba)$_2$ (x mol %),
L47 (0.5–5 mol %),
NaHMDS (2.2 eq), toluene, rt, 12 h



I

Ref. 75

R^1	R^2	x	
H	H	0.5	(75)
2-Me	H	1.0	(88)
4-MeO	H	1.0	(82)
4-CF_3	H	5.0	(74)
3-F	4-Ph	2.0	(66)

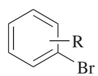


Pd(OAc)$_2$ (3.0 mol %),
L17 (6.3 mol %),
LiHMDS (2.5 eq), toluene, 80°

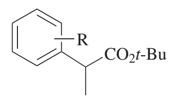
I

Ref. 74

R^1	R^2	Time (h)	
2-Me	H	2	(82)
2-H_2C=CH	H	2	(77)
2-*i*-Pr	H	2	(88)
3-CF_3	H	1	(81)
4-PhO	H	2	(71)
4-Ph	H	0.5	(86)
2-Me	6-Me	2	(68)
3-F	4-Ph	0.3	(86)

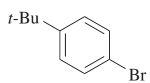


1. LiNCy$_2$ (1.3 eq), toluene, rt, 10 min
2. [PdP(t-Bu)$_3$Br]$_2$ (x mol %), rt, 4 h

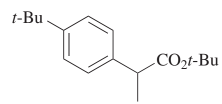


Ref. 157

R	x	
2-MeO	0.25	(87)
3-MeO	0.25	(84)
3-F	0.2	(90)
4-MeO	0.25	(87)
4-F	0.2	(88)
4-Cl	0.2	(83)



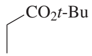
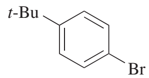
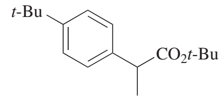
1. LiNCy$_2$ (1.3 eq), toluene, 0°, 20 min
2. [PdP(t-Bu)$_3$Br]$_2$ (0.2 mol %), rt, 4 h



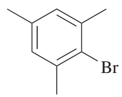
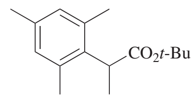
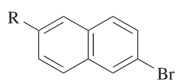
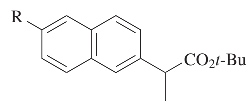
(79)

Ref. 157

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7 		1. Base (1.3 eq), toluene, rt, 10 min 2. Catalyst (*x* mol %), ligand (*y* mol %), rt, 4 h		157

Base	Catalyst	*x*	Ligand	*y*	
NaHMDS	$[PdP(t\text{-}Bu)_3Br]_2$	0.25	none	—	(100)
LiHMDS	$[PdP(t\text{-}Bu)_3Br]_2$	0.25	none	—	(20)
$LiNCy_2$	$[PdP(t\text{-}Bu)_3Br]_2$	0.25	none	—	(100)
$LiNCy_2$	$[PdP(t\text{-}Bu)_3Br]_2$	0.05	none	—	(80)
$LiNCy_2$	$Pd(dba)_2$	0.1	$P(t\text{-}Bu)_3$	0.1	(75)
$LiNCy_2$	$Pd(dba)_2$	0.25	$P(t\text{-}Bu)_3$	0.25	(91)
$LiNCy_2$	$Pd(dba)_2$	0.25	$[HP(t\text{-}Bu)_3]\ BF_4$	0.25	(60)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(dba)_2$ (1 mol %), $P(t\text{-}Bu)_3$ (1 mol %), NaHMDS (2.3 eq), rt, 12 h	 **I** (74)	77
		$Pd(dba)_2$ (1 mol %), **L47** (1 mol %), NaHMDS (2.2 eq), toluene, rt, 12 h	**I** (74)	75
		1. $LiNCy_2$ (1.3 eq), toluene, rt, 10 min 2. $[PdP(t\text{-}Bu)_3Br]_2$ (0.05 mol %), rt, 4 h	**I** (72)	157
		$Pd(OAc)_2$ (3 mol %), **L17** (6.3 mol %), LiHMDS (2.5 eq), toluene		74

R	Temp	Time (h)	
H	rt	17	(84)
H	80°	0.25	(92)
MeO	rt	15	(79)
MeO	80°	0.5	(74)

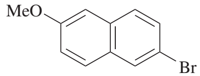
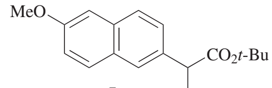
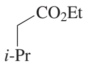
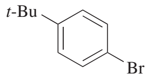
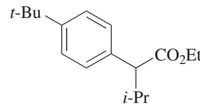
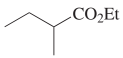
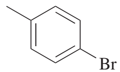
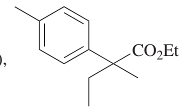
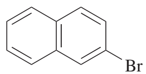
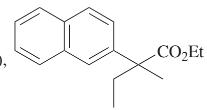
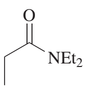
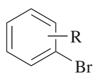
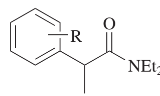
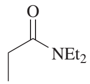
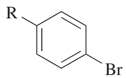
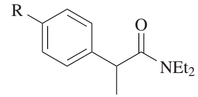
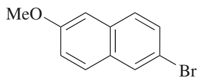
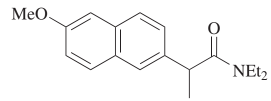
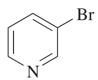
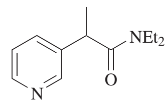
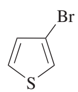
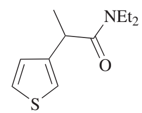
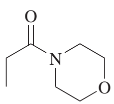
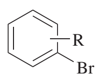
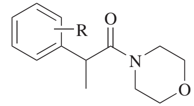
		Pd(dba)$_2$ (1 mol %), **L47** (1 mol %), NaHMDS (2.2 eq), toluene, rt, 12 h	 (83) **I**	75
	"	Pd(dba)$_2$ (1 mol %), **L47** (1 mol %), NaHMDS (2.3 eq), rt, 12 h	**I** (83)	77
	"	1. LiNCy$_2$ (1.3 eq), toluene, rt, 10 min 2. [PdP(t-Bu)$_3$Br]$_2$ (0.2 mol %), rt, 4 h	**I** (75)	157
		Pd(dba)$_2$ (5 mol %), **L47** (5 mol %), NaHMDS (2.3 eq), rt, 12 h	 (95)	77
		Pd(OAc)$_2$ (3.0 mol %), **L26** (6.3 mol %), LiHMDS (2.5 eq), toluene, 80°, 0.5 h	 (48)	74
		Pd(OAc)$_2$ (3.0 mol %), **L26** (6.3 mol %), LiHMDS (2.5 eq), toluene, 40°, 17 h	 (54)	74
		1. s-BuLi (1.2 eq), THF, –78°, 1 h 2. ZnCl$_2$ (2.4 eq), rt, 10 min 3. Pd(dba)$_2$ (x mol %), **L12** (x mol %), rt, 24 h	 R | x | 2-MeO | 3 | (88) 2-F | 3 | (86) 2-Me | 3 | (98) 4-O$_2$N | 3 | (87) 4-MeO | 1 | (94) 4-MeS | 1 | (91) 4-Cl | 1 | (87) 4-NC | 3 | (91) 4-CF$_3$ | 1 | (90)	68

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7 		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $[PdP(t\text{-}Bu)_3Br]_2$ (1 mol %), KH (1.05 eq), rt, 24 h	 R H_2N (90) HO (95)	68
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (2 mol %), **L12** (2 mol %), rt, 24 h	 (92)	68
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (3 mol %), **L12** (3 mol %), 70°, 24 h	 (86)	68
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (1 mol %), **L12** (1 mol %), 70°, 24 h	 (92)	68
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (4 mol %), **L12** (4 mol %), rt, 24 h	 R 2-F (69) 2-Me (79) 4-MeO (91) 4-Cl (89) 4-CF_3 (82) 4-EtO_2C (85) 4-PhCO (65)	68

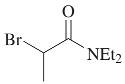
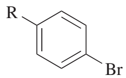
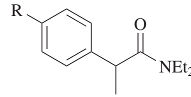
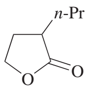
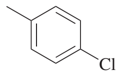
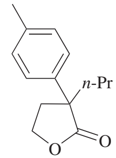
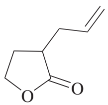
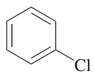
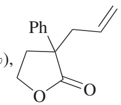
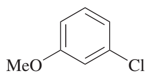
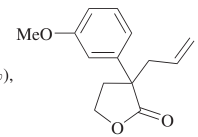
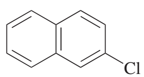
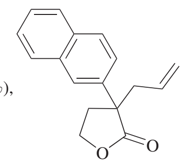
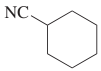
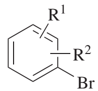
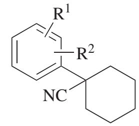
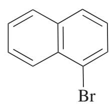
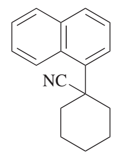
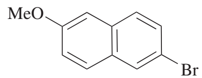
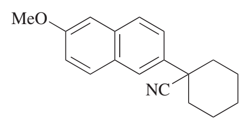
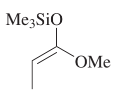
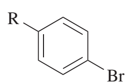
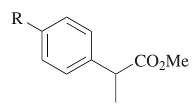
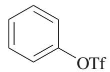
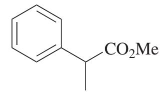
		1. Zn (1.5 eq), THF, rt, 0.5 h 2. $Pd(dba)_2$ (1 mol %), **L12** (1 mol %), THF, 6 h		68
	R	Temp		
	Me_2N	70°	(89)	
	MeO_2C	rt	(87)	
		$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), $ZnBr_2$ (15 mol %), NaHMDS (2.3 eq), toluene/THF (3:1), 60°, 17–20 h	 (84), 98% ee	33
		$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), $ZnBr_2$ (15 mol %), NaHMDS (2.3 eq), toluene/THF (3:1), 60°, 17–20 h	 (25), 83% ee	33
		$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), $ZnBr_2$ (15 mol %), NaHMDS (2.3 eq), toluene/THF (3:1), 60°, 17–20 h	 (56), 95% ee	33
		$Ni(cod)_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), $ZnBr_2$ (15 mol %), NaHMDS (2.3 eq), toluene/THF (3:1), 60°, 17–20 h	 (80), 89% ee	33

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7 		$Pd(OAc)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), $ZnCl_2$ (1.2 eq), THF, rt		80
	R¹ / R²			
	2-Me / H		(87)	
	4-Me_2N / H		(82)	
	4-MeO / H		(72)	
	4-NC / H		(71)	
	4-EtO_2C / H		(63)	
	4-*t*-Bu / H		(85)	
	4-PhCO / H		(75)	
	2-Me / 5-*t*-Bu		(91)	
		$Pd(OAc)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), $ZnCl_2$ (1.2 eq), THF, rt	 (91)	80
		$Pd(OAc)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), $ZnCl_2$ (1.2 eq), THF, rt	 (81)	80
		$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (5 mol %), **L1** (20 mol %), TlOAc (1 eq)	 R: H (70); O_2N (40); MeO (70)	100

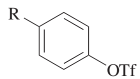


$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (x mol %), ligand (y mol %), LiOAc (2 eq), THF, reflux

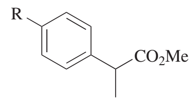


100

x	Ligand	y	Time (h)	
2	PPh_3	6	6	(15)
2	dppe	4	6	trace
2	dppp	4	12	(10)
2	dppb	4	6	(24)
2	**L1**	2	6	(13)
2	**L1**	4	6	(73)
1	**L1**	4	6	(72)
0.5	**L1**	4	6	(70)

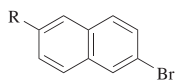


$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (x mol %), **L1** (y mol %), LiOAc (2 eq), reflux, 6 h

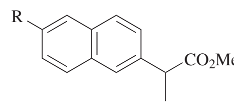


100

R	x	y	Solvent	
O_2N	2	8	DME	(25)
MeO	5	20	THF	(30)



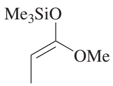
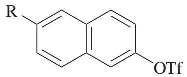
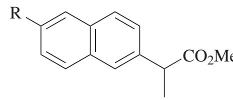
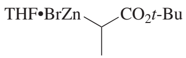
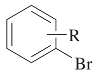
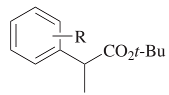
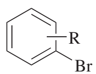
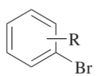
$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (5 mol %), **L1** (20 mol %), TlOAc (1 eq)



100

R	
H	(80)
MeO	(80)

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (*x* mol %), **L1** (*y* mol %), LiOAc (2 eq), reflux, 6 h		100
	R	*x* / *y* / Solvent		
	H	2 / 8 / THF	trace	
	H	2 / 8 / DME	(70)	
	MeO	5 / 20 / THF	(40)	
		$Pd(dba)_2$ (1–2 mol %), **L12**, THF	 **I**	22
	R	Temp		
	2-HO	rt	(95)	
	2-NC	rt	(85)	
	4-H_2N	rt	(67)	
	4-MeO_2C	rt	(87)	
	4-PhCO	70°	(89)	
		$Pd(dba)_2$ (1 mol %), **L12** (1 mol %), THF, 4 h	**I** R / Temp 2-NC / rt / (85)[e] 4-PhCO / 70° / (89) 4-MeO_2C / rt / (87)	76
		$[PdP(t\text{-Bu})_3Br]_2$ (0.5 mol %), THF, rt	**I** R / Time (h) 4-H_2N / 12 / (70) 4-MeO_2C / 4 / (81)	76

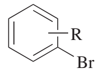
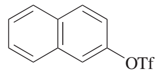
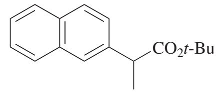
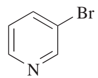
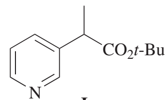
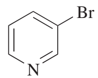
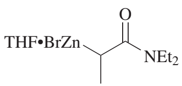
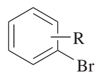
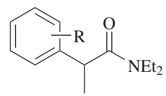
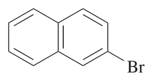
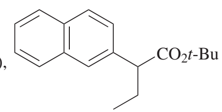
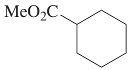
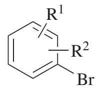
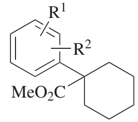
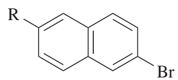
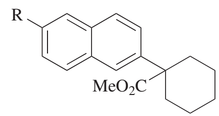
		$[PdP(t\text{-}Bu)_3Br]_2$ (0.5 mol %), KH (1.05 eq), THF, rt	**I** R / Time (h) 4-H_2N / 24 / (66) 4-HO / 4 / (95)	76
		$PdCl_2$, **L1** (15 mol %), THF, rt, overnight	 (18)	159
		$Pd(dba)_2$ (1–2 mol %), **L12**, THF, rt	 **I** (91)	22
		$Pd(dba)_2$ (1 mol %), **L12** (1 mol %), THF, 70°, 4 h	**I** (91)	76
		$Pd(dba)_2$ (2 mol %), **L12** (2 mol %), dioxane, rt, 6 h	 R 3-MeO (88) 4-O_2N (97) 4-EtO_2C (95) 4-CF_3 (88) 4-*t*-Bu (88)	68, 76
C_8 		$Pd(OAc)_2$ (3.0 mol %), **L17** (6.3 mol %), LiHMDS (2.5 eq), toluene, 80°, 2 h	 (81)	74

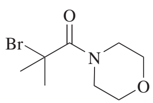
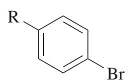
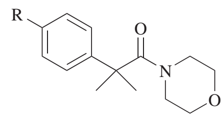
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8 		$Pd(dba)_2$ (x mol %), $P(t\text{-}Bu)_3$ (0.1–0.5 mol %), $LiNCy_2$ (1.3 eq), toluene, rt		75

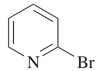
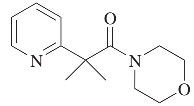
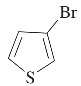
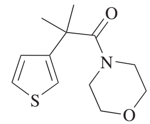
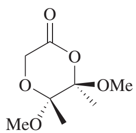
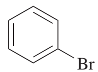
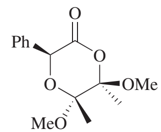
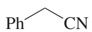
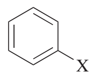
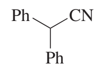
R^1	R^2	x	Time (h)	Yield (%)
3-MeO	H	0.1	20	(94)
3-F	H	0.1	24	(94)
3-Me	H	0.2	24	(92)
3-CF_3	H	0.5	8	(90)
4-MeO	H	0.2	12	(94)
4-F	H	0.1	24	(82)
4-Me	H	0.2	24	(95)
4-CF_3	H	0.5	10	(78)
4-Ph	H	0.5	18	(86)
3-F	4-Ph	0.5	18	(90)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(dba)_2$ (0.1 mol %), $P(t\text{-}Bu)_3$ (0.1 mol %), $LiNCy_2$ (1.3 eq), toluene, rt		75

R	Time (h)	Yield (%)
H	18	(91)
MeO	10	(97)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		1. Zn (1.5 eq), THF, rt, 0.5 h 2. $[PdP(t\text{-}Bu)_3Br]_2$ (2.5 mol %), THF/toluene (2:8), 12 h		68

R	Temp	Yield (%)
Me_2N	70°	(88)
MeO	rt	(97)
Cl	rt	(91)
CF_3	rt	(85)
t-Bu	rt	(93)

		1. Zn (1.5 eq), THF, rt, 0.5 h 2. $[PdP(t\text{-}Bu)_3Br]_2$ (2.5 mol %), THF/toluene (2:8), 70°, 12 h	 (92)	68
		1. Zn (1.5 eq), THF, rt, 0.5 h 2. $[PdP(t\text{-}Bu)_3Br]_2$ (2.5 mol %), THF/toluene (2:8), rt, 12 h	 (72)	68
		$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), $LiNCy_2$, toluene, rt or $Pd(dba)_2$, carbene[b], NaHMDS, toluene, rt	 (<5)	99
		$PdCl_2$ (5 mol %), ligand (10–20 mol %), Cs_2CO_3 (1.2 eq)		73

X	Ligand	Temp (°)	Time (h)	
Br	PPh_3	100	6	(47)
Br	PPh_3	130	2	(68)
I	none	100	2	(18)

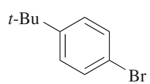
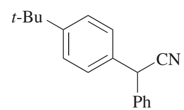
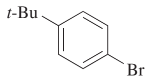
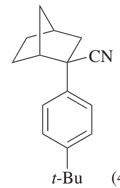
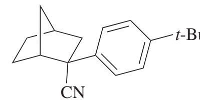
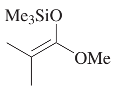
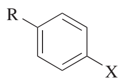
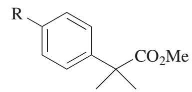
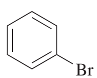
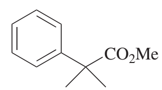
		$Pd(OAc)_2$ (2 mol %), **L23** (2 mol %), KO*t*-Bu (1.3 eq), toluene, 100°, 2 h	 (95)	26

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8				
		$Pd(OAc)_2$ (2 mol %), **L23** (2 mol %), NaHMDS (1.3 eq), toluene, 100°, 4 h	 (46) +  (23)	26
		$Pd(dba)_2$ (1 mol %), $P(t\text{-}Bu)_3$ (2 mol %), ZnF_2 (0.5 eq), DMF, 80°, 12 h		
	X R			
	Cl O_2N		$(95)^e$	99
	Cl MeO_2C		$(96)^e$	99
	Br H		(91)	99, 76
	Br O_2N		(98)	99, 76
	Br MeO		(88)	99, 76
	Br CF_3		(95)	76
	Br MeO_2C		(94)	99, 76, 22
	Br MeCO		(78)	99, 76, 22
	Br PhCO		(99)	99, 76, 22
		$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), additive (*x* eq), 80°, 12 h		99

Additive	x	Solvent	
none	—	DMF	(—)
LiCl	1	DMF	(—)
ZnF_2	0.5	DMF/DME (1:1)	(95)
ZnF_2	0.5	DMF	(100)
ZnF_2	0.25	DMF	(93)
$ZnCl_2$	0.5	DME	(0)
$ZnCl_2$	0.5	DMF/DME (1:1)	(—)
$ZnCl_2$	0.25	DMF/DME (1:1)	(66)
$ZnBr_2$	0.25	DMF/DME (1:1)	(38)

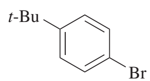
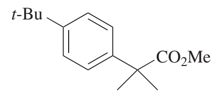
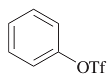
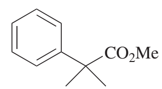
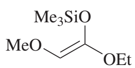
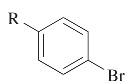
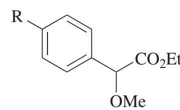
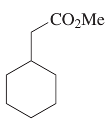
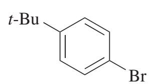
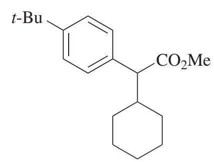
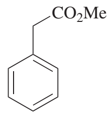
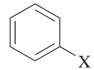
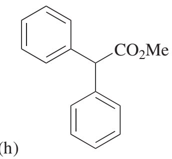
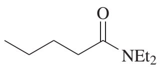
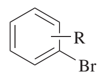
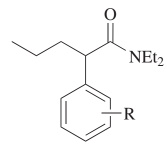
		$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), additive, dioxane, 100°, 12 h	 (0) Additive: none, $ZnCl_2$, CuCl	99
		[η^3-$C_4H_7Pd(OAc)]_2$ (5 mol %), **L1** (20 mol %), LiOAc (2 eq), THF, reflux, 6 h	 (0)	100
		$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), ZnF_2 (0.5 eq), DMF, 80°, 12 h	 R: MeO_2C (63); t-Bu (54)	99
C_9 		$Pd(dba)_2$ (5 mol %), **L47** (5 mol %), NaHMDS (2.3 eq), rt, 12 h	 (98)	77

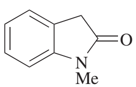
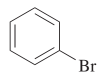
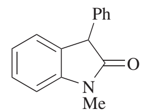
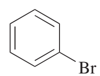
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9				
		$PdCl_2$ (5 mol %), ligand (10–20 mol %), Cs_2CO_3 (1.2 eq), additive		73

X	Ligand	Additive	Temp (°)	Time (h)	
Br	PPh_3	4 Å MS	130	4	(9)
I	none	none	100	50	(7)
I	none	4 Å MS	100	2	(60)

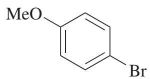
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		1. *s*-BuLi (1.2 eq), THF, –78°, 1 h 2. $ZnCl_2$ (2.4 eq), rt, 10 min 3. $Pd(dba)_2$ (3 mol %), **L12** (3 mol %), rt, 24 h		68

R	
2-MeO	(78)
4-MeO	(87)
4-NC	(97)
4-MeO_2C	(88)
4-*t*-Bu	(85)

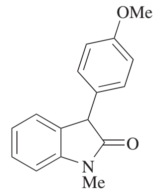
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$ (2 mol %), PCy_3 (3 mol %), NaO*t*-Bu, dioxane, 70°, 3 h	 (0) **I**	160
		$Pd(dba)_2$ (2 mol %), ligand (3 mol %), base (*x* eq), THF/toluene	**I**	160

Ligand	Base	*x*	Temp	Time (h)	
PCy_3	KHMDS	2.0	70°	3	(0)
$P(t\text{-Bu})_3 \cdot HBF_4$	KHMDS	2.0	70°	3	(<2)
L1	KHMDS	2.0	70°	3	(0)

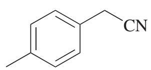
L20	KHMDS	2.0	70°	3	(20)
L21	NaH	1.1	70°	3	(44)
L21	NaHMDS	1.1	70°	3	(81)
L21	KHMDS	1.1	rt	3	(0)
L21	KHMDS	1.1	70°	0.5	(95)
L21	KHMDS	1.1	70°	1	(90)
L21	KHMDS	1.1	70°	3	(90)
L21	KHMDS	2.0	70°	3	(91)
L23	KHMDS	2.0	70°	3	(0)

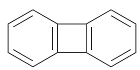


Pd(dba)$_2$ (2 mol %), **L21** (3 mol %), KHMDS, THF/toluene, 70°

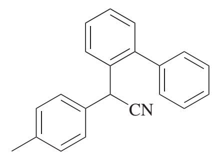


(—) 160

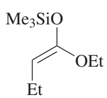


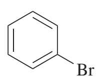


Pd(PPh$_3$)$_4$ (5 mol %), *p*-cresol (10 mol %), C_6D_6, 120°, 1 d

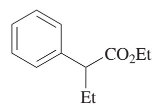


(85) 59





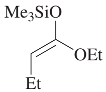
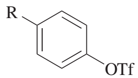
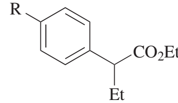
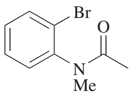
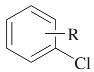
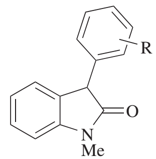
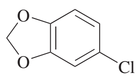
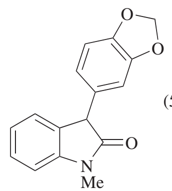
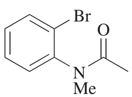
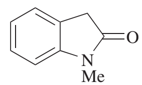
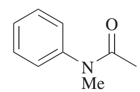
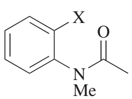
[η^3-C$_4$H$_7$Pd(OAc)]$_2$ (5 mol %), ligand (*x* mol %), TlOAc (1 eq)



Ligand	*x*	
PPh$_3$	15	(10)
dppe	20	trace
dppb	20	(8)
L1	20	(80)

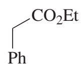
100

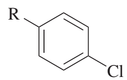
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 		$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (2 mol %), **L1** (10 mol %), LiOAc (2 eq), solvent, reflux, 6 h	 R / Solvent: H, THF (80); O_2N, DME (30)	100
		$Pd(OAc)_2$ (10 mol %), PCy_3 (10 mol %), NaO*t*-Bu (1.5 eq), dioxane, 70°, 12 h	 R: H (61); 2-MeO (60); 2-Me (56); 4-Me (55)	32
		$Pd(OAc)_2$ (10 mol %), PCy_3 (10 mol %), NaO*t*-Bu (1.5 eq), dioxane, 70°, 12 h	 (56)	32
		$Pd(dba)_2$ (5 mol %), **L23** (7.5 mol %), NaO*t*-Bu (1.5 eq), 2 h	 **I** (60) +  (1)	67
		$Pd(OAc)_2$ (5 mol %), ligand (5 mol %), NaO*t*-Bu (1.5 eq), dioxane	**I**	32

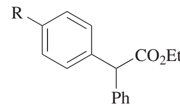
X	Ligand	Temp (°)	Time (h)	
Cl	PCy_3	70	5	(68)
Br	P(*t*-Bu)$_3$	50	10	(9)
Br	PCy_3	50	3	(62)
Br	PCy_3	50	10	(62)
Br	**L15**	50	10	(33)
Br	**L18**	50	10	(29)
Br	**L47**	50	10	(39)
Br	**L51**	50	10	(10)

C_{10}

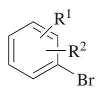




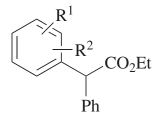
$Pd_2(dba)_3$ (1.5 mol %), **L14** (6.3 mol %), LiHMDS (2.5 eq), toluene, 80°



R	Time (h)		
MeO	1	(87)	74
Me	2	(82)	

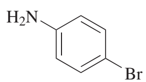


$Pd(OAc)_2$ (3.0 mol %), **L17** (6.3 mol %), LiHMDS (2.5 eq), toluene, 80°

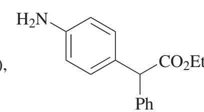


74

R^1	R^2	Time (h)	
3-Cl	H	1	(79)
4-Me_2N	H	3	(49)
4-Me	H	0.5	(85)
4-Et_2NCO	H	1	(88)
4-*t*-BuO_2C	H	0.5	(75)
2-Me	6-Me	2	(71)

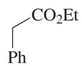
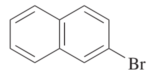
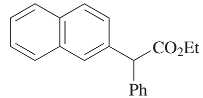
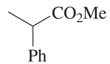
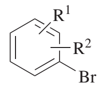
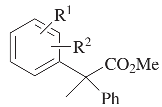
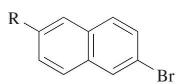
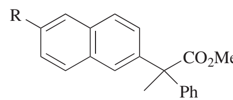
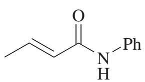
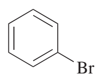
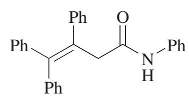


$Pd_2(dba)_3$ (1.5 mol %), **L14** (6.3 mol %), LiHMDS (2.5 eq), toluene, 80°, 0.2 h



(90) 74

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} 		$Pd(OAc)_2$ (3 mol %), **L17** (6.3 mol %), LiHMDS (2.5 eq), toluene, 80°, 3 h	 (88)	74
		$Pd(dba)_2$ (*x* mol %), $P(t\text{-}Bu)_3$ (0.5–1.0 mol %), $LiNCy_2$ (1.3 eq), toluene, rt		75
	R^1 / R^2	*x* / Time (h)		
	3-F / H	1.0 / 15	(82)	
	3-Me / H	0.5 / 8	(89)	
	4-F / H	1.0 / 15	(84)	
	4-Me / H	0.5 / 8	(87)	
	4-Ph / H	0.5 / 15	(93)	
	3-F / 4-Ph	1.0 / 15	(97)	
		$Pd(dba)_2$ (*x* mol %), $P(t\text{-}Bu)_3$ (0.5–1.0 mol %), $LiNCy_2$ (1.3 eq), toluene, rt, 15 h		75
	R	*x*		
	H	0.5	(78)	
	MeO	1.0	(82)	
		$Pd(OAc)_2$, $P(t\text{-}Bu)_3$, Cs_2CO_3, *o*-xylene	 (—)	47

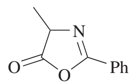
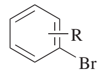
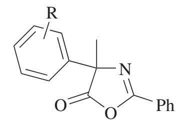
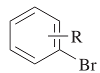
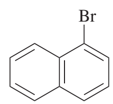
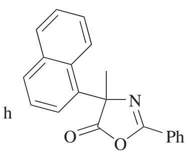
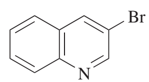
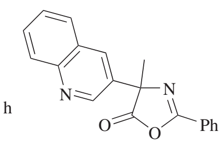
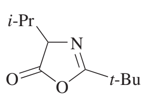
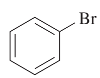
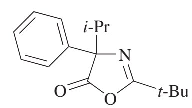
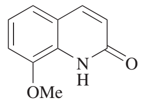
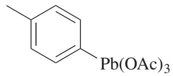
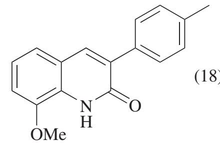
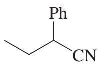
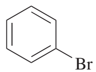
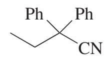
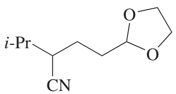
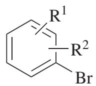
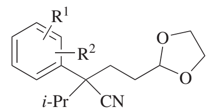
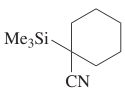
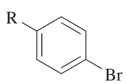
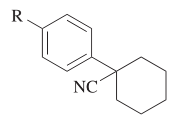
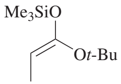
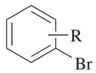
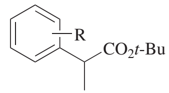
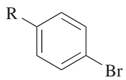
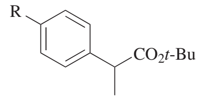
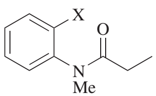
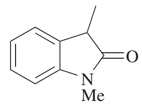
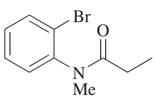
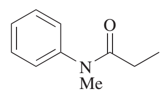
		Pd(OAc) (5 mol %), **L34** (5 mol %), K_3PO_4 (3.3 eq), toluene, 80°, 14 h	 **I** R | H (85) 3-CF_3 (75) 4-MeO (85)	79
		$Pd(dba)_2$ (5 mol %), **L34** (10 mol %), K_2CO_3 (3.3 eq), toluene, 100°, 14–36 h	**I** R | H (77) 2-Me (80) 3-CF_3 (66) 4-O_2N (62) 4-MeO (75) 4-F (75) 4-NC (58) 4-H_2C=CH (75) 4-*t*-Bu (83)	79
		$Pd(dba)_2$ (5 mol %), **L34** (10 mol %), K_2CO_3 (3.3 eq), toluene, 100°, 14–36 h	 (83)	79
		$Pd(dba)_2$ (5 mol %), **L34** (10 mol %), K_2CO_3 (3.3 eq), toluene, 100°, 14–36 h	 (40)	79
		Pd(OAc) (5 mol %), **L34** (10 mol %), K_3PO_4 (3.3 eq), toluene, 100°, 36 h	 (63)	79

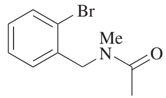
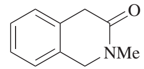
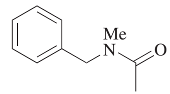
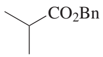
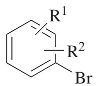
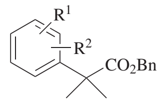
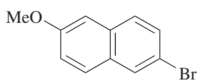
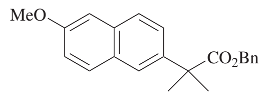
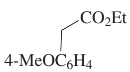
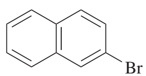
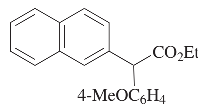
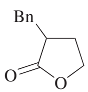
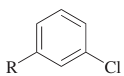
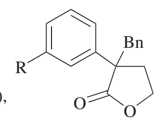
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

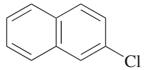
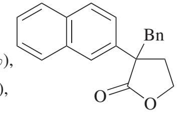
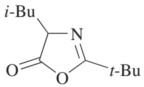
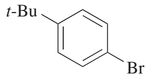
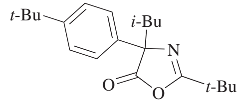
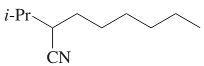
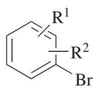
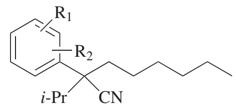
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} 		$Cu(OAc)_2$ (0.1 eq)	 (18)	133
		$Pd_2(dba)_3$•$CHCl_3$ (1 mol %), $P(t\text{-}Bu)_3$ (2 mol %), LiHMDS (1.3 eq), toluene, 70°, 3 h	 (89)	26
		$Pd(OAc)_2$ (2 mol %), ligand (4 mol %), $ZnCl_2$ (1.2 eq), THF, rt		80
	R^1 / R^2	Ligand		
	4-*t*-Bu / H	$P(t\text{-}Bu)_3$	(76)	
	4-*t*-Bu / H	**L33**	(80)	
	4-PhCO / H	$P(t\text{-}Bu)_3$	(86)	
	4-PhCO / H	**L33**	(77)	
	3-MeO / 4-MeO	$P(t\text{-}Bu)_3$	(82)	
		$Pd_2(dba)_3$ (2 mol %), **L23** (2 mol %), KF (1 eq), DMF, 90°, 24 h		80
	R			
	H		(68)	
	MeO		(77)	
	EtO_2C		(84)	
	t-Bu		(62)	

		Pd(dba)$_2$ (1 mol %), P(*t*-Bu)$_3$ (2 mol %), ZnF$_2$ (0.5 eq), DMF, 80°, 12 h	 R — 2-NC (75); 3-NC (67); 4-O_2N (76); 4-MeO_2C (80); 4-MeCO (68)	76, 99
		Pd(dba)$_2$ (1 mol %), P(*t*-Bu)$_3$ (2 mol %), ZnF$_2$ (0.5 eq), DMF, 80°, 12 h	 R — MeO_2C (80); MeOC (68)	22
		Pd(OAc)$_2$ (5 mol %), ligand (5 mol %), NaO*t*-Bu (1.5 eq), dioxane	 **I**	32
		Pd(dba)$_2$ (5 mol %), **L23** (7.5 mol %), NaO*t*-Bu (1.5 eq), 15 h	**I** (52) +  (8)	67

X	Ligand	Temp (°)	Time (h)	**I**
Cl	PCy$_3$	70	24	(8)
Br	P(*t*-Bu)$_3$	50	10	(3)
Br	PCy$_3$	50	3	(10)
Br	PCy$_3$	50	10	(6)
Br	**L15**	50	10	(10)
Br	**L18**	50	10	(14)
Br	**L47**	50	10	(29)
Br	**L51**	50	10	(11)

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} 		$Pd(dba)_2$ (5 mol %), **L23** (7.5 mol %), NaO*t*-Bu (1.5 eq), dioxane, 100°, 0.5 h	 (5) +  (7)	67
C_{11} 		$Pd(dba)_2$(1.0 mol %), $P(t\text{-}Bu)_3$ (1.0 mol %), $LiNCy_2$ (1.8 eq), toluene, rt, 12 h		75
	R^1 / R^2			
	3-Me / H		(93)	
	3-CF_3 / H		(80)	
	4-MeO / H		(83)	
	4-F / H		(82)	
	4-Me / H		(90)	
	3-F / 4-Ph		(90)	
		$Pd(dba)_2$ (1.0 mol %), $P(t\text{-}Bu)_3$ (1.0 mol %), $LiNCy_2$ (1.8 eq), toluene, rt, 12 h	 (88)	75
		$Pd(OAc)_2$ (3 mol %), **L17** (6.3 mol %), LiHMDS (2.5 eq), toluene, 80°, 0.5 h	 (83)	74
		$Ni(cod)_2$ (10 mol %), (*S*)-**L23** (17 mol %), $ZnBr_2$ (15 mol %), NaHMDS (1.15 eq), toluene/THF (3:1), 80°, 17–20 h	 R / % ee: Me_2N (58) 96; MeO (63) 94	33

		Ni(cod)$_2$ (5 mol %), (*S*)-**L23** (8.5 mol %), ZnBr$_2$ (15 mol %), NaHMDS (1.15 eq), toluene/THF (3:1), 60°, 17–20 h	 (91), 96% ee	33
		Pd(OAc) (5 mol %), **L35** (10 mol %), K_3PO_4 (3.3 eq), toluene, 80°, 36 h	 (82)	79
		Pd(OAc)$_2$ (2 mol %), ligand (4 mol %), ZnCl$_2$ (1.2 eq), THF, rt		80

R^1	R^2	Ligand	
4-Me$_2$N	H	P(*t*-Bu)$_3$	(69)
4-MeO	H	P(*t*-Bu)$_3$	(72)
4-EtO$_2$C	H	P(*t*-Bu)$_3$	(47)
4-EtO$_2$C	H	**L33**	(55)
4-*t*-Bu	H	P(*t*-Bu)$_3$	(85)
4-PhCO	H	P(*t*-Bu)$_3$	(78)
3-MeO	4-MeO	P(*t*-Bu)$_3$	(68)
3-MeO	4-MeO	**L33**	(72)

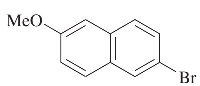
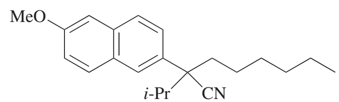
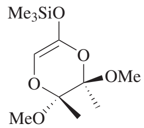
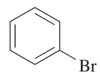
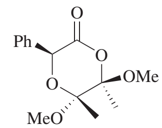
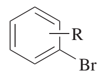
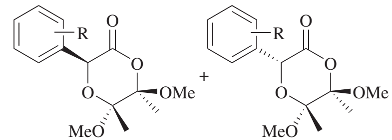
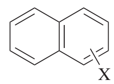
		Pd(OAc)$_2$ (2 mol %), **L33** (4 mol %), ZnCl$_2$ (1.2 eq), THF, rt	 (81)	80

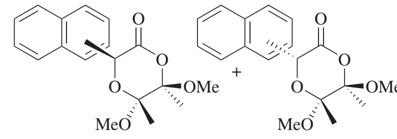
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

	Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}			$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), ZnF_2, DMF, 80° or $Zn(Ot\text{-}Bu)_2$, DMF, rt	 (67–73)	99
			$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), zinc additive (*x* eq), DMF, 12 h	 **I** + **II**	99

R	Zinc Additive	*x*	Temp	**I + II**	**I:II**
H	ZnF_2	0.5	80°	(67)	>50:1
H	$Zn(Ot\text{-}Bu)_2$	0.25	rt	(73)	>50:1
2-Cl	ZnF_2	1	80°	(78)	20:1
$3\text{-}O_2N$	ZnF_2	1	80°	(64)	>26:1
$3\text{-}O_2N$	$Zn(Ot\text{-}Bu)_2$	0.5	rt	(89)	>50:1
$3\text{-}O_2N$	$Zn(Ot\text{-}Bu)_2$	0.25	rt	(78)	>50:1
3-MeCO	ZnF_2	1	80°	(76)	25:1
4-MeO	ZnF_2	0.5	80°	(57)	>50:1
$4\text{-}MeO_2C$	$Zn(Ot\text{-}Bu)_2$	0.5	rt	(95)	>50:1
$4\text{-}MeO_2C$	$Zn(Ot\text{-}Bu)_2$	0.25	rt	(80)	>50:1



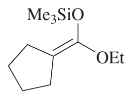
Pd(dba)$_2$ (5 mol %),
P(t-Bu)$_3$ (10 mol %), ZnF$_2$ (x eq),
DMF, 80°, 12 h

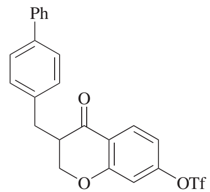


I + **II**

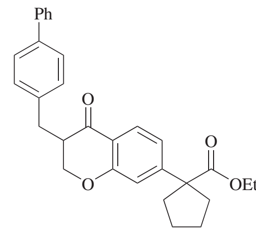
99

X	x	**I + II**	**I:II**
1-Br	1	(72)	>50:1
2-Br	0.5	(58)	>50:1

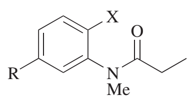




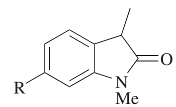
PdCl$_2$(PhCN)$_2$, P(o-tol)$_3$,
ZnCl$_2$, DMF/DME (1:1), 80°



(87) 161

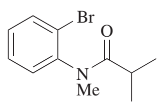


Pd$_2$(dba)$_3$ (1.5–3 mol %),
L52 (3–6 mol %),
LiHMDS (1.5–2 eq), THF, 68°, 1–4 h

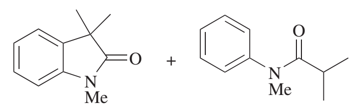


X	R	
Cl	Me	(43)
Br	MeO	(67)
Br	Me	(80)

69



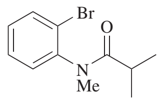
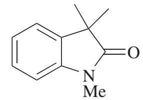
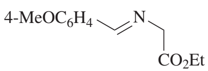
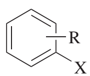
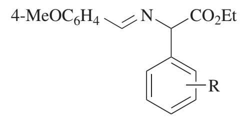
Pd(dba)$_2$ (5 mol %), **L23** (7.5 mol %),
NaOt-Bu (1.5 eq), 3 h



(75) + (2)

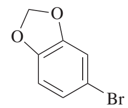
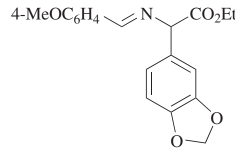
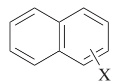
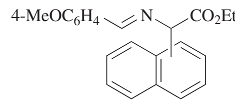
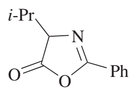
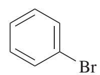
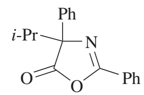
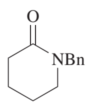
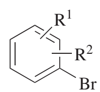
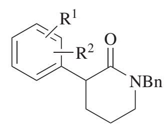
67

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11} 		Catalyst (5 mol %), ligand (5 mol %), NaO*t*-Bu (1.5 eq), dioxane		32
C_{12} 		$Pd(dba)_2$ (2 mol %), P(*t*-Bu)$_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 20 h		77

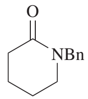
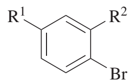
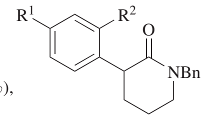
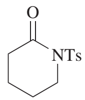
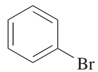
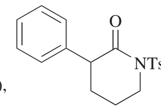
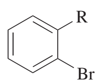
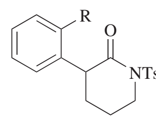
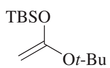
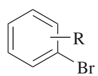
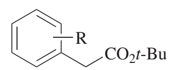
Catalyst	Ligand	Temp (°)	Time (h)	
$Pd(dba)_2$	P(*t*-Bu)$_3$	100	5	(62)
$Pd(dba)_2$	PCy_3	50	3	(62)
$Pd(dba)_2$	PCy_3	100	1	(82)
$Pd(dba)_2$	**L3**	100	5	(41)
$Pd(dba)_2$	**L4**	100	4	(42)
$Pd(dba)_2$	**L23**	100	3	(53)
$Pd(OAc)_2$	P(*t*-Bu)$_3$	50	3	(21)
$Pd(OAc)_2$	PCy_3	50	3	(99)
$Pd(OAc)_2$	**L15**	50	3	(67)
$Pd(OAc)_2$	**L18**	50	3	(11)
$Pd(OAc)_2$	**L47**	50	3	(99)
$Pd(OAc)_2$	**L51**	50	3	(99)

X	R	Temp (°)	
Cl	H	120	(67)
Cl	4-CF_3	120	(67)
Br	H	100	(75)
Br	2-Me	100	(72)
Br	4-MeO	100	(71)
Br	4-F	100	(67)
Br	4-CF_3	100	(73)
Br	4-Ph	100	(80)

		$Pd(dba)_2$ (2 mol %), P(t-Bu)$_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 100°, 20 h		(71)	77
		$Pd(dba)_2$ (2 mol %), P(t-Bu)$_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 100°, 20 h		X: 1-Br (74); 2-Br (74)	77
		Pd(OAc) (5 mol %), **L3** (10 mol %), K_3PO_4 (3.3 eq), toluene, 80°, 14 h		(29)	79
		1. LiHMDS (2.0 eq), $ZnCl_2$ (2.2 eq), –20° 2. $Pd(dba)_2$ (5 mol %), **L17** (7.5 mol %), THF, 65°			72

R^1	R^2	
H	H	(98)
2-Me	H	(46)
3-MeO	H	(50)
4-MeO	H	(77)
4-Me	H	(52)
2-MeO	4-MeO	(84)
2-Me	4-Me	(0)

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12} 		1. LiHMDS (2.5 eq), $ZnCl_2$ (2.2 eq), –20° 2. $Pd(OAc)_2$ (3 mol %), **L17** (6.3 mol %), toluene, 80°	 R^1 / R^2 H / H (86) Me / H (35) MeO / MeO (16)	72
		1. LiHMDS (*x* eq), ZnX_2 (*y* eq), –20° 2. Pd(OAc) (5 mol %), **L17** (7.5 mol %), THF, rt		72
		x / ZnX_2 / *y* 2.0 / none / — 0.95 / $ZnCl_2$ / 1.1 2.0 / $ZnCl_2$ / 2.2 2.0 / $ZnBr_2$ / 2.2	 (22) (48) (48) (0)	
		1. LiHMDS (2.0 eq), ZnX_2 (2.2 eq), –20° 2. $Pd(dba)_2$ (5 mol %), **L17** (7.5 mol %), THF, 65°	 R H (92) Me (41)	72
		$PdCl_2[P(o\text{-tol})_3]_2$ (2–5 mol %), Bu_3SnF (2 eq), benzene, reflux	 **I**	98
	R 2-MeO 4-MeO 4-MeCO 4-MeO_2C	Time (h) 20 22 6 22	 (42) (51) (80) (82)	

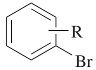
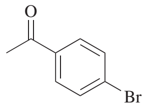
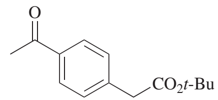
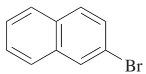
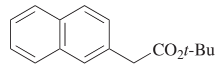
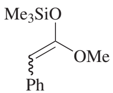
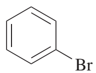
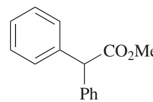
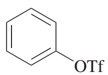
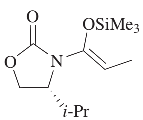
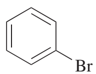
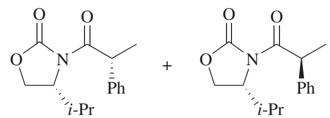
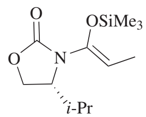
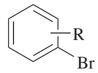
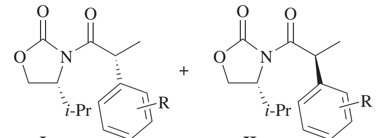
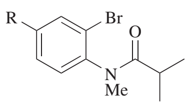
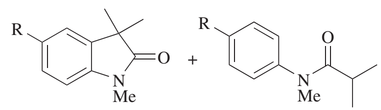
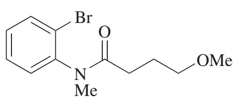
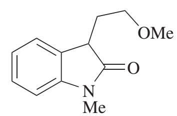
		$PdCl_2[P(o\text{-tol})_3]_2$ (2–5 mol %), Bu_3SnF (2 eq), THF, reflux	**I** R / Time (h) 2-MeO / 22 / (81) 4-MeO / 28 / (95) 4-MeCO / 9 / (76) 4-MeO_2C / 22 / (73)	98
		$PdCl_2[P(o\text{-tol})_3]_2$ (2–5 mol %), CuF_2 (2 eq), benzene, reflux, 6 h	 (87)	98
		$PdCl_2[P(o\text{-tol})_3]_2$ (2–5 mol %), Bu_3SnF (2 eq), THF, reflux, 16 h	 (75)	98
		$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (5 mol %), **L1** (20 mol %), TlOAc (1 eq)	 (20) **I**	100
		$[\eta^3\text{-}C_4H_7Pd(OAc)]_2$ (5 mol %), **L1** (20 mol %), LiOAc (2 eq), THF, reflux, 6 h	**I** (60)	100
		$Pd(dba)_2$, $P(t\text{-Bu})_3$, ZnF_2, DMF, 80°	 **I** **II** **I** + **II** (67), **I**:**II** = 88:12	76, 22
		$Pd(dba)_2$, $P(t\text{-Bu})_3$, $Zn(Ot\text{-Bu})_2$, DMF, rt	**I** + **II** (70), **I**:**II** = 91:9	22

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12} 		$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), ZnF_2 (0.5 eq), DMF, 80°, 12 h	 I + II	99
	R		**I + II** / **I:II**	
	H		(67) 87:13	
	H[f]		(70) 91:9	
	2-Me		(78) 92:8	
	3-MeCO		(75) 84:16	
	4-NC		(65) 77:23	
	4-*t*-Bu		(57) 83:17	
		$Pd(dba)_2$ (5 mol %), **L23** (7.5 mol %), NaO*t*-Bu (1.5 eq)	 I + II	67
R		**Time (h)**	**I** / **II**	
MeO		12	(80) (2)	
NC[g]		4	(83) (1)	
		$Pd_2(dba)_3$ (1.5–3 mol %), **L52** (3–6 mol %), LiHMDS (1.5–2 eq), THF, 68°, 1–4 h	 (82)	69

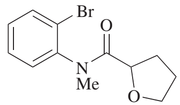
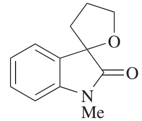
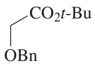
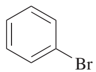
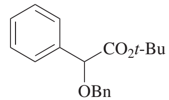
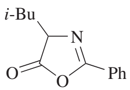
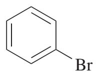
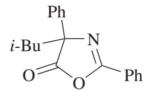
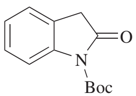
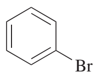
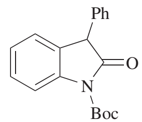
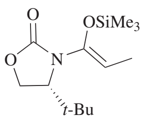
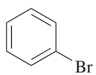
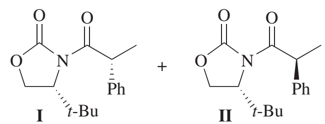
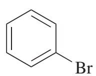
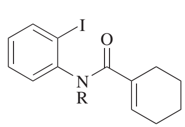
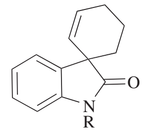
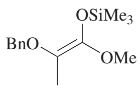
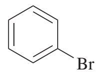
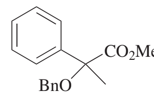
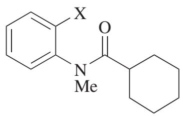
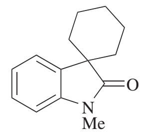
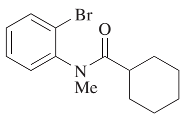
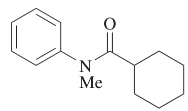
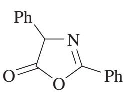
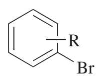
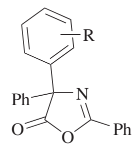
Substrate	Aryl Halide	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), NaO*t*-Bu (1.5 eq), dioxane, 50°, 24 h	 (98)	32
C_{13}				
		$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), $LiNCy_2$, toluene, rt or $Pd(dba)_2$, carbene[b], NaHMDS, toluene, rt	 (<20)	99
		Pd(OAc) (5 mol %), **L35** (10 mol %), K_3PO_4 (3.3 eq), toluene, 80°, 14 h	 (47)	79
		$Pd(dba)_2$ (2 mol %), **L20** (3 mol %), KHMDS (1.1 eq), THF/toluene, 70°, 30 min	 (60)	160
		$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), ZnF_2 (0.5 eq), additive (0.25 eq), DMF, 12 h		99
		Additive / Temp none / 80° $Zn(Ot\text{-}Bu)_2$ / rt	**I + II** / **I**:**II** (58) / 92:8 (61) / 95:5	
		$Pd(dba)_2$, $P(t\text{-}Bu)_3$, $Zn(Ot\text{-}Bu)_2$, DMF, rt	**I + II** (61), **I**:**II** = 95:5	22

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}				
		$Pd(OAc)_2$, PPh_3, $AgNO_3$, Et_3N, rt	 (68)[i]	111
C_{14}				
		$Pd(dba)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), ZnF_2 (0.5 eq), DMF, 80°, 12 h	 (75)	99
		$Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), NaO*t*-Bu (1.5 eq), dioxane	 **I** X | Temp (°) | Time (h) | Cl | 70 | 4 | (90) Br | 50 | 1 | (93)	32
		$Pd(dba)_2$ (5 mol %), **L23** (7.5 mol %), NaO*t*-Bu (1.5 eq), 4 h	**I** (82) +  (1)	67
C_{15}				
		$Pd(OAc)$ (5 mol %), **L12** (5 mol %), K_3PO_4 (3.3 eq), toluene, 80°, 14 h	 **I** R | H | (94) 3-CF_3 | (92) 4-MeO | (75)	79

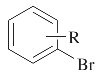
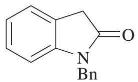
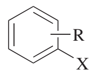
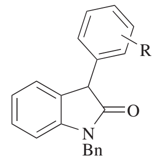
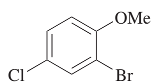
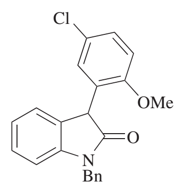
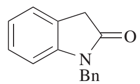
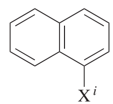
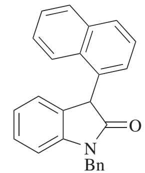
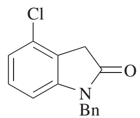
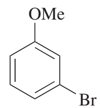
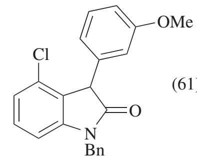
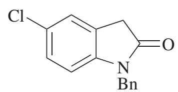
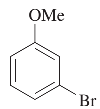
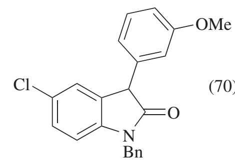
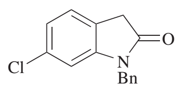
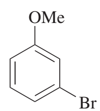
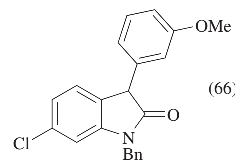
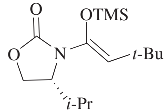
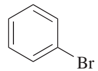
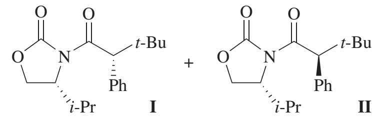
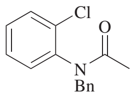
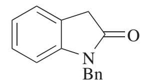
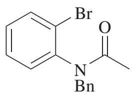
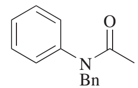
		Pd(dba)$_2$ (5 mol %), **L35** (10 mol %), K_2CO_3 (3.3 eq), toluene, 100°, 14 h	**I**		R		79
					H	(55)	
					3-CF_3	(55)	
					4-MeO	(30)	
		Pd(dba)$_2$ (2 mol %), **L21** (3 mol %), KHMDS (1.1 eq), THF/toluene, 70°, 30 min		X	R		160
				Cl	H	(70)	
				Cl	2-Me	(60)	
				Cl	4-MeO	(70)	
				Cl	4-CF_3	(66)	
				Br	H	(91)	
				Br	2-Me	(74)	
				Br	3-MeO	(85)	
				Br	3-Cl	(73)	
				Br	3-Me	(77)	
				Br	4-MeO	(85)	
				Br	4-Cl	(70)	
				Br	4-CF_3	(80)	
				Br	4-*t*-Bu	(79)	
				OTf	H	(85)	
				OTf	4-Cl	(70)	
		Pd(dba)$_2$ (2 mol %), **L21** (3 mol %), KHMDS (1.1 eq), THF/toluene, 70°, 30 min		(77)			160

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15}				
		$Pd(dba)_2$ (2 mol %), **L21** (3 mol %), KHMDS (1.1 eq), THF/toluene, 70°, 30 min	 (80)	160
		$Pd(dba)_2$ (2 mol %), **L21** (3 mol %), KHMDS (1.1 eq), THF/toluene, 70°, 2.5 h	 (61)	160
		$Pd(dba)_2$ (2 mol %), **L21** (3 mol %), KHMDS (1.1 eq), THF/toluene, 70°, 2.5 h	 (70)	160
		$Pd(dba)_2$ (2 mol %), **L21** (3 mol %), KHMDS (1.1 eq), THF/toluene, 70°, 1 h	 (66)	160

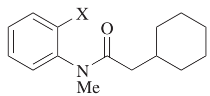
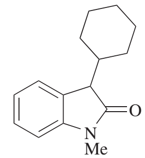
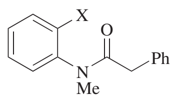
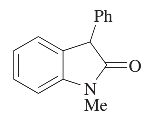
		Pd(dba)$_2$ (5 mol %), P(t-Bu)$_3$ (10 mol %), ZnF$_2$ (0.5 eq), DMF, 80°, 12 h	 **I** + **II** (35), **I**:**II** = 89:11	99
		Pd(OAc)$_2$ (5 mol %), PCy$_3$ (5 mol %), NaOt-Bu (1.5 eq), dioxane, 70°, 5 h	 (64) **I**	32
		Pd(dba)$_2$ (5 mol %), ligand (7.5 mol %), base (1.5 eq), THF	**I** +  **II**	67

Ligand	Base	Temp (°)	Time (h)	I	II
L1	KHMDS	75	19	trace	(14)
L1	NaOt-Bu	75	19	(56)	(13)
L1	NaOt-Bu	100	3	(53)	(9)
L23	NaOt-Bu	75	23	(65)	(2)
L23	NaOt-Bu	100	3	(57)	(2)

Pd(dba)$_2$ (5 mol %), ligand (7.5 mol %), NaOt-Bu (1.5 eq), dioxane — **I** + **II** — 67

Ligand	Temp (°)	Time (h)	I	II
P(o-tol)$_3$	100	4	(6)	(—)
L1	75	23	(10)	(1)
L1	100	3	(43)	(10)
L23	75	23	(50)	(1)
L23	100	3	(64)	(1)

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15}				
		$Pd(OAc)_2$ (5 mol %), ligand (5 mol %), NaO*t*-Bu (1.5 eq), dioxane		32
X		Ligand / Temp (°) / Time (h)		
Cl		PCy_3 / 70 / 24	(35)	
Cl		**L31** / 70 / 24	(64)	
Br		P(*t*-Bu)$_3$ / 50 / 10	(34)	
Br		PCy_3 / 50 / 3	(43)	
Br		PCy_3 / 50 / 10	(45)	
Br		**L15** / 50 / 10	(36)	
Br		**L18** / 50 / 10	(31)	
Br		**L47** / 50 / 10	(77)	
Br		**L47** / 50 / 20	(75)	
Br		**L51** / 50 / 10	(56)	
		$Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), NaO*t*-Bu (1.5 eq), dioxane, 3 h	 **I**	32
X		Temp (°)		
Cl		70	(89)	
Br		50	(92)	
		$Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), NaO*t*-Bu (1.5 eq), dioxane	**I**	32

X	Temp (°)	Time (h)	
Cl	70	24	(69)
Br	50	1.5	(82)

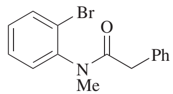
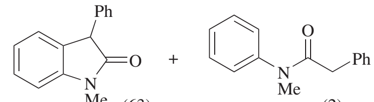
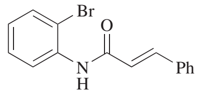
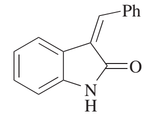
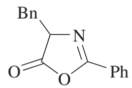
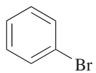
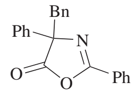
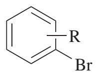
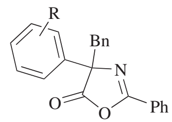
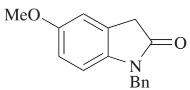
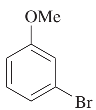
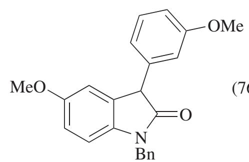
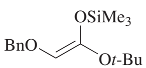
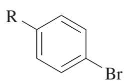
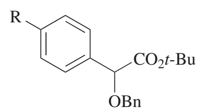
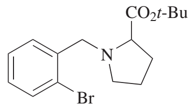
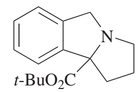
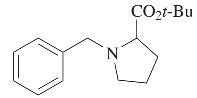
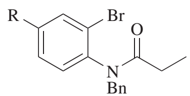
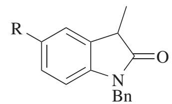
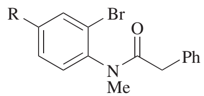
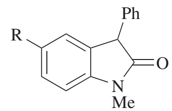
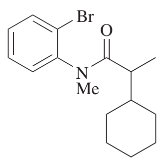
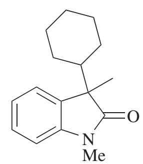
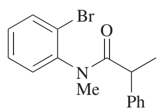
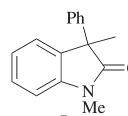
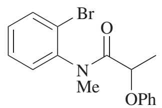
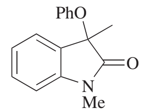
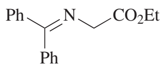
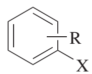
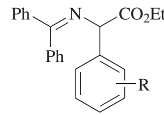
Reactant	Aryl Halide	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(dba)_2$ (5 mol %), **L23** (7.5 mol %), NaO*t*-Bu (1.5 eq), 10 h	 (63) + (2)	67
		$Pd(OAc)_2$, $P(o\text{-tol})_3$, Et_3N	 (—)	111
C_{16}				
		$Pd(dba)_2$ (5 mol %), **L35** (10 mol %), K_2CO_3 (3.3 eq), toluene, 100°, 14 h	 (65)	79
		Pd(OAc) (5 mol %), **L35** (5 mol %), K_3PO_4 (3.3 eq), toluene, 80°, 14 h	 R: H (78); 3-CF_3 (74)	79
		$Pd(dba)_2$ (2 mol %), **L21** (3 mol %), KHMDS (1.1 eq), THF/toluene, 70°, 30 min	 (76)	160
		$Pd(dba)_2$ (5 mol %), $P(t\text{-Bu})_3$ (10 mol %), ZnF_2 (0.5 eq), DMF, 80°, 12 h	 R: H (85); O_2N (79); MeO (87)	99

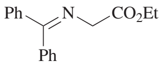
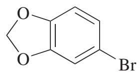
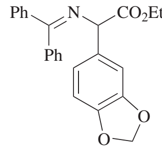
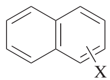
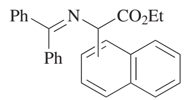
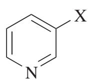
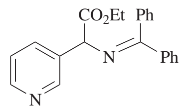
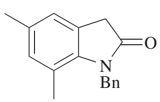
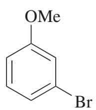
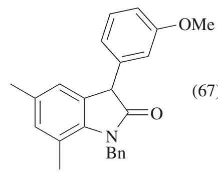
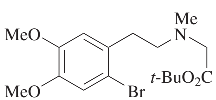
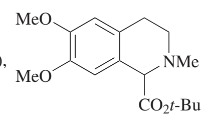
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16} 		$Pd_2(dba)_3$ (*x* mol %), ligand (*y* mol %), LiO*t*-Bu (2 eq), dioxane, 85°, 20 h *x* / Ligand / *y* 3.8 / PCy_3 / 8 2.3 / **L17** / 2.5	 **I** +  **II** **I** / **II** (55) / (8) (62) / (—)	78
		$Pd_2(dba)_3$ (1.5–3 mol %), **L52** (3–6 mol %), LiHMDS (1.5–2 eq), THF, 68°, 1–4 h	 R H (90) F (40)	69
		$Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), NaO*t*-Bu (1.5 eq), dioxane, 50°	 R / Time (h) MeO / 4 / (83) NC / 9 / (66)	32
		$Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), NaO*t*-Bu (1.5 eq), dioxane, 50°, 14 h	 (64)	32
		$Pd(dba)_2$ (*x* mol %), ligand, rt, 24 h	 **I** *x* / Ligand / / % ee 10 / **L49** / (94) / 34 5 / **L50** / (74) / 57	32

	Pd(OAc)$_2$ (5 mol %), PCy$_3$ (5 mol %), NaO*t*-Bu (1.5 eq), dioxane, 50°, 14 h	**I** (99)	32
	Pd(OAc)$_2$ (5 mol %), PCy$_3$ (5 mol %), NaO*t*-Bu (1.5 eq), dioxane	 (0)	32
C_{17} 	 Pd(dba)$_2$ (2 mol %), P(*t*-Bu)$_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 20 h		77

X	R	Temp (°)	
Cl	H	120	(82)
Cl	2-Me	120	(81)
Cl	4-MeO	120	(83)
Cl	4-F	120	(83)
Cl	4-NC	120	(85)
Cl	4-CF_3	120	(84)
Br	H	100	(88)
Br	2-MeO	100	(89)
Br	2-Me	100	(84)
Br	4-MeO	100	(85)
Br	4-PhO	100	(90)
Br	4-F	100	(86)
Br	4-NC	100	(89)
Br	4-MeO_2C	100	(89)
Br	4-CF_3	100	(86)
Br	4-Ph	100	(92)

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{17}				
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 20 h	 (87)	77
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 100°, 20 h	 X: 1-Br (87); 2-Br (89)	77
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 20 h	 X, Temp (°): Cl, 120 (80); Br, 100 (85)	77
		$Pd(dba)_2$ (2 mol %), **L21** (3 mol %), KHMDS (1.1 eq), THF/toluene, 70°, 30 min	 (67)	160
		$Pd_2(dba)_3$ (2.3 mol %), **L13** (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 85°, 3 h	 (75)	78

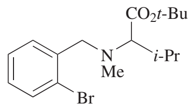
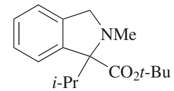
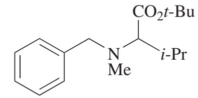
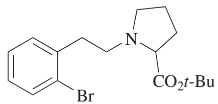
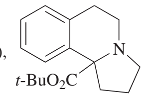
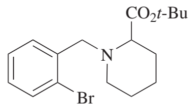
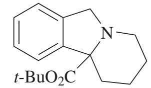
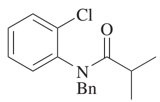
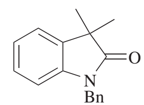
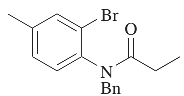
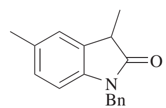
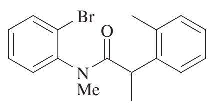
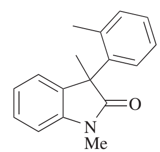
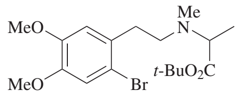
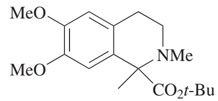
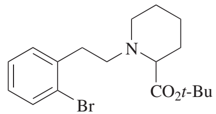
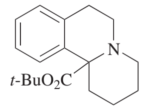
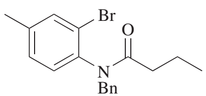
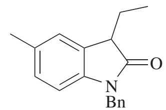
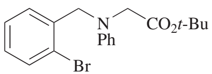
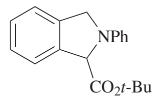
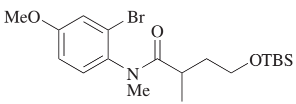
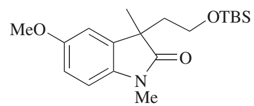
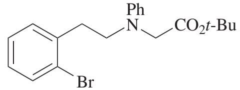
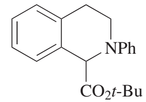
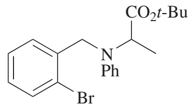
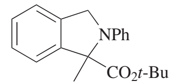
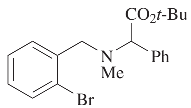
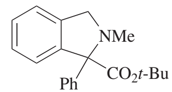
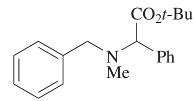
	$Pd_2(dba)_3$ (3.8 mol %), **L13** (8 mol %), LiO*t*-Bu (2 eq), dioxane, 110°, 48 h	 (51) +  (8)	78
	$Pd_2(dba)_3$ (2.3 mol %), **L17** (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 90°, 24 h	 (74)	78
	$Pd_2(dba)_3$ (2.3 mol %), ligand (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 85°, 20 h	 Ligand PCy_3 (39) **L17** (84)	78
	$Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), NaO*t*-Bu (1.5 eq), dioxane, 70°, 3 h	 (93)	32
	$Pd_2(dba)_3$ (1.5–3 mol %), **L52** (3–6 mol %), LiHMDS (1.5–2 eq), THF, 68°, 1–4 h	 (83)	69
	$Pd(dba)_2$ (*x* mol %), ligand, rt, 24 h	 *x* Ligand % ee 10 **L49** (97) 33 5 **L50** (95) 42	32

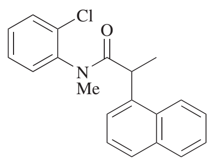
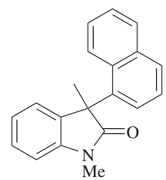
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18} 		$Pd_2(dba)_3$ (2.3 mol %), **L13** (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 100°, 24 h	 (66)	78
		$Pd_2(dba)_3$ (2.3 mol %), ligand (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 90°, 24 h	 Ligand: **L13** (81); **L17** (66)	78
		$Pd_2(dba)_3$ (1.5–3 mol %), **L52** (3–6 mol %), LiHMDS (1.5–2 eq), THF, 68°, 1–4 h	 (62)	69
C_{19} 		$Pd_2(dba)_3$ (2.3 mol %), **L17** (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 85°, 1 h	 (79)	78
		See table		70

Catalyst	Ligand	Base	Solvent	Temp (°)	
$Pd(OAc)_2$	(*R*)-**L23**	LiHMDS	THF	68	(60), 11% ee
$Pd_2(dba)_3$	P(*t*-Bu)$_3$	LiHMDS	THF	68	(<1)
$Pd_2(dba)_3$	**L1**	LiHMDS	THF	68	(<1)
$Pd_2(dba)_3$	**L23**	LiHMDS	THF	68	(50)
$Pd_2(dba)_3$	**L23**	KHMDS	toluene	70	(<5)

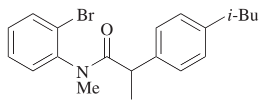
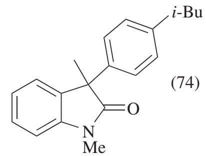
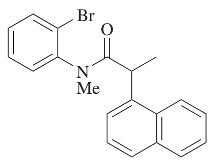
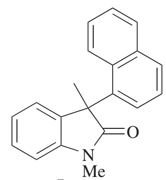
C_{20} 	$Pd_2(dba)_3$ (2.3 mol %), **L13** (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 85°, 8 h	 (79)	78
	$Pd_2(dba)_3$ (2.3 mol %), **L17** (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 85°, 24 h	 **I** (91)	78
	$Pd_2(dba)_3$ (2.3 mol %), PCy_3 (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 85°, 24 h	**I** (89)	78
	$Pd_2(dba)_3$ (2.3 mol %), ligand (2.5 mol %), LiO*t*-Bu (2 eq), dioxane	 **I** +  **II**	78

Ligand	Temp (°)	Time (h)	I	II
none	90	17	(35)	(5)
L13	50	20	(65)	(—)
L13	70	3.5	(95)	(—)
L13	90	2	(99)	(—)

	Pd(dba)$_2$ (10 mol %), ligand		32

Ligand	Temp (°)	Time (h)		% ee
L49	50	26	(91)	69
L50	0	48	(5)	58

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20}				
		$Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), NaO*t*-Bu (1.5 eq), dioxane, 50°, 14 h	 **I** (74)	32
		$Pd(dba)_2$ (*x* mol %), ligand, rt	**I** (see table below)	32
		Catalyst (5 mol %), **L49** (5 mol %), base (1.5 eq)	 **I** (see table below)	32

Pd(dba)$_2$ (*x* mol %), ligand, rt → **I**:

x	Ligand	Time (h)		% ee
10	**L49**	24	(73)	40
5	**L50**	20	(87)	50

Catalyst (5 mol %), **L49** (5 mol %), base (1.5 eq) → **I**:

Catalyst	Base	Solvent	Temp	Time (h)		% ee
$Pd(OAc)_2$	NaO*t*-Bu	toluene	50°	14	(50)	34
$Pd(OAc)_2$	NaO*t*-Bu	*m*-xylene	50°	14	(60)	28
$Pd(OAc)_2$	NaO*t*-Bu	THF	50°	14	(55)	42
$Pd(OAc)_2$	NaO*t*-Bu	DME	50°	14	(64)	55
$Pd(OAc)_2$	NaO*t*-Bu	diglyme	50°	14	(61)	51
$Pd(dba)_2$	LiO*t*-Bu	DME	50°	36	(20)	50
$Pd(dba)_2$	NaO*t*-Bu	DME	rt	14	(93)	67
$Pd(dba)_2$	NaO*t*-Bu	DME	50°	16	(89)	59
$Pd(dba)_2$	KO*t*-Bu	DME	50°	36	(5)	11
$Pd(dba)_2$	NaHMDS	DME	50°	14	(56)	48
$Pd(dba)_2$	KHMDS	DME	50°	16	(57)	6

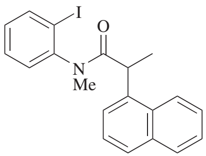
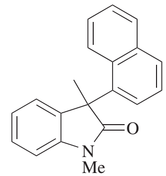
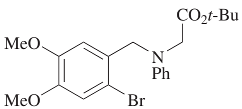
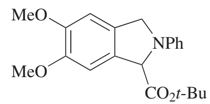
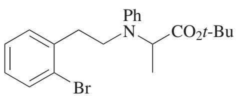
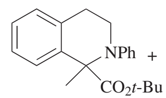
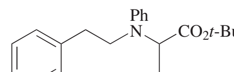
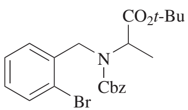
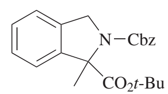
Pd(dba)$_2$ (x mol %), ligand **I** 32

x	Ligand	Temp	Time (h)		% ee
10	**L49**	50°	8	(93)	59
1	**L50**	rt	26	(91)	69
10	**L50**	0°	40	(27)	70

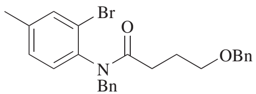
Pd(OAc)$_2$ (5 mol %), ligand (5 mol %), NaO*t*-Bu (1.5 eq), dioxane **I** 32

Ligand	Temp (°)	Time (h)		% ee
PCy$_3$	50	12	(89)	—
L5	70	24	(57)	38 (+)
L6	70	24	(67)	41 (+)
L7	100	24	(70)	61 (+)
L8	100	6	(55)	31 (–)
L9	100	24	(56)	61 (+)
L10	100	14	(24)	38 (+)
L11	100	12	(60)	15 (–)
(*R*)-**L23**	100	3	(49)	46 (–)
(*R*)-**L24**	100	3	(45)	18 (–)
(*R*)-**L29**	100	24	(49)	7 (+)
(*R*)-**L30**	50	3	(63)	0
(*R*)-**L31**	100	24	(50)	2 (–)
L39	70	24	(72)	6 (–)
L40	100	12	(72)	2 (–)
L41	100	24	(66)	16 (+)
L42	70	9	(75)	53 (+)
L43	50	24	(82)	20 (–)
L44	100	36	(37)	4 (+)
L45	100	36	(18)	5 (–)
L48	70	20	(35)	4
L49	50	12	(56)	34

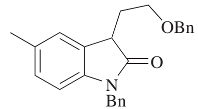
TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20} 		$Pd(dba)_2$ (10 mol %), ligand		32
		Ligand / Temp (°) / Time (h) **L49** / 50 / 6 **L50** / 0 / 36	% ee (75) 0 (30) 40	
C_{21} 		$Pd_2(dba)_3$ (2.3 mol %), **L17** (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 85°, 24 h	 (89)	78
		$Pd_2(dba)_3$ (2.3 mol %), ligand (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 85°, 24 h	 **I** +  **II**	78
		Ligand PPh_3 **L13** **L18**	**I** **II** (12) (7) (62) (—) (27) (—)	
C_{22} 		$Pd_2(dba)_3$ (2.3 mol %), **L17** (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 90°, 24 h	 (67)	78

C_{25}

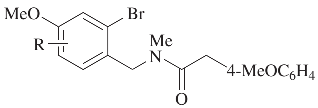


$Pd_2(dba)_3$ (1.5–3 mol %), **L52** (3–6 mol %), LiHMDS (1.5–2 eq), THF, 68°, 1–4 h

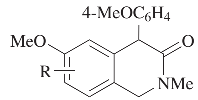


(47)

70



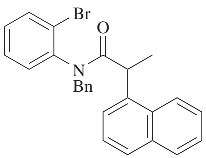
$Pd(dba)_2$, dppe, KO*t*-Bu, dioxane, 100°



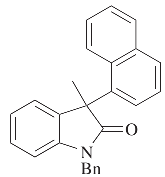
R	
3-OBn	(54)
5-OBn	(81)

71

C_{26}



$Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), NaO*t*-Bu (1.5 eq), dioxane, 50°, 12 h



I

(97)

32

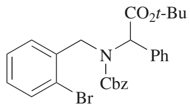
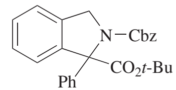
$Pd(dba)_2$ (*x* mol %), ligand

I

32

x	Ligand	Temp	Time (h)		% ee
10	**L49**	rt	24	(88)	67
2	**L50**	rt	24	(80)	71
10	**L50**	10°	40	(75)	76

TABLE 2. ARYLATION OF ESTERS, AMIDES, LACTONES, LACTAMS, NITRILES, KETENE ACETALS, AND PREFORMED ENOLATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{27} 		$Pd_2(dba)_3$ (2.3 mol %), **L13** (2.5 mol %), LiO*t*-Bu (2 eq), dioxane, 90°, 2 h	 (86)	78

[a] The amount of amide used was 0.5 eq.

[b] The carbene was not identified.

[c] The reaction was performed at 70°.

[d] $Pd(dba)_2$ (2 mol %) and **L12** (2 mol %) were used.

[e] The reaction was performed with 5 mol % of catalyst.

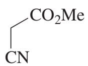
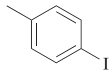
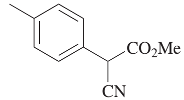
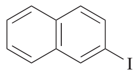
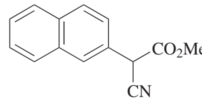
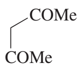
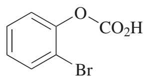
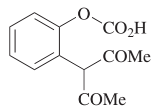
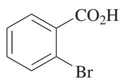
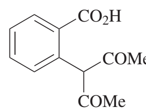
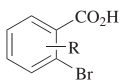
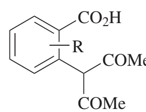
[f] The reaction was performed at room temperature with Zn(O*t*-Bu)$_2$ (0.25 eq).

[g] The reaction was performed with 10 mol % of $Pd(dba)_2$.

[h] The R group was not defined.

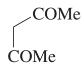
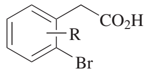
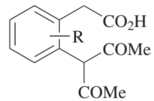
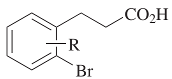
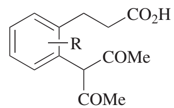
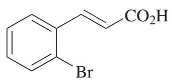
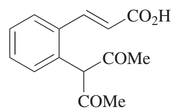
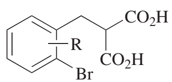
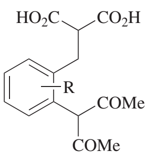
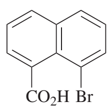
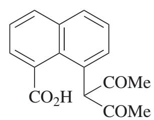
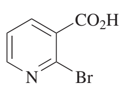
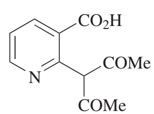
[i] The X group was not defined.

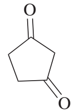
TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES

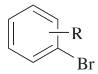
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_4				
		$PdCl_2(PPh_3)_2$ (4 mol %), KO*t*-Bu (2.2 eq), monoglyme, 70°, 6 h	 (83)	88
		$PdCl_2(PPh_3)_2$ (4 mol %), KO*t*-Bu (2.2 eq), monoglyme, 70°, 6 h	 (88)	88
C_5				
		CuBr (cat), NaH (2 eq), 16 h	 (0)	101
		Cu (6 mol %), NaOEt, EtOH	 (34)	101
		CuBr (cat), NaH (2 eq), neat		101

R	Time (h)	
H	1	(91)
3-O_2N	5	(0)
3-HO_2C	38	(40)
4-O_2N	0.5	(91)
4-Me	0.8	(82)
5-H_2N	6	(73)
5-HO	6.5	(77)
4,5-$(MeO)_2$	3	(59)
3,4,5-$(MeO)_3$	7	(84)

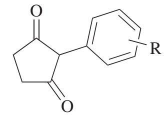
TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5 		CuBr (cat), NaH (2 eq)	 R / Time (h) H / 18 / (72) 4,5-$(MeO)_2$ / 24 / (25) 4,6-Br_2 / 32 / (—)	101
		CuBr (cat), NaH (3 eq)	 (0) R / Time (h) H / 24 4,5-$(MeO)_2$ / 24 4,6-Br_2 / 30	101
		CuBr (cat), NaH (2 eq), 16 h	 (0)	101
		CuBr (cat), NaH (4 eq)	 (0) R / Time (h) H / 32 4,6-Br_2 / 30	101
		CuBr (cat), NaH, 10 min	 (78)	101
		CuBr (cat), NaH, 5 min	 (—)	101





Pd(OAc)$_2$ (1 mol %), **L16** (2.2 mol %), K_3PO_4 (2.3 eq)



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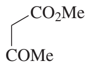
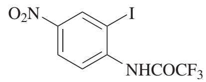
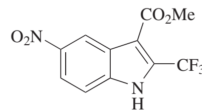
R	Solvent	Temp (°)	Time (h)	
3-MeO_2C	dioxane	100	19	(96)
4-*t*-Bu	THF	80	23	(96)





CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO, 50°, 12 h



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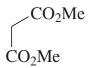
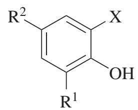
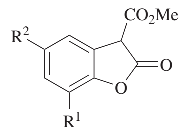




Catalyst (20 mol %), NaH or NaOMe (2 eq), 80°, 4–6 d



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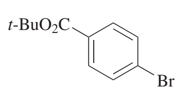
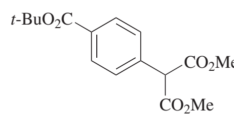
X	R^1	R^2	Catalyst	
Br	H	H	CuBr	(79)
Br	H	H	CuI	(27)
Br	Br	H	CuBr	(85)
Br	Br	H	CuBr•SMe_2	(36)
Br	H	Me	CuBr	(60)
Br	Br	F	CuBr	(48)
I	H	H	CuBr	(33)
I	H	H	CuI	(8)



$Pd_2(dba)_3$, P(*t*-Bu)$_3$, K_3PO_4, toluene



(—)

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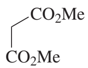
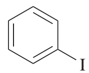
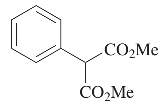
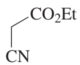
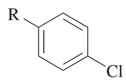
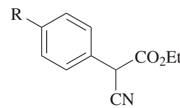
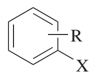
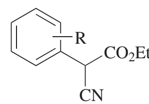
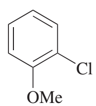
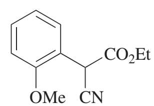
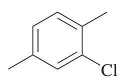
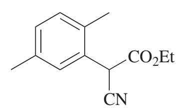
TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5				
		CuI (5 mol %), 2-picolinic acid (10 mol %), Cs_2CO_3 (3 eq), dioxane, 70°, 25 h	 (82)	106
		$[Pd(allyl)Cl]_2$ (1 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 100°, 12 h	 R: H (86); MeO (90); F (82)	82
		$[Pd(allyl)Cl]_2$ (1 mol %), ligand (4 mol %), Na_3PO_4 (3 eq), toluene, 100°		90

X	R	Ligand	Time (h)	Yield (%)
Cl	H	$P(t\text{-}Bu)_3$	12	(86)
Cl	4-MeO	$P(t\text{-}Bu)_3$	12	(90)
Br	2-MeO	$P(t\text{-}Bu)_3$	8	(83)
Br	4-MeO	$P(t\text{-}Bu)_3$	7	(89)
Br	4-MeO	**L33**	7	(85)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$[Pd(allyl)Cl]_2$ (1 mol %), **L12** (4 mol %), Na_3PO_4 (3 eq), toluene, 100°, 12 h	 (81)	82
		$[Pd(allyl)Cl]_2$ (1 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 100°, 12 h	 (87)	82, 90

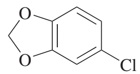
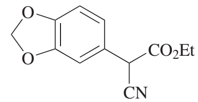
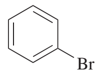
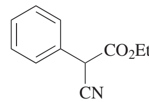
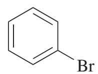
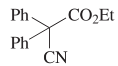
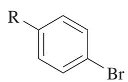
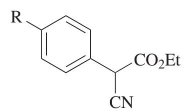
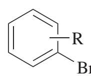
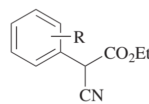
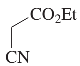
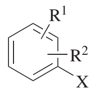
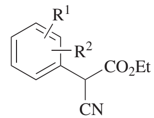
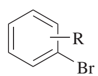
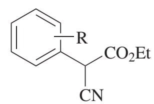
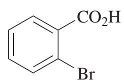
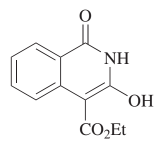
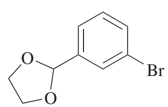
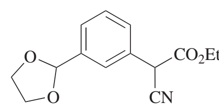
	[Pd(allyl)Cl]$_2$ (1 mol %), **L12** (4 mol %), Na_3PO_4 (3 eq), toluene, 100°, 12 h	 (86)	82
	[Pd(allyl)Cl]$_2$ (0.05 mol %), P(*t*-Bu)$_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 100°, 7 h	 (89)	90
	Pd(dba)$_2$ (4 mol %), P(*t*-Bu)$_3$ (8 mol %), Na_3PO_4 (3 eq), toluene, 70°, 12 h	 (90)	90
	Pd(dba)$_2$ (2 mol %), ligand (4 mol %), Na_3PO_4 (3 eq), toluene, 4 h		90
R	Ligand / Temp		
H	P(*t*-Bu)$_3$ / 70°	(87)	
H	**L33** / rt	(87)	
F	P(*t*-Bu)$_3$ / 70°	(91)	
	Pd(OAc)$_2$ (1 mol %), **L1** (4 mol %), KO*t*-Bu (2.5 eq), dioxane, 70°, 1–4 h	 R: H (90); 2-MeO (—); 2-Me (90); 4-F (—); 4-Cl (—)	164

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5 		$PdCl_2(PPh_3)_2$ (4 mol %), KO*t*-Bu (2.2 eq), monoglyme, 70°		88

X	R^1	R^2	Time (h)	Yield (%)
Br	H	H	6	(8)
I	H	H	5	(73)
I	2-MeO	H	24	(44)
I	2-F	H	6	(36)
I	2-Me	H	8	(45)
I	4-MeO	H	6	(71)
I	4-F	H	10	(46)
I	4-Cl	H	9	(45)
I	4-Me	H	5	(78)
I	3-Cl	4-Cl	10	(42)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 70°, 6 h	 R: 2-Me (85); 3-CF_3 (87); 4-PhO (90)	82
		CuBr (cat), NaH	 (36)	101
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 70°, 4 h	 (81)	90

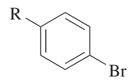
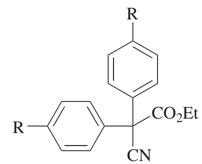
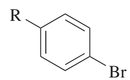
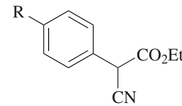
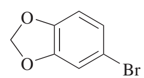
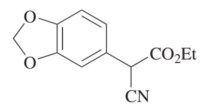
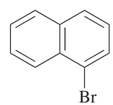
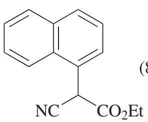
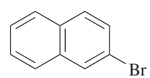
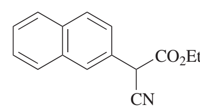
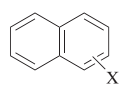
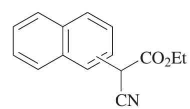
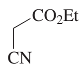
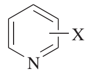
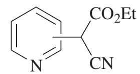
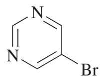
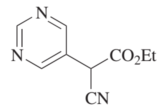
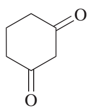
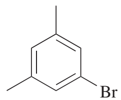
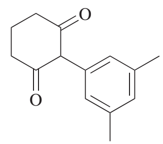
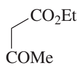
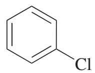
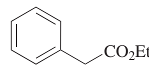
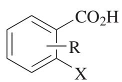
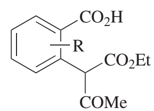
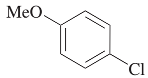
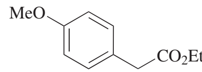
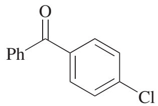
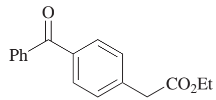
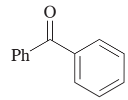
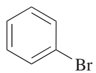
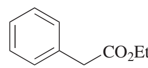
	$Pd(dba)_2$ (4 mol %), $P(t\text{-}Bu)_3$ (8 mol %), Na_3PO_4 (3 eq), toluene, 70°, 16 h		R MeO (93) CF_3 (95)	82
	$[Pd(allyl)Cl]_2$ (1 mol %), **L12** (4 mol %), Na_3PO_4 (3 eq), toluene, 100°, 12 h		R CF_3 (87) Ph (91)	82
	$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 70°, 4 h		(84)	90
	$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 70°, 4 h		(83)	90
	$[Pd(allyl)Cl]_2$ (1 mol %), **L12** (4 mol %), Na_3PO_4 (3 eq), toluene, 100°, 12 h		(91)	82
	$PdCl_2(PPh_3)_2$ (4 mol %), KO*t*-Bu (2.2 eq), monoglyme, 70°		X Time (h) 1-I 12 (47) 2-I 6 (85)	88

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5 		$Pd(OAc)_2$ (1 mol %), **L1** (4 mol %), KO*t*-Bu (2.5 eq), dioxane, 70°, 1–4 h	 X: 2-Br (84); 3-Br (85)	164
		$Pd(OAc)_2$ (1 mol %), **L1** (4 mol %), KO*t*-Bu (2.5 eq), dioxane, 70°, 1–4 h	 (85)	164
C_6 		$Pd(OAc)_2$ (1 mol %), **L16** (2.2 mol %), K_3PO_4 (2.3 eq), THF, 80°, 15 h	 (84)	43
		$Pd(OAc)_2$ (2 mol %), **L16** (4 mol %), K_3PO_4 (2.8 eq), toluene, 90°, 16 h	 (93)	87
		See table		101

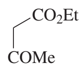
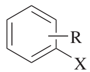
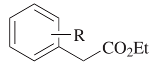
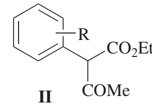
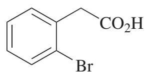
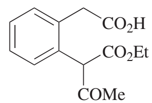
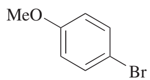
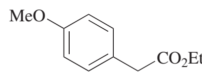
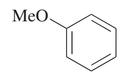
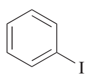
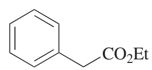
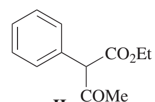
X	R	Catalyst	Base	Solvent	Time (h)	
Cl	H	CuBr	NaH (2 eq)	none	0.8	(91)
Br	H	Cu (6 mol %)	NaOEt	EtOH	—	(56)
Br	H	CuBr	NaH (2 eq)	none	0.3	(96)
Br	3-O_2N	CuBr	NaH (2 eq)	none	2.5	(51)
Br	4-O_2N	CuBr	NaH (2 eq)	none	0.7	(98)
Br	4-Me	CuBr	NaH (2 eq)	none	1	(99)

Br	5-MeO	CuBr	NaH (2 eq)	none	2	(98)
Br	4,5-(MeO)$_2$	CuBr	NaH (2 eq)	none	2.5	(90)
Br	3,4,5-(MeO)$_3$	CuBr	NaH (2 eq)	none	7	(99)

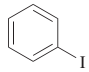
Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$ (0.5 mol %), **L16** (1 mol %), K_3PO_4 (2.8 eq), toluene, 90°, 40 h	 (75)	87
	Pd(OAc)$_2$ (1 mol %), P(t-Bu)$_3$•HBF_4 (2 mol %), K_3PO_4 (2.8 eq), toluene, 90°, 16 h	 (30) +  (40)	87
	Catalyst, ligand, K_3PO_4 (2.8 eq), toluene, 90°, 16 h		87

Catalyst	Ligand	
Pd(dba)$_2$ (1 mol %)	P(t-Bu)$_3$ (2 mol %)	(45)
Pd(OAc)$_2$ (1 mol %)	P(t-Bu)$_3$ (2 mol %)	(48)
Pd(OAc)$_2$ (5 mol %)	PPh$_3$ (20 mol %)	(0)
Pd(dba)$_2$ (1 mol %)	PCy$_3$ (2 mol %)	(0)
Pd(OAc)$_2$ (1 mol %)	**L15** (2 mol %)	(56)
Pd(OAc)$_2$ (1 mol %)	**L16** (2 mol %)	(89)
Pd(OAc)$_2$ (2 mol %)	**L15** (4 mol %)	(68)
Pd(OAc)$_2$ (2 mol %)	**L16** (4 mol %)	(93)

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		CuI (20 mol %), K_2CO_3 (7.5 eq), DMSO, 80°, 20 h	 **I** +  **II**	165
	X / R		**I** / **II**	
	Br / H		(2) / (—)	
	Br / 4-MeO		(0) / (0)	
	Br / 4-NC		(6) / (13)	
	Br / 4-MeCO		(48) / (22)	
	I / 2-Me		(19) / (41)	
	I / 4-MeO		(93) / (7)	
	I / 4-EtO_2C		(53) / (41)	
	I / 4-MeCO		(63) / (35)	
		CuBr (cat), NaH (2 eq), 16 h	 (—)	101
		$Pd(OAc)_2$ (1 mol %), $P(t\text{-}Bu)_3$•HBF_4 (2 mol %), K_3PO_4 (2.8 eq), toluene, 90°, 16 h	 (40) +  (35)	87
		Copper catalyst (x mol %), K_2CO_3 (y eq), DMSO, 80°	 **I** +  **II**	165

Copper Catalyst	x	y	Time (h)	**I**	**II**
CuBr	20	4	20	(56)	(—)
CuI	5	5	24	(85)	(11)
CuI	10	7.5	20	(85)	(9)

	CuI (20 mol %), ligand (40 mol %), K_2CO_3 (4 eq), 80°, 20 h	**I + II**	165

Ligand	Solvent	I	II
none	DMSO	(54)	(18)
none	dioxane	(12)	(—)
none	NMP	(42)	(—)
none	DMF	(43)	(—)
ethylenediamine	DMSO	(29)	(—)
ethylenediamine	dioxane	(48)	(—)
ethylenediamine	toluene	(38)	(—)
N,*N*'-dimethylethylenediamine	dioxane	(26)	(—)
N,*N*'-dimethylethylenediamine	toluene	(23)	(—)
1,8-diaminonaphthalene	DMSO	(47)	(22)
1,1'-bipyridine	DMSO	(54)	(20)
1,10-phenanthroline	DMSO	(41)	(17)
2-phenylphenol	DMSO	(41)	(—)
2-phenylphenol	dioxane	(5)	(—)
proline	DMSO	(45)	(8)
phenylalanine	DMSO	(48)	(6)
phenylalanine	dioxane	(42)	(8)
tryptophan	DMSO	(37)	(11)
ornithine	DMSO	(17)	(7)
2,4-diaminobutyric acid	dioxane	(18)	(6)

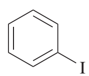
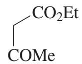
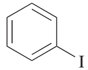
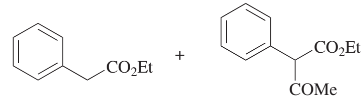
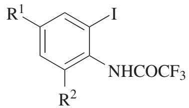
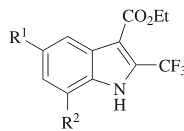
	CuI (5 mol %), 2-picolinic acid (10 mol %), Cs_2CO_3 (3 eq), dioxane, 70°, 25 h	**II** (78)	106

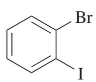
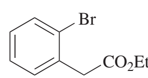
TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		CuI (20 mol %), ligand (40 mol %), base (*x* eq)	 **I** + **II**	165

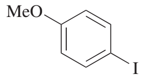
Ligand	Base	*x*	Solvent	Temp (°)	Time (h)	**I**	**II**
none	K_3PO_4	1	DMSO	80	20	(20)	(26)
none	Cs_2CO_3	4	DMSO	80	20	(7)	(17)
none	K_2CO_3	1	DMSO	80	7	(16)	(34)
none	K_2CO_3	2	DMSO	80	20	(53)	(16)
none	K_2CO_3	4	DMSO	40	40	(38)	(38)
none	K_2CO_3	4	DMSO	80	20	(54)	(18)
none	K_2CO_3	7.5	DMSO	40	20	(17)	(65)
none	K_2CO_3	7.5	DMSO	40	40	(37)	(56)
none	K_2CO_3	7.5	DMSO	80	20	(86)	(4)
none	K_2CO_3	7.5	dioxane	80	44	(58)	(7)
ethylenediamine	K_2CO_3	7.5	dioxane	80	40	(72)	(3)
ethylenediamine	K_3PO_4	5	toluene	80	44	(15)	(0)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO		162

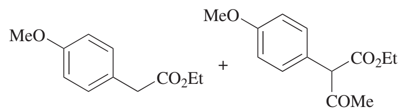
R^1	R^2	Temp (°)	Time (h)	
H	H	80	15	(27)
O_2N	H	50	12	(85)
I	MeO_2C	40	12	(78)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		CuI (5 mol %), ligand (10 mol %), K_2CO_3 (1.5 eq)		104

Ligand	Solvent	Temp (°)	
none	dioxane	100	(57)
none	DMSO	100	(19)
none	toluene	100	(25)
none	THF	100	(83)
none	THF	70	(28)
L-proline	THF	70	(9)
L-proline	DMSO	40	(0)



CuI (5 mol %),
K_2CO_3 (1.5 eq),
THF, 100°, 24 h



(45) (29)

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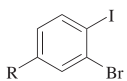
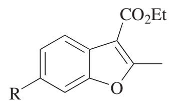


CuI (5 mol %),
K_2CO_3 (1.5 eq), 100°



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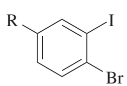
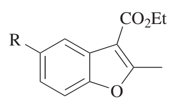
R	Time (h)	
Cl	24	(75)
Me	24	(88)
CF_3	26	(82)
$HOCH_2$	26	(32)
$TBSOCH_2$	26	(75)
MeCO	30	(78)
MeO_2C	26	(79)



CuI (5 mol %),
K_2CO_3 (1.5 eq), 100°



R	Time (h)	
O_2N	30	(52)
MeO	26	(78)
F	24	(80)

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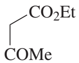
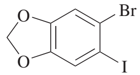
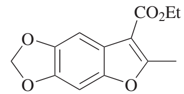
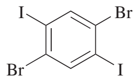
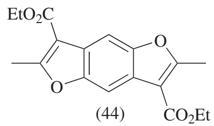
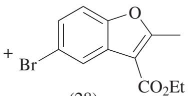
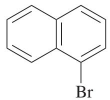
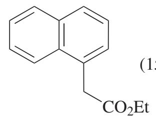
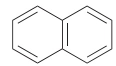
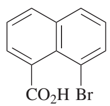
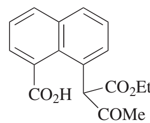
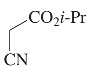
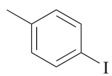
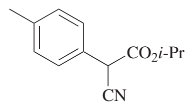
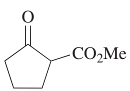
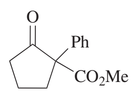
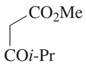
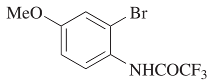
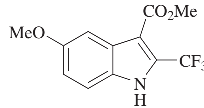
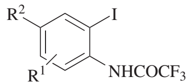
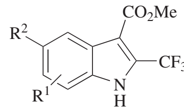
TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		CuI (5 mol %), K_2CO_3 (1.5 eq), THF, 100°, 26 h	 (70)	104
		CuI (20 mol %), K_2CO_3 (1.5 eq), THF, 100°, 24 h	 (44) +  (28)	104
		$Pd(OAc)_2$ (1 mol %), $P(t\text{-}Bu)_3$•HBF_4 (2 mol %), K_3PO_4 (2.8 eq), toluene, 90°, 16 h	 (15) +  (58)	87
		CuBr (cat), NaH, 5 min	 (81)	101
		$PdCl_2(PPh_3)_2$ (4 mol %), KO*t*-Bu (2.2 eq), monoglyme, 70°, 6 h	 (74)	88
C_7 	$PhB(OH)_2$	$(BzO)_2Pb$, **L38**, $Hg(OAc)_2$ (cat), pyridine (3 eq)	 (69), 10% ee	133

Reactant	Aryl halide	Conditions	Product(s) and Yield(s) (%)		Refs.
		CuI (20 mol %), L-proline (40 mol %), Cs_2CO_3 (4 eq), DMSO, 80°, 18 h		(55)	162
		CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO			162

R^1	R^2	Temp (°)	Time (h)	
H	H	80	15	(80)
5-MeO	H	75	15	(70)
5-MeCO	H	70	15	(65)
H	O_2N	50	12	(84)
H	Me	70	18	(63)
H	MeCO	60	12	(93)
6-Cl	I	60	12	(77)
5-Me	I	75	15	(79)

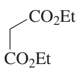
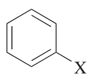
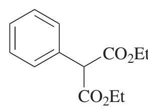
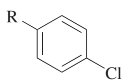
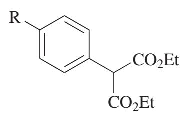
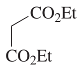
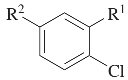
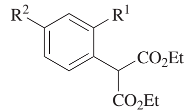
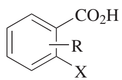
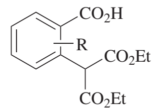
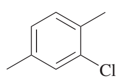
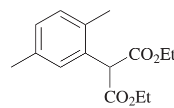
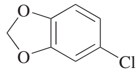
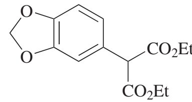
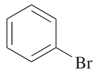
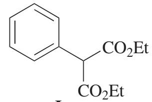
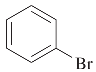
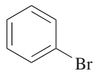
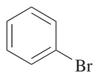
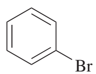
Reactant	Aryl halide	Conditions	Product(s) and Yield(s) (%)		Refs.
		Na_2PdCl_4 (2 mol %), $Ba(OH)_2$ (2 eq), DMA		X: Cl (93); Br (99); I (100)	84
		$Pd(dba)_2$ (2 mol %), **L33** (4 mol %), K_3PO_4 (3 eq), toluene, 100°, 16–21 h		R: H (85); MeO (90); CF_3 (86)	82

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

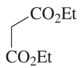
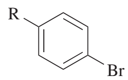
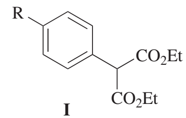
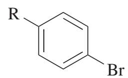
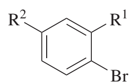
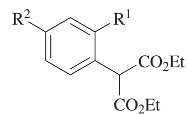
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7 		Pd(dba)$_2$ (2 mol %), **L12** (4 mol %), K_3PO_4 (3 eq), toluene, 100°, 16–21 h		82
			R^1 / R^2: H / H (81); MeO / H (87); H / MeO (86); H / CF_3 (89)	
		CuBr (cat), NaH (2 eq), neat		101
		Pd(dba)$_2$ (2 mol %), **L12** (4 mol %), K_3PO_4 (3 eq), toluene, 100°, 16–21 h	 (91)	82

X	R	Time (h)	Yield (%)
Cl	H	20	(80)
Br	H	1.7	(92)
Br	3-O_2N	2	(70)
Br	3-HO_2C	25	(85)
Br	4-O_2N	0.8	(88)
Br	4-Me	2	(90)
Br	5-H_2N	6	(70)
Br	5-HO	12	(27)
Br	4,5-$(MeO)_2$	4	(92)
Br	4,6-Br_2	4.5	(83)
Br	3,4,5-$(MeO)_3$	3	(84)

	$Pd(dba)_2$ (2 mol %), **L12** (4 mol %), K_3PO_4 (3 eq), toluene, 100°, 16–21 h	 (85)	82
	$Pd(OAc)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (2.5 mol %), NaO*t*-Bu (1.1 eq), dioxane, 70°, 3 h	 **I** (80)	40
	CuBr (20 mol %), NaH (1.1 eq), dioxane, reflux, 5 h	**I** (28)	124
	$[Pd(allyl)Cl]_2$ (0.05 mol %), **L3** (0.1 mol %), K_3PO_4 (3 eq), toluene, 100°, 12 h	**I** (91)	82
	CuI (10 mol %), 2-picolinic acid (20 mol %), Cs_2CO_3 (3 eq), dioxane, 110°, 32 h	**I** (79)	106
	Na_2PdCl_4 (2 mol %), base (2 eq), DMA	**I**	84

Base	Time (h)	% Conv. by GC
Li_2CO_3	24	14.3
Na_2CO_3	24	41.7
K_2CO_3	24	93.1
$Ca(OH)_2$	20	96.1
$Ba(OH)_2$	14	99.0
MgO	24	6.0
MgO/CaO	24	6.5
MgO/Al_2O_3	24	16.5
MgO/Ga_2O_3	24	8.3

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)			Refs.
C_7 		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 70°	 **I**			82
			R	Time (h)		
			H	5	(88)	
			MeCO	14	(89)	
			PhCO	14	(90)	
		Catalyst (1 mol %), NaO*t*-Bu (2 eq), THF, 110°, 20 h	**I**			83
			R	Catalyst		
			H	$Pd(OAc)_2$–NaY zeolite	(41)	
			H	$Pd(OAc)_2$, PPh_3 (4 mol %)	(50)	
			O_2N	$Pd(OAc)_2$–NaY zeolite	(84)	
			O_2N	$Pd(OAc)_2$, PPh_3 (4 mol %)	(78)	
			MeO	$Pd(OAc)_2$–NaY zeolite	(45)	
			MeO	$Pd(OAc)_2$, PPh_3 (4 mol %)	(48)	
			F	$Pd(OAc)_2$–NaY zeolite	(50)	
			F	$Pd(OAc)_2$, PPh_3 (4 mol %)	(60)	
			Me	$Pd(OAc)_2$–NaY zeolite	(38)	
			Me	$Pd(OAc)_2$, PPh_3 (4 mol %)	(56)	
			MeCO	$Pd(OAc)_2$–NaY zeolite	(62)	
			MeCO	$Pd(OAc)_2$, PPh_3 (4 mol %)	(64)	
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaH (1.1 eq), THF, 70°				82
	R^1 / R^2	Time (h)				
	H / H	1	(89)			
	MeO / H	8	(89)			
	Me / H	8	(84)			
	H / Me_2N	6	(87)			
	H / MeO	3	(89)			
	H / PhO	8	(85)			

H	F	3	(82)	
H	CF_3	3	(91)	
H	MeO_2C	3	(91)	
H	Ph	4	(91)	

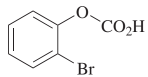
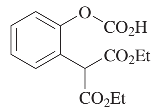
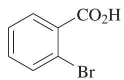
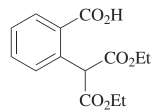
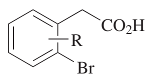
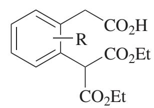
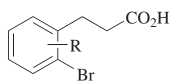
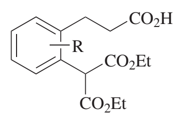
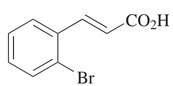
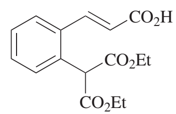
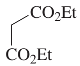
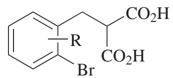
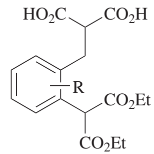
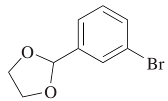
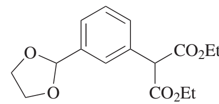
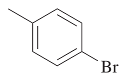
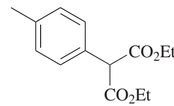
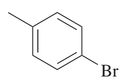
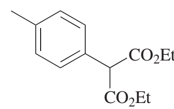
	CuBr (cat), NaH (2 eq), 16 h		(—)	101
	$Cu(OAc)_2$ (4 mol %), NaOEt, EtOH		(34)	101
	CuBr (cat), NaH (2 eq)		R / Time (h): H, 24 (41); 4,5-$(MeO)_2$, 7 (95); 4,6-Br_2, 32 (—)	101
	CuBr (cat), NaH (3 eq), 30 h		R: H (—); 4,6-Br_2 (—)	101
	CuBr (cat), NaH (2 eq), 30 h		(—)	101

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		CuBr (cat), NaH (4 eq)	 R / Time (h) H / 32 / (0) 4,6-Br_2 / 30 / (0)	101
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 70°, 6 h	 (87)	82
		Catalyst (1 mol %), ligand (4 mol %), NaO*t*-Bu (2 eq), THF, 110°, 20 h		83
		Catalyst (1 mol %), base (2 eq), 110°, 20 h		83

Catalyst	Ligand	
Pd(0)–NaY zeolite	none	(21)
Pd(II)–NaY zeolite	none	(32)
$Pd(NH_3)_4$–NaY zeolite	none	(38)
$Pd(OAc)_2$–NaY zeolite	none	(29)
$Pd(OAc)_2$	PPh_3	(56)

Catalyst	Base	Solvent	
$Pd(OAc)_2$–NaY zeolite	NaO*t*-Bu	THF	(41)
$Pd(OAc)_2$–NaY zeolite	NaO*t*-Bu	DMF	(45)
$Pd(OAc)_2$–NaY zeolite	KO*t*-Bu	THF	(39)
$Pd(OAc)_2$–NaY zeolite	KO*t*-Bu	DMF	(46)
$Pd(OAc)_2$–NaY zeolite	K_2CO_3	THF	(6)
$Pd(OAc)_2$–NaY zeolite	K_2CO_3	DMF	(24)
$Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %)	NaO*t*-Bu	THF	(65)
$Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %)	NaO*t*-Bu	DMF	(67)
$Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %)	KO*t*-Bu	THF	(40)
$Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %)	KO*t*-Bu	DMF	(60)
$Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %)	K_2CO_3	THF	(8)
$Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %)	K_2CO_3	DMF	(32)

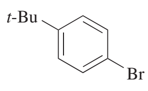
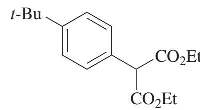
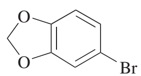
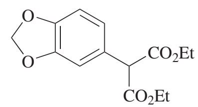
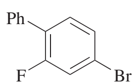
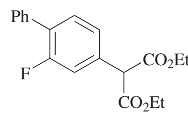
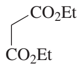
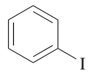
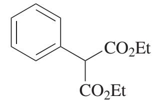
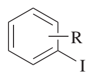
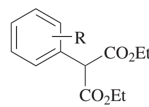
	$Pd(OAc)_2$ (1 mol %), **L16** (2.2 mol %), K_3PO_4 (2.3 eq), THF, 70°, 10 h		(92)	43
	$Pd(dba)_2$ (2 mol %), P(*t*-Bu)$_3$ (4 mol %), NaH (1.1 eq), THF, 70°, 6 h		(83)	82
	$Pd(dba)_2$ (2 mol %), P(*t*-Bu)$_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 70°, 12 h		(89)	82

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

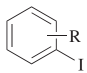
Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7 		CuI (5 mol %), ligand (*x* mol %), Cs_2CO_3 (3 eq), dioxane, 20 h		106

Ligand	*x*	Temp	
phenol	10	70°	(2)
2-dioxolanephenol	10	70°	(15)
2-*t*-butylphenol	10	70°	(9)
2-phenylphenol	10	70°	(83)
2-phenylphenol	20	rt	(48)
2-phenylphenol	20	70°	(90)
2,4-dimethylphenol	10	70°	(4)
2,6-di-*t*-butylphenol	10	70°	(<1)
benzoic acid	10	70°	(79)
thiophene-2-carboxylic acid	10	70°	(60)
indole-2-carboxylic acid	10	70°	(66)
2-picolinic acid	10	rt	(92)
2-picolinic acid	10	70°	(99)
2-picolinic acid	10	70°	(93)[a]
2-picolinic acid	10	70°	(90)[b]

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
		CuI (5 mol %), 2-phenylphenol (10 mol %), Cs_2CO_3 (1.5 eq), THF, 70°	 **I**	105

R	Time (h)	**I**
H	24	(91)
3-O_2N	24	(84)
3-F	24	(87)
3-NC	24	(61)

3-CF_2	24	(89)	
3-EtO_2C	24	(86)	
4-H_2N	29	(70)	
4-Cl	24	(94)	
4-MeCO	24	(86)	



CuI (5 mol %), 2-picolinic acid (10 mol %), Cs_2CO_3 (3 eq), dioxane — **I** — 106

R	Temp	Time (h)	
2-MeO	rt	20	(92)
2-Me	70°	20	(84)^c
3-MeO	rt	20	(79)
3-EtO_2C	rt	20	(96)
4-MeO	rt	20	(80)
4-F	rt	20	(73)
4-NC	rt	20	(82)
2,4-$(MeO)_2$	70°	25	(88)
3,5-Me_2	rt	28	(88)
3,4,5-$(MeO)_3$	rt	28	(81)

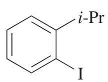
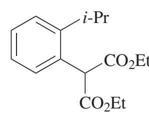
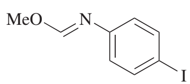
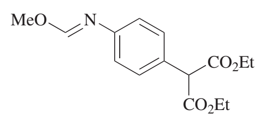
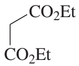
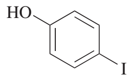
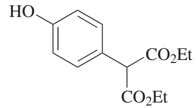
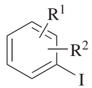
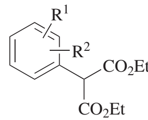
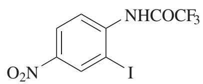
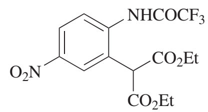
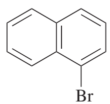
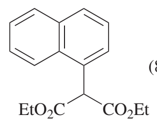
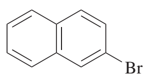
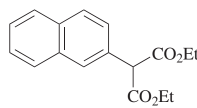
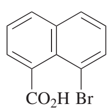
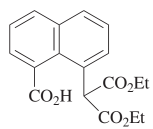
Substrate	Conditions	Product and Yield (%)		Refs.
	CuI (10 mol %), 2-phenylphenol (15 mol %), Cs_2CO_3 (1.5 eq), THF, 70°, 31 h		(84)	105
	CuI (10 mol %), 2-phenylphenol (15 mol %), Cs_2CO_3 (2.5 eq), THF, 70°, 29 h		(75)	105

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7 		CuI (10 mol %), 2-phenylphenol (15 mol %), Cs_2CO_3 (3.5 eq), THF, 70°, 29 h	 (80)	105
		CuI (5 mol %), 2-phenylphenol (10 mol %), Cs_2CO_3 (1.5 eq), THF, 70°		105
	R^1 / R^2	Time (h)		
	2-MeO / 4-MeO	30	(90)	
	3-Me / 5-Me	27	(95)	
		CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO, 50°, 12 h	 (64)	162
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaH (1.1 eq), THF, 70°, 6 h	 (83)	82
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaH (1.1 eq), THF, 70°, 6 h	 (89)	82
		CuBr (cat), NaH, 50 min	 (84)	101

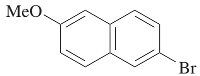
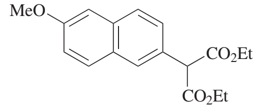
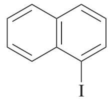
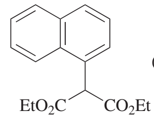
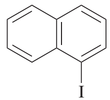
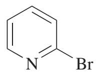
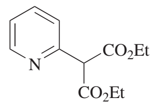
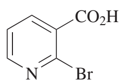
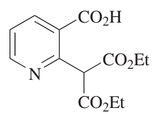
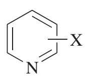
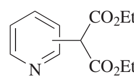
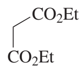
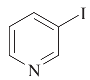
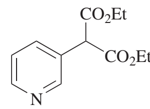
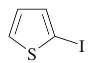
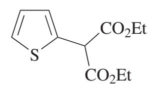
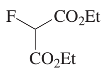
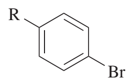
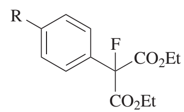
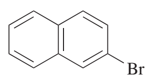
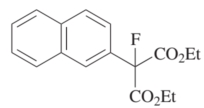
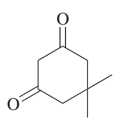
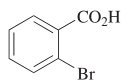
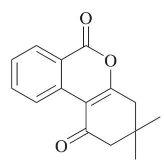
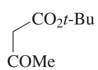
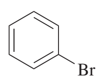
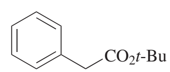
	$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), K_3PO_4 (3 eq), toluene, 70°, 12 h	 (92)	82
	CuI (10 mol %), 2-picolinic acid (10 mol %), Cs_2CO_3 (3 eq), dioxane, rt, 20 h	 **I** (95)	106
	CuI (5 mol %), 2-phenylphenol (10 mol %), Cs_2CO_3 (1.5 eq), THF, 70°, 30 h	**I** (98)	105
	CuI (5 mol %), 2-picolinic acid (20 mol %), Cs_2CO_3 (3 eq), dioxane, 110°, 32 h	 (88)	106
	CuBr (cat), NaH, 30 min	 (77)	101
	CuI (5 mol %), 2-picolinic acid (10 mol %), Cs_2CO_3 (3 eq), dioxane, rt, 20 h	 X 2-I (90) 3-I (77)	106

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		CuI (5 mol %), 2-phenylphenol (10 mol %), Cs_2CO_3 (1.5 eq), THF, 70°, 26.5 h	 (73)	105
		CuI (5 mol %), 2-picolinic acid (10 mol %), Cs_2CO_3 (3 eq), dioxane, rt, 20 h	 (68)	106
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaH (1.1 eq), THF, 70°, 6 h	 R: H (84); MeO (88); MeO_2C (89); *t*-Bu (86)	82
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaH (1.1 eq), THF, 70°, 6 h	 (79)	82
C_8				
		CuBr (cat), NaH	 (63)	166
		$Pd(dba)_2$ (1 mol %), $P(t\text{-}Bu)_3$ (2 mol %), K_3PO_4 (2.8 eq), toluene, 90°, 16 h	 (55)	87

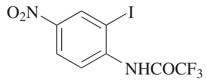
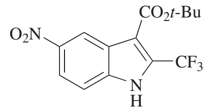
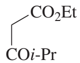
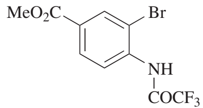
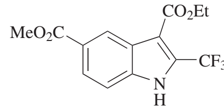
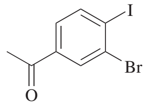
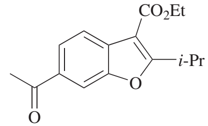
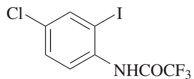
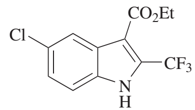
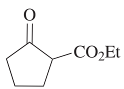
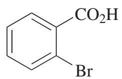
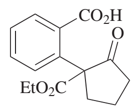
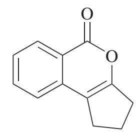
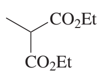
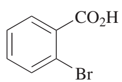
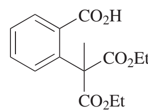
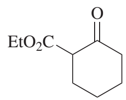
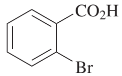
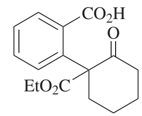
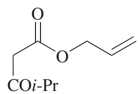
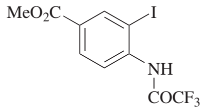
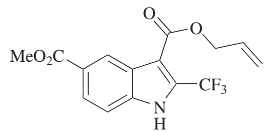
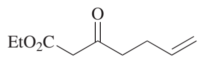
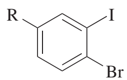
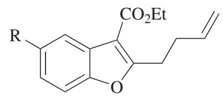
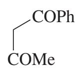
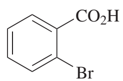
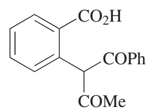
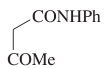
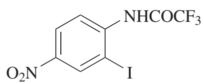
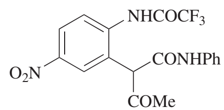
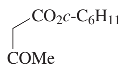
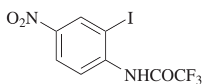
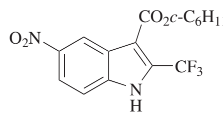
		CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO, 50°, 12 h	 (81)	162
		CuI (20 mol %), L-proline (40 mol %), Cs_2CO_3 (4 eq), DMSO, 70°, 15 h	 (72)	162
		CuI (5 mol %), K_2CO_3 (1.5 eq), THF, 100°, 26 h	 (48)	104
		CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO, 70°, 15 h	 (81)	162
		CuBr (cat), NaH, 80°, 6 h	 **I** +  **II**	166
		Solvent: none[d]	**I** (38), **II** (37)	
		Solvent: benzene	**I** (87), **II** (0)	
		CuBr (cat), NaH	 (83)	166

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 		CuBr (cat), NaH, 80°, 6 h	 Solvent: none[d] (72); benzene (58)	166
		CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO, 70°, 15 h	 (72)	162
		CuI (5 mol %), K_2CO_3 (1.5 eq), THF, 100°	 R, Time (h): H, 24, (75); MeO, 26, (74)	104
C_{10} 		Cu (6 mol %), NaOEt, EtOH	 (78)	101
		CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO, 50°, 12 h	 (78)	162
		CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO, 50°, 12 h	 (80)	162

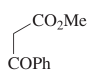
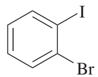
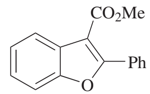
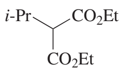
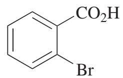
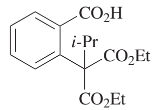
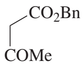
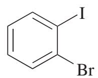
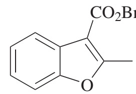
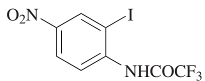
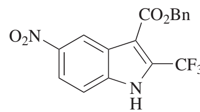
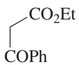
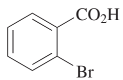
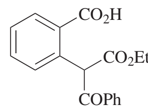
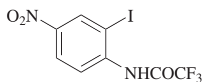
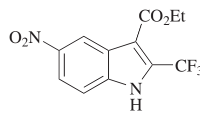
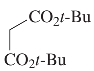
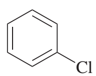
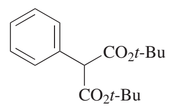
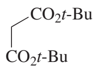
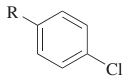
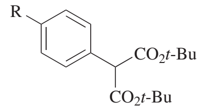
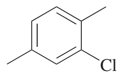
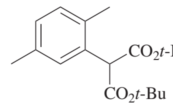
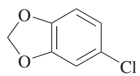
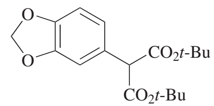
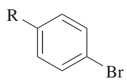
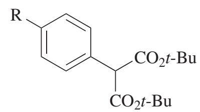
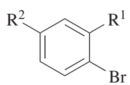
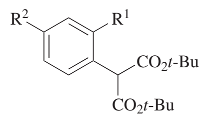
			CuI (5 mol %), K_2CO_3 (1.5 eq), THF, 100°, 24 h	 (0)	104
			CuBr (cat), NaH	 (0)	166
C_{11}			CuI (5 mol %), K_2CO_3 (1.5 eq), THF, 100°, 26 h	 (71)	104
			CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO, 50°, 12 h	 (83)	162
			CuBr (cat), NaH (2 eq), 1 h	 (98)	101
			CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO, 50°, 12 h	 (78)	162
			$Pd(dba)_2$ (2 mol %), **L3** (2.5 mol %), NaO*t*-Bu (1.1 eq), dioxane, 100°, 12 h	 (78)	40

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11} 		$[Pd(allyl)Cl]_2$ (1 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaO*t*-Bu (1.1 eq), dioxane, 100°, 12 h	 R: H (88); MeO (84); CF_3 (86)	82
		$[Pd(allyl)Cl]_2$ (1 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaO*t*-Bu (1.1 eq), dioxane, 100°, 12 h	 (90)	82
		$[Pd(allyl)Cl]_2$ (1 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaO*t*-Bu (1.1 eq), dioxane, 100°, 12 h	 (87)	82
		$[Pd(allyl)Cl]_2$ (1 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaO*t*-Bu (1.1 eq), dioxane, 45°, 8 h	 R: H (91); CF_3 (90)	82
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaH (1.1 eq), THF, 70°		82
	R^1 / R^2	Time (h)		
	H / H	6	(89)	
	MeO / H	12	(86)	
	Me / H	12	(85)	
	H / Me_2N	6	(90)	
	H / MeO	6	(90)	
	H / CF_3	6	(88)	

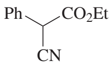
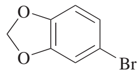
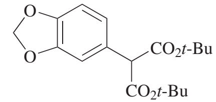
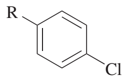
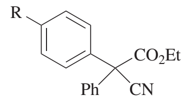
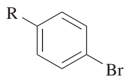
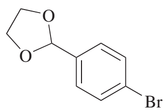
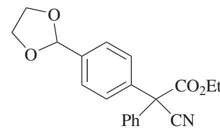
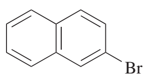
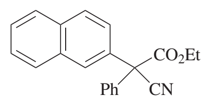
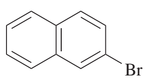
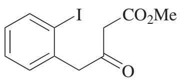
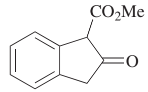
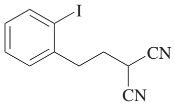
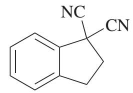
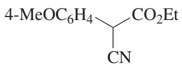
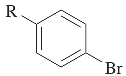
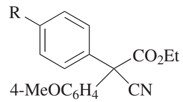
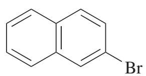
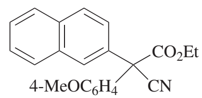
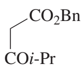
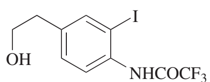
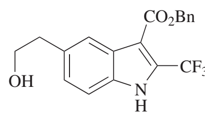
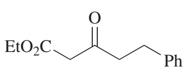
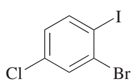
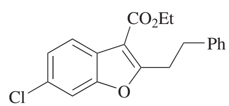
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), NaH (1.1 eq), THF, 70°, 6 h	 (87)	82
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 100°, 16 h	 **I** R: H (89); MeO (91)	82
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 70°, 16 h	**I** R: MeO (93); F (89); CF_3 (91); MeO_2C (92); MeCO (92); Ph (90); PhCO (93)	82
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 70°, 16 h	 (94)	82
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4	 (93) **I**	90
		$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 70°, 12 h	**I** (93)	90

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

	Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}			$Pd(PPh_3)_4$, NaH, DMF, 130–140°	 (0)	85
			$Pd(PPh_3)_4$, NaH, DMF, 130–140°	 (54)	85
C_{12}			$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 70°	 R / Time (h): MeO, 20, (94); CF_3, 16, (90)	82
			$Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), Na_3PO_4 (3 eq), toluene, 70°, 20 h	 (91)	82
C_{13}			CuI (10 mol %), L-proline (20 mol %), Cs_2CO_3 (4 eq), DMSO, 80°, 15 h	 (67)	162
			CuI (5 mol %), K_2CO_3 (1.5 eq), THF, 100°, 26 h	 (78)	104

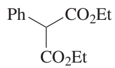
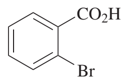
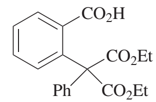
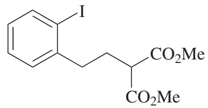
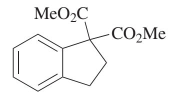
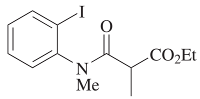
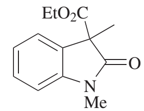
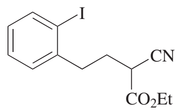
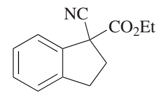
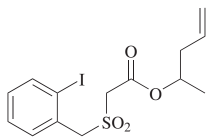
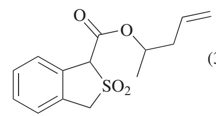
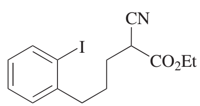
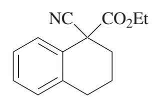
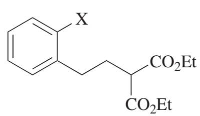
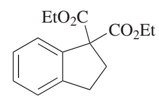
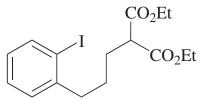
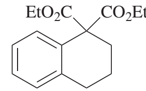
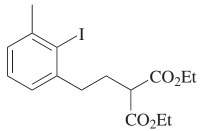
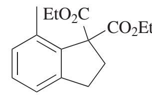
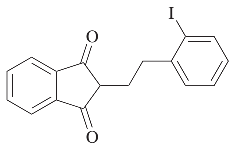
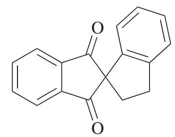
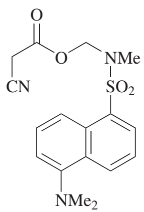
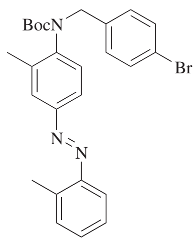
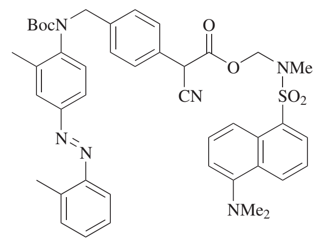
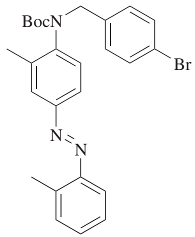
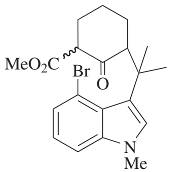
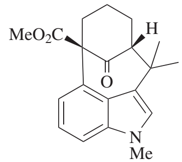
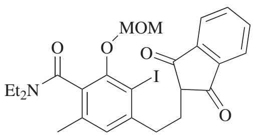
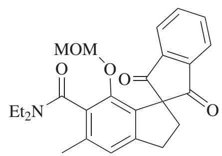
			CuBr (cat), NaH	 (45)	166
			$Pd(PPh_3)_4$, NaH, DMF, 130–140°	 (53)	85
			$Pd(PPh_3)_4$, NaH, DMF, 130–140°	 (31)	85
			$Pd(PPh_3)_4$, NaH, DMF, 130–140°	 (38)	85
C_{14}			$Pd(PPh_3)_4$, NaH, DMF, 130–140°	 (37)	85
			$Pd(PPh_3)_4$, NaH, DMF, 130–140°	 (49)	85
C_{15}			$Pd(PPh_3)_4$, NaH, DMF, 130–140°	 X: Br (48); I (62)	85

TABLE 3. ARYLATION OF 1,3-DICARBONYLS AND CYANOACETATES (*Continued*)

Substrate	Aryl Compound	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16} 		$Pd(PPh_3)_4$, NaH, DMF, 130–140°	 (41)	85
		$Pd(PPh_3)_4$, NaH, DMF, 130–140°	 (75)	85
C_{17} 		$Pd(PPh_3)_4$ (10 mol %), NaH, DMF, 130°, 6 h	 (68)	15
		Catalyst	 **I** (—)	90

		Pd catalyst, ligand	**I** (—) Ligand: P(t-Bu)$_3$; **L33**; **L34**	1
C_{20}		Pd(OAc)$_2$ (0.3 eq), P(t-Bu)$_3$ (0.6 eq), KOt-Bu (2 eq), toluene, 70°	 (74)	86
C_{25}		Pd(PPh$_3$)$_4$, NaH, DMF, 135°	 (76)	85

[a] The reaction was performed in 2 hours.

[b] CuI (1 mol %) was used.

[c] CuI (10 mol %) was used.

[d] The ester reactant was used as the solvent .

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CHAPTER 3

INDOLES VIA PALLADIUM-CATALYZED CYCLIZATION

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INTRODUCTION

The palladium-catalyzed assembly of the functionalized pyrrole nucleus on a benzenoid scaffold is a widely used synthetic tool for the preparation of indole derivatives.[1–10] This construction can be categorized into four main types: (1) cyclization of alkynes, (2) cyclization of alkenes, (3) cyclization via *C*-vinylation reactions, and (4) cyclization via *N*-arylation or *N*-vinylation reactions. The first approach is by far the most versatile in terms of the range of the added functional groups and of the bonds that can be created in the construction of the pyrrole ring. This method is based on the utilization of precursors containing nitrogen nucleophiles and carbon–carbon triple bonds. The nitrogen nucleophile and alkyne moiety may be part of the same molecule or belong to two different molecules. Some of the most general and versatile alkyne-based cyclizations to indoles are summarized in Fig. 1.

Assembly of the pyrrole nucleus from precursors containing nitrogen nucleophiles and carbon–carbon double bonds entails only intramolecular cyclizations and, considering the bonds that can be created in the cyclization step, appears less versatile than the alkyne-based approach. Alkene-based cyclizations to give indoles are summarized in Fig. 2.

Cyclization to indoles via arene vinylation has limited synthetic scope. However, it is interesting that, unlike the above alkyne- and alkene-based procedures where the site of the oxidative addition of the carbon–X bond to the palladium(0) species is located on the benzenoid ring (Figures 1 and 2), the oxidative addition site is located in a vinylic fragment tethered to the benzenoid ring in this type of cyclization. Furthermore, it is the sole example of the construction of the pyrrole ring via palladium-catalyzed vinylation of an o*rtho*-unfunctionalized aromatic ring (Fig. 3). Such direct arene vinylation and arylation processes are of great current interest.[11–14]

Finally, indoles can be prepared via cyclizations proceeding through *N*-arylation and *N*-vinylation reactions (Fig. 4) that are based on the pioneering work[15–22]

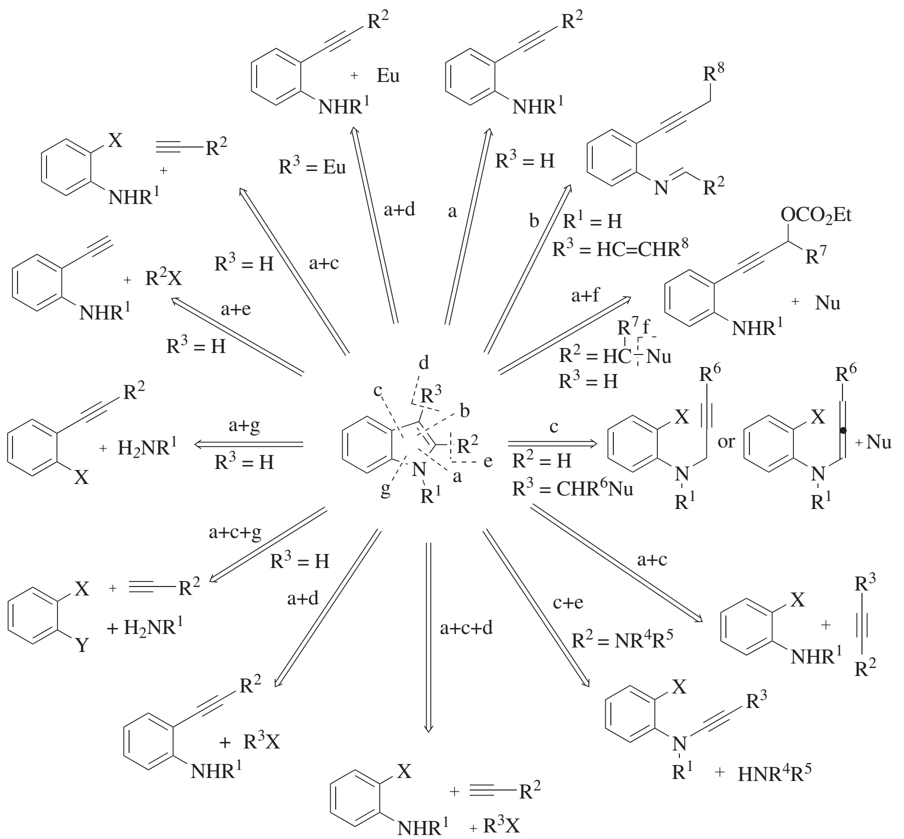


Figure 1. Retrosynthetic representation of the main alkyne-based, palladium-catalyzed constructions of the pyrrole ring. (Nu = nucleophile, E = electrophile).

on palladium-catalyzed carbon–nitrogen bond forming reactions from aryl halides or triflates with amines, amides, and carbamates.

In general, only synthetic procedures where palladium catalysis is involved in the pyrrole ring construction event are discussed herein. Palladium-catalyzed reactions producing indole-related compounds, such as azaindoles, indazoles, indolines, oxindoles, bis(indolyl)methanes, and related systems, or condensed polycyclic compounds, such as carbolines, carbazoles, indoloquinolines, indoloquinazolines, and related systems, are not discussed. Indoles are classified as 2-substituted, 3-substituted, and 2,3-disubstituted derivatives without considering the functionalization of the nitrogen atom.

MECHANISMS

A variety of reaction parameters such as solvents, temperature, the nature of the substrates and ligands, bases, and additives, and sometimes even their

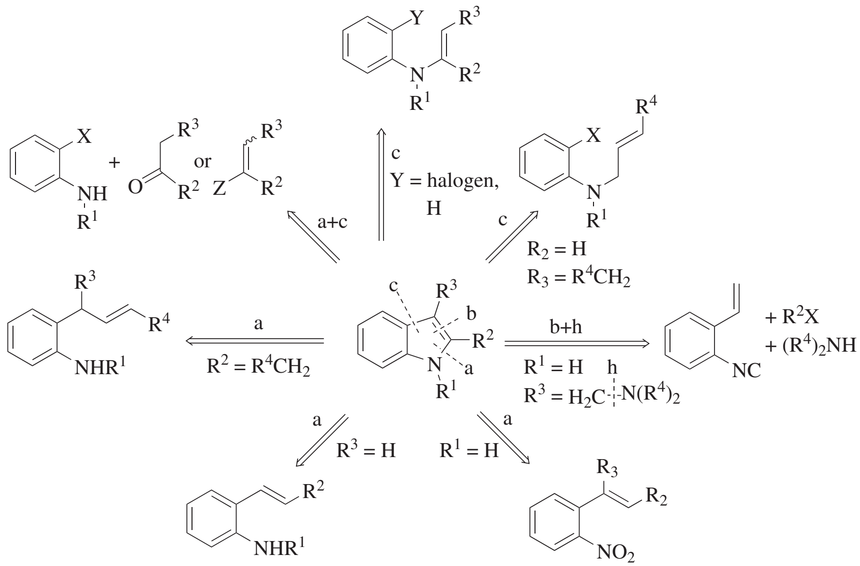


Figure 2. Retrosynthetic representation of the main alkene-based, palladium-catalyzed constructions of the pyrrole ring.

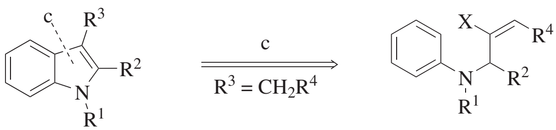


Figure 3. Retrosynthetic representation of the palladium-catalyzed construction of the pyrrole ring via intramolecular arene vinylation.

combination can influence the mechanism operating in this reaction. In addition, catalytic cycles usually consist of several consecutive steps and the chemical nature as well as the reactivity of each intermediate can differ depending on reaction conditions. Some reaction parameters can also exhibit opposing effects on different steps of a catalytic cycle. In view of this complexity, it is not surprising that the literature contains few detailed mechanistic studies. Therefore, the word mechanism is used in this section to indicate a plausible rationalization of how products are formed rather than an experimentally supported mechanism. These plausible rationalizations are categorized into two main types corresponding to two main sections: palladium(II)- and palladium(0)-catalyzed reactions. The two main sections are subclassified by the proposed reaction mechanisms. Since the palladium-catalyzed cyclization to indoles is an extremely diverse class of reactions from a mechanistic point of view, only the main mechanistic proposals are discussed below.

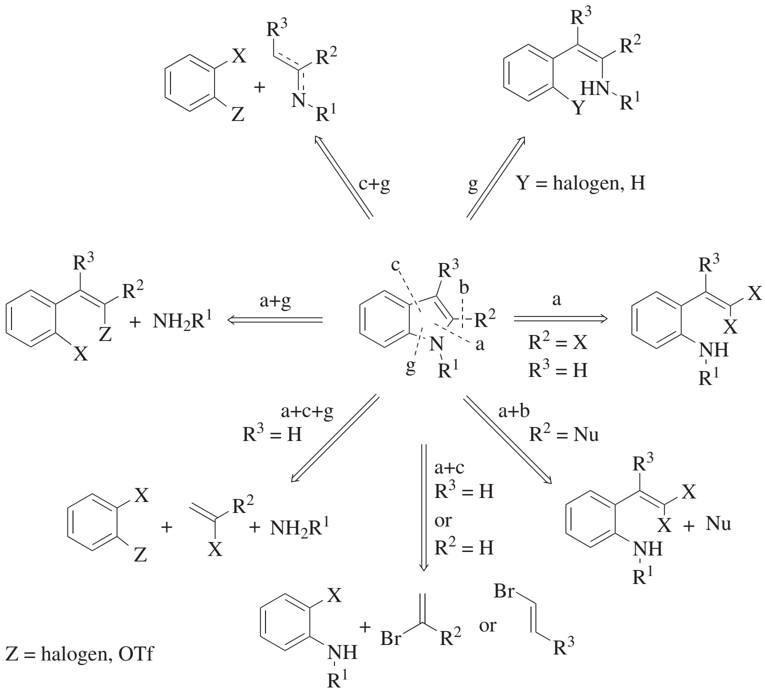
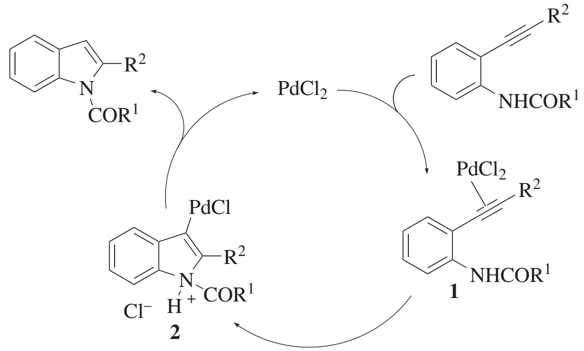


Figure 4. Retrosynthetic representation of the main palladium-catalyzed constructions of the pyrrole ring via *N*-vinylation and *N*-arylation reactions.

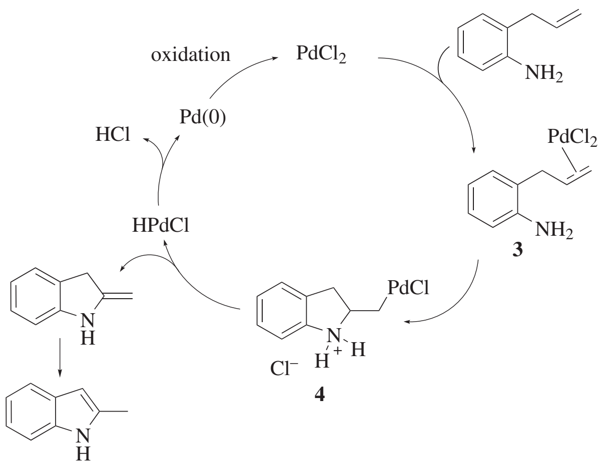
Palladium(II)-Catalyzed Cyclizations

Most of the syntheses of indoles catalyzed by Pd(II) salts involve cyclizations of aryl alkynes containing *ortho*-nitrogen nucleophiles (Fig. 1, disconnections a and a+d) or allylic and vinylic arenes containing *ortho*-nitrogen nucleophiles (Fig. 2, disconnection a)."

Palladium(II) salts are fairly electrophilic species. For that reason, the first event leading to cyclization in palladium(II)-catalyzed reactions is usually considered to be the coordination of acetylenic or olefinic π-electrons to a palladium(II) species. As shown in Schemes 1 and 2 for 2-alkynylanilides[23] and 2-allylanilines,[24] the resultant π-palladium complexes **1** and **3** subsequently undergo an intramolecular nucleophilic attack of a nitrogen nucleophile across the activated carbon–carbon multiple bond to give the aminopalladation adducts **2** and **4**, respectively. With acetylenic precursors, protonolysis of the carbon–palladium bond of **2** forms 2-substituted indoles and regenerates the active catalytic species. This approach to the construction of the pyrrole ring, which ultimately allows for the addition of nitrogen–hydrogen bonds across carbon–carbon multiple bonds, is frequently described as a hydroamination reaction. With alkene precursors, the conversion of aminopalladation adducts **4** into indole derivatives



Scheme 1. Catalytic cycle of the palladium(II)-catalyzed cyclization of 2-alkynylanilides via the hydroamination pathway.



Scheme 2. Catalytic cycle of the palladium(II)-catalyzed cyclization of 2-allylanilines.

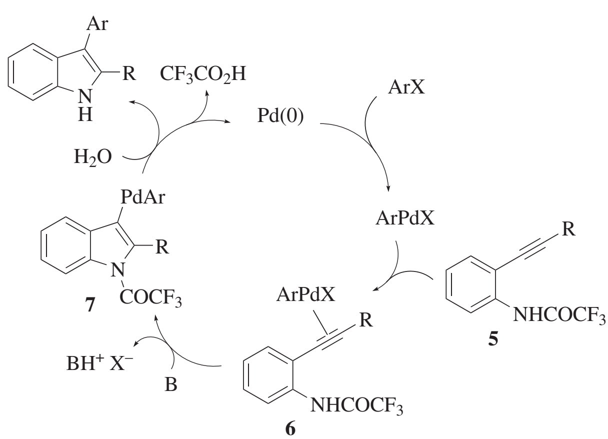
involves a β-elimination step that ultimately leads to the formation of palladium(0) species. Consequently, for the reaction to be catalytic with respect to palladium(II), the presence of stoichiometric amounts of oxidants such as $CuCl_2$, $Cu(OAc)_2$, benzoquinone, *tert*-butyl hydroperoxide (TBHP), or MnO_2 is required to allow for the in situ conversion of palladium(0) into palladium(II).

Palladium(0)-Catalyzed Cyclizations

Cyclizations to indoles catalyzed by a palladium(0) species provide a wider variety of applications than palladium(II)-catalyzed cyclizations, and some are among the most efficient and generally applicable methods. They include the great majority of alkyne-based syntheses described in Figure 1, a variety of alkene-based syntheses (Fig. 2, disconnection c, a + c, b + h), cyclization to indoles via arene vinylation (Fig. 3), and cyclizations based on *N*-vinylation and *N*-arylation reactions (Fig. 4).

Palladium(0) complexes are usually nucleophilic and the initial step of the vast majority of palladium(0)-catalyzed cyclizations to indoles involves an oxidative addition of carbon–X bonds (X = I, Br, Cl, OTf) to coordinatively unsaturated palladium(0) species to give carbon–palladium(II)–X intermediates that contain an electrophilic palladium. In general, the oxidative addition step is favored by increasing the electron density on palladium. The observed rate of oxidative addition with $\text{carbon}_{\text{aryl}}$–halogen bonds increases in the order C–F < C–Cl < C–Br < C–I (aryl fluorides are almost inert).[25] The reactivity of aryl triflates is approximately between that of aryl iodides and aryl bromides. In the presence of monodentate ligands, a *cis*-complex is likely to be the initial product of the oxidative addition. Subsequently, isomerization gives rise to the thermodynamically more stable *trans*-complex. With bidentate ligands, the *cis*-complex is the usual intermediate.

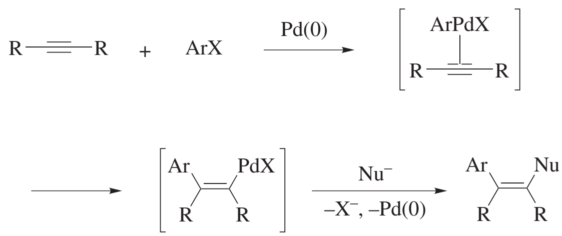
The aminopalladation/reductive elimination mechanism has been suggested to account for the cyclization to indoles of 2-alkynyltrifluoroacetanilides,[7] 2-alkynylisocyanobenzenes,[26] 2-alkynylisocyanatobenzenes[27,28] (Fig. 1, disconnection a+d) and 2-halo-*N*-alkynylanilides[29] (Fig. 1, disconnection c+e). Although some differences exist in the details of the mechanistic proposals for the cyclization of these compounds, the general features of the aminopalladation/reductive elimination pathway are well described by the example shown in Scheme 3 for the synthesis of free (NH) 2,3-disubstituted indoles from 2-alkynyltrifluoroacetanilides **5**. In this mechanism, coordination of π-acetylenic electrons to organopalladium complexes, generated in situ through oxidative addition of organic precursors to palladium(0) species, affords π-alkyne-organopalladium complexes **6** that subsequently undergo nucleophilic attack of the nitrogen atom across the activated carbon–carbon triple bond to give the σ-indolylpalladium intermediates **7** (the aminopalladation adduct). The free



Scheme 3. Catalytic cycle of the cyclization of alkynes via the aminopalladation/reductive elimination pathway.

indole product (NH) is formed by hydrolysis of the amide bond and a reductive elimination step (not necessarily in this order) that produces a new carbon–carbon bond and regenerates the active palladium(0) catalyst.

The palladium-catalyzed reaction of aryl halides with alkynes not containing nucleophiles close to the carbon–carbon triple bond may form π-alkyne-σ-arylpalladium complexes that, unable to undergo an intramolecular nucleophilic attack across the carbon–carbon triple bond, afford carbopalladation adducts **8** (Eq. 1). These adducts, depending on reaction conditions, can be converted into a variety of products via an intermolecular process, as exemplified in Eq. 1.



8

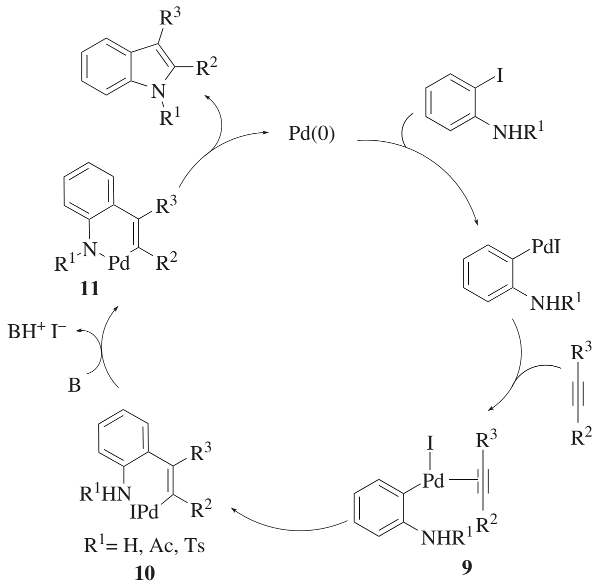
(Eq. 1)

When the aryl moiety added to palladium(0) contains a nitrogen nucleophile adjacent to the oxidative addition site, as shown in Scheme 4, the carbopalladation adduct **10** can undergo an intramolecular halide displacement from the palladium to give a nitrogen-containing palladacycle **11** that subsequently affords the indole product via a reductive elimination step.[30,31] This carbopalladation route (Fig. 1, disconnection a+c) is one of the most versatile and efficient indole syntheses.

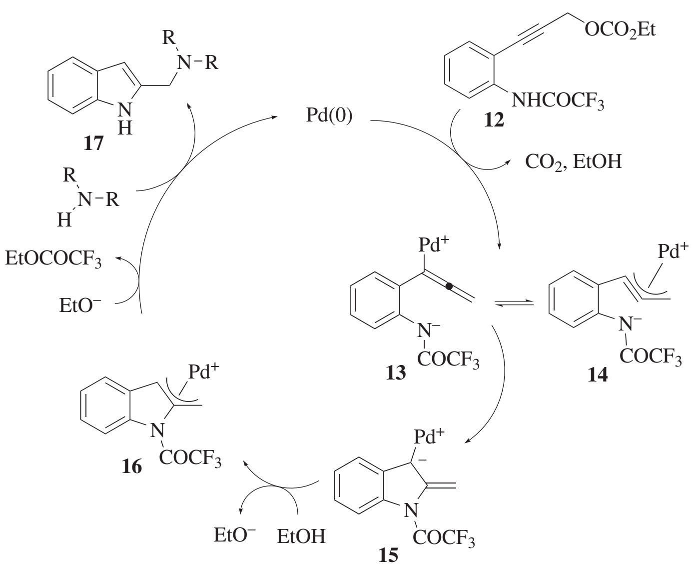
Alkynes or allenes containing a tethered aryl halide fragment such as 2-iodo-*N*-propargylanilides or *N*-2-halophenylallenamides can form carbopalladation adducts intramolecularly (Fig. 1, disconnection c). The addition intermediates derived from alkynes have been trapped by norbornene to give indoles containing polycyclic substituents at C(3).[32] Palladium acetate and (n-Bu)$_3$P catalyze the cyclization of 2-alkynyl-*N*-alkylidene-anilines to indoles (Fig. 1, disconnection b).[33]

The formation of 2-aminomethylindoles **17** from 3-(2-trifluoroacetamidophenyl)-1-propargyl carbonate ester **12**[34] (Fig. 1, disconnection a+f) is likely to proceed through the following basic steps (Scheme 5): (a) initial formation of the σ-allenylpalladium complex **13**—via an S_N2' reaction of the palladium complex with ester **12**—that is in equilibrium with the π-propargylpalladium intermediate **14**;[35] (b) intramolecular nucleophilic attack of the nitrogen at the central carbon of the allenyl/propargylpalladium complex;[36–42] (c) protonation of the resultant carbene complex **15** to give the π-allylpalladium complex **16**; (d) site selective intermolecular nucleophilic attack of the nitrogen nucleophile at the less-hindered allylic terminus of **16**. A similar mechanism is most probably operating for the conversion of ester **12** into 2-alkylindoles.[43]

The intramolecular version of the Heck reaction has been used for the construction of the indole ring[44] (Fig. 2, disconnection c) and an intramolecular halide displacement within arylpalladium intermediates by carbon nucleophiles has been



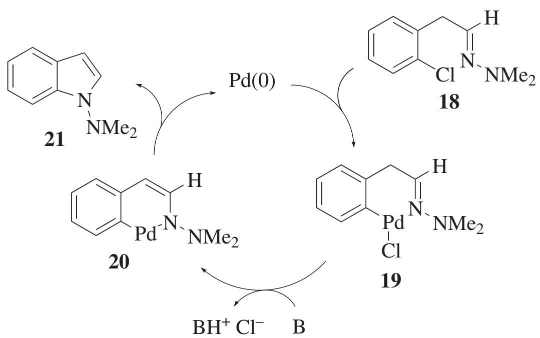
Scheme 4. Catalytic cycle of the palladium(0)-catalyzed annulation of 2-iodoanilines or 2-iodoanilides with internal alkynes.



Scheme 5. Catalytic cycle of the palladium(0)-catalyzed cyclization of 3-(2-trifluoro-acetamidophenyl)-1-propargyl carbonate esters.

proposed to account for the cyclization of 2-haloanilino enamines to indoles (Fig. 2, disconnection c).[45,46] Phenolic carbamates containing a bromovinylic fragment bound to the nitrogen atom are thought to give indole carbamates through an arene vinylation mechanism (Fig. 3).[47]

The general features of the *N*-arylation and *N*-vinylation method (Fig. 4) are shown in Scheme 6 for the cyclization of 2-chlorophenylacetaldehyde *N*,*N*-dimethylhydrazone (**18**) to 1-dimethylaminoindole (**21**)[48] and entail (a) an oxidative addition of the aryl chloride fragment to a palladium(0) species to afford the σ-arylpalladium intermediate **19**, (b) an intramolecular chloride displacement by nitrogen to give the palladacycle **20**, and (c) a subsequent reductive elimination leading to the formation of 1-dimethylaminoindole (**21**).

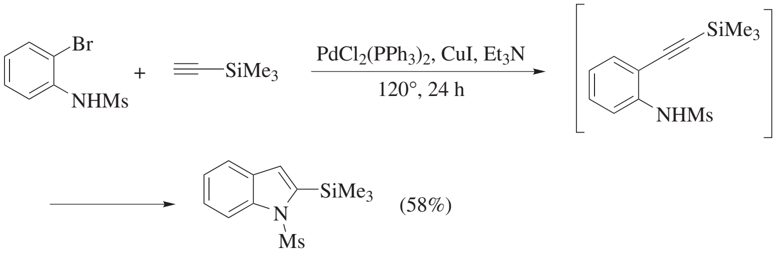


Scheme 6. Catalytic cycle of the palladium(0)-catalyzed cyclization via intramolecular *N*-arylation.

SCOPE AND LIMITATIONS

Indole Formation from Alkynes

2-Substituted Indoles. *From 2-Alkynylanilid(n)es.* The majority of the examples describing the alkyne-based synthesis of 2-substituted indoles originate from the observation that these indole derivatives can be prepared via palladium (II)-catalyzed cyclization of 2-alkynylanilides (Fig. 1, disconnection a; Scheme 1). The main variations of this method involve the synthesis of the starting 2-alkynylanilides. In early examples, the preparation of 2-alkynylanilides features the coupling of preformed copper(I) salts of terminal alkynes with 2-thallated anilides in acetonitrile.[23] This procedure has rarely found applications in indole synthesis, very likely because of the toxicity of the metal used. 2-Bromoacetanilides have subsequently been used in the coupling reaction,[49] but the 2-alkynylacetanilides are prepared through palladium(0)-catalyzed reaction of 2-bromoacetanilides with alkynylstannanes, a procedure that still uses toxic reagents. A significant improvement came with the discovery[50] that treatment of terminal alkynes with 2-haloanilides under Sonogashira conditions[51,52] can directly afford indole products in a single step through a tandem coupling–cyclization process (Eq. 2; Fig. 1, disconnection a+c).



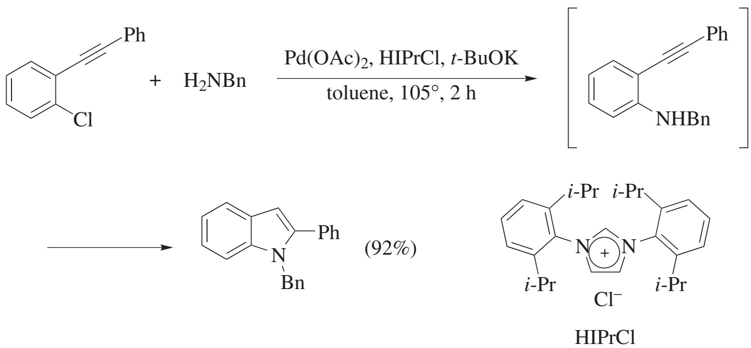
(Eq. 2)

The palladium-catalyzed coupling of terminal alkynes with aryl halides or triflates containing a nitrogen nucleophile in the *ortho* position followed by a palladium-catalyzed cyclization step has been extensively applied, providing stepwise and tandem syntheses of 2-substituted indoles. The cyclization of the coupling products can also be performed using base-mediated[50,53–64] and copper-catalyzed protocols.[50,65–69] The involvement of both palladium and copper catalysis in the cyclization of 2-alkynylanilines or their *N*-substituted derivatives has also been reported.[50,68] In some cases, particularly when indole products are obtained through tandem processes based on Sonogashira cross-coupling followed by a cyclization reaction, the specific role of the palladium catalyst and/or the base and/or copper in the formation of the pyrrole ring are not clearly established.

Cyclizations of 2-alkynylanilines or 2-alkynylanilides in the presence of palladium(II) are performed using $PdCl_2$, $PdCl_2(MeCN)_2$, or $PdCl_2(PPh_3)_2$ in acetonitrile, $PdCl_2/Bu_4NCl$ or Bu_4NBr in a biphasic aqueous HCl/CH_2Cl_2 system, or $PdBr_2$ in toluene.[23,49,70–76] Sodium tetrachloropalladate in dichloroethane at 100° is used in the related cyclization of 2-alkynylisocyanatobenzenes.[28] The combination of $FeCl_3$ and $PdCl_2$ in dichloroethane can give good results for the cyclization of 2-alkynylanilines, where iron may facilitate the in situ reoxidation of palladium(0) to palladium(II).[77]

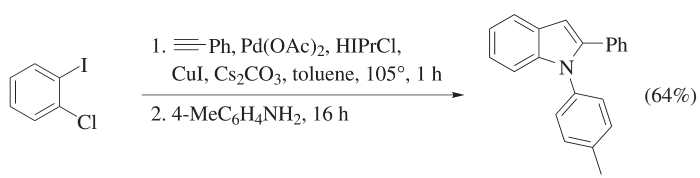
Tandem coupling/cyclization processes are typically carried out in the presence of copper(I) salts (in general CuI), with $PdCl_2(PPh)_3$ or $Pd(PPh_3)_4$ as precatalyst, *i*-Pr_2NH or Et_3N as nitrogen base, and MeCN, DMF or DMA/H_2O as the solvent.[50,78–85]

From 1,2-Dihaloarenes. The recently reported use of 1,2-dihaloarenes as the arene partners in the synthesis of 2-substituted indoles is an alternative to the classical methods based on 2-haloanilines or their derivatives.[86–88] 1,2-Dihaloarenes can engage in a cross-coupling reaction with terminal alkynes to give 2-alkynylhaloarenes that subsequently undergo a palladium-catalyzed *N*-arylation/cyclization reaction to give the corresponding indoles. A palladium complex generated from the commercially available imidazolium salt HIPrCl in combination with *t*-BuOK is an efficient catalyst for the conversion of 2-alkynylhaloarenes into indoles (Eq. 3; Fig. 1, disconnection a+g).[86] Mild bases such as Cs_2CO_3 or K_3PO_4 can also be used; however, longer reaction times and, in some cases, incomplete cyclization of the coupling intermediates are observed using these bases. These problems can be circumvented by adding CuI to the reaction mixture. 2-Alkynylhaloarenes can also be cyclized to indoles using $Pd(OAc)_2$ and $(t\text{-}Bu)_3P$, with *t*-BuOK (in toluene) or K_3PO_4 (in DMA) as the bases.[87]



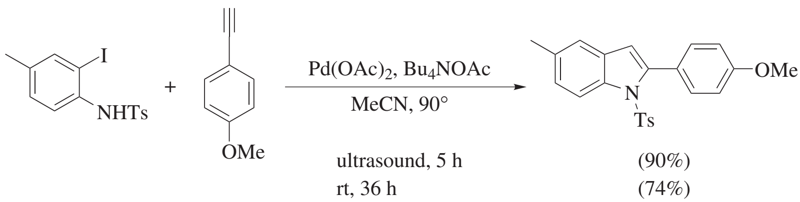
(Eq. 3)

The entire process (cross-coupling/*N*-arylation/cyclization) can be conducted as a one-pot protocol (Fig. 1, disconnection a+c+g).[86,87] An example is shown in Eq. 4.[86,89]

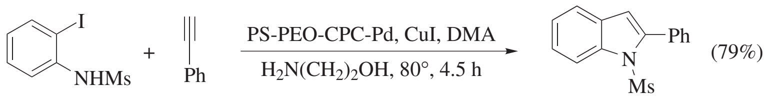


(Eq. 4)

Under Copper- and/or Phosphine-Free Conditions. Although the coupling/cyclization methods mentioned above are usually efficient and versatile, and their synthetic scope is quite large, they suffer from some drawbacks, such as terminal alkyne homocoupling in the presence of copper(I) cocatalysts[90] and/or the use of oxygen-sensitive phosphine ligands. Because of these limitations, some recent studies feature examples of copper- and/or phosphine-free protocols. Thus, 2-iodoanilides and terminal alkynes are converted into 2-substituted indoles via a one-pot coupling/cyclization process with $Pd(OAc)_2$ in the presence of Bu_4NOAc as the base under ultrasonic irradiation or standard conditions (Eq. 5).[84] Palladium nanoparticles stabilized in micelles formed by polystyrene-co-poly(ethylene oxide) and cetylpyridinium chloride as a surfactant (PS-PEO-CPC-Pd) are used in the tandem cross-coupling/cyclization of *N*-mesyl-2-iodoaniline with phenylacetylene (Eq. 6).[85] Both 2-iodoaniline and 2-iodotrifluoroacetanilide give lower yields. The activity of the colloidal catalyst is slightly lower than that of $PdCl_2(MeCN)_2$. Indoles can be prepared from 2-iodoaniline and a terminal alkyne under copper-free conditions in the presence of $Pd(OAc)_2$, Ph_3P, K_2CO_3, Bu_4NCl in DMF at 100°.[91] Access to 2-substituted indoles from 2-iodoaniline or 2-iodotrifluoroacetanilide and terminal alkynes without any copper promoter is also known in the presence of $Pd(OAc)_2$, TPPTS, and Et_3N in an $MeCN/H_2O$ mixture.[92]



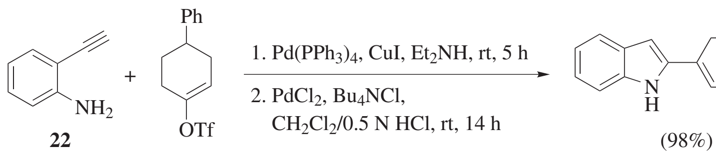
(Eq. 5)



(Eq. 6)

Via Coupling/Cyclization Methods with Supported Palladium Catalysts. In addition to soluble palladium complexes, supported palladium precatalysts may be used in the coupling/cyclization protocol. 2-Phenylindole can be prepared through a tandem process from 2-iodoaniline and phenylacetylene in 72% yield by employing palladium on activated carbon in the presence of CuI in DMF/H_2O (120°, 6 hours).[93] Palladium on activated carbon can also provide access to a variety of 2-substituted indoles from terminal alkynes and 2-iodoanilides in water.[94] Reactions are carried out in the presence of Ph_3P, CuI, and 2-aminoethanol as the base at 80°. Potassium-fluoride-doped alumina in the presence of palladium powder, CuI, and Ph_3P is another precatalyst system that furnishes 2-phenylindole in 80% yield from *N*-mesyl-2-iodoaniline under solvent-free and microwave-assisted conditions.[95] The use of a Pd(II)-NaY zeolite precatalyst in DMF at 140° in the presence of LiCl and Cs_2CO_3 allows for the conversion of 2-iodoanilides and terminal alkynes into the corresponding 2-substituted indoles.[96] The catalyst can be recycled up to five times by adding LiCl and Cs_2CO_3 to each reaction. However, slightly lower yields are obtained and a longer reaction time is necessary with each recycle.

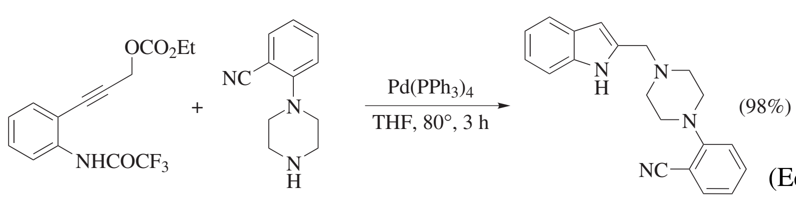
From 2-Ethynylaniline. All the procedures mentioned above require specific 1-alkynes for each indole, and this can limit their substrate scope. Furthermore, 2-haloanilides are used as starting materials in many cases and this usually requires an additional step to liberate the free indole (NH) derivatives. To circumvent this problem, an alternative approach has been developed in which free 2-substituted indoles (NH) can be synthesized from the same acetylenic building block (Fig. 1, disconnection a+e). Thus, 2-ethynylaniline (**22**) is used as the acetylenic building block. This compound can be prepared in 81% overall yield through a straightforward palladium-catalyzed coupling of 2-iodoaniline with ethynyltrimethylsilane, followed by desilylation with KF.[74] This indole synthesis features a palladium-catalyzed reaction of 2-ethynylaniline with vinylic or aryl triflates or halides followed by a palladium-catalyzed cyclization of the resultant coupling product.[74] The cyclization step can be performed in an acidic two-phase system at room temperature to give yields comparable with or higher than those obtained with $PdCl_2$ in MeCN at 60–80°. The acidic medium does not prevent the unprotected amino group from attacking the activated carbon−carbon triple bond. The entire coupling/cyclization process can be conducted as a one-pot process, as shown in Eq. 7.[71]



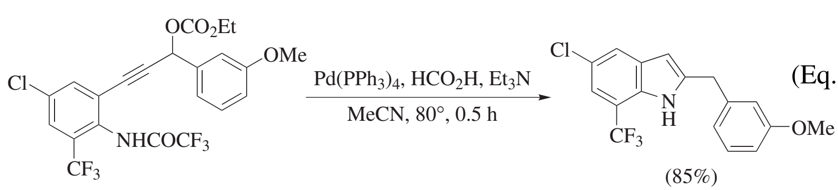
22

(Eq. 7)

From 3-(2-Trifluoroacetamidophenyl)-1-propargyl Carbonate Esters. A recent alkyne-based cyclization to 2-substituted indoles uses 3-(2-trifluoroacetamidophenyl)-1-propargyl carbonate esters as the starting materials and involves an intramolecular palladium-catalyzed heterocyclization followed by an intermolecular nucleophilic attack on a π-allylpalladium intermediate (Scheme 5; Fig. 1, disconnection a+f). The trifluoroacetyl group plays a key role in this process by increasing the acidity of the amide, thus aiding the formation of a strong, anionic nucleophile for the intramolecular attack. In addition, the trifluoroacetyl group is easily removed under the reaction conditions and/or upon workup so that free indoles (NH) can be obtained directly. Secondary amines and formate anions can be used as external nucleophiles in this process to prepare 2-aminomethylindoles (Eq. 8)[34] and 2-alkylindoles (Eq. 9),[43] respectively. Steric effects appear to influence the reaction outcome with secondary amines; for example, a moderate yield is obtained with diisopropylamine. With primary amines, the efficiency of the reaction is reduced by the occurrence of side reactions producing complex reaction mixtures. Interestingly, these indole syntheses give excellent results using a monodentate phosphine ligand such as Ph_3P, although it has been reported that bidentate ligands afford more stable π-propargylpalladium complexes,[97,98] the suggested intermediates of this cyclization, and that the best ligands for the palladium-catalyzed reaction of propargyl halides[99] and carbonates[36] with soft nucleophiles are the bidentate ligands.

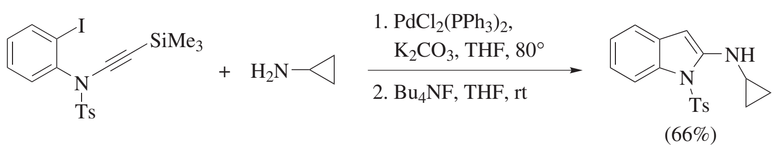


(Eq. 8)



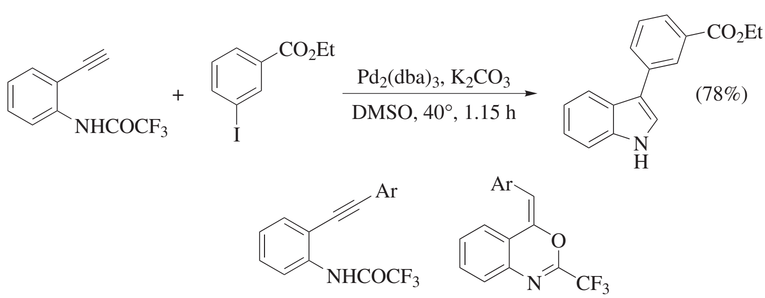
(Eq. 9)

From 2-Halo-N-alkynylanilides. A common feature of all the syntheses of 2-substituted indoles described above is that the cyclization event involves aniline derivatives bearing an acetylenic moiety adjacent to the nitrogen functionality. An alternative approach uses acetylenic precursors in which the alkyne fragment is directly bound to the nitrogen atom. In particular, 2-halo-*N*-alkynylanilides are converted into 2-aminoindoles via an aminopalladation/reductive elimination process in the presence of primary and secondary amines (Eq. 10; Fig. 1, disconnection c+e).[29] Among the bases investigated, K_2CO_3 and Cs_2CO_3 are the most efficient; $PdCl_2(PPh_3)_2$ as the precatalyst gives higher yields than $Pd(PPh_3)_4$, and THF is more suitable than DMF or toluene as the solvent.



(Eq. 10)

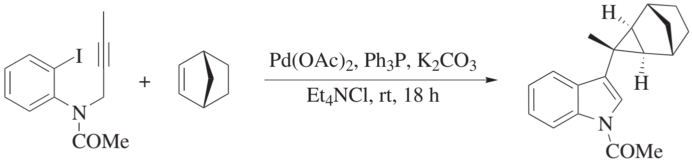
3-Substituted Indoles. Only a few studies have been reported that describe the direct synthesis of 2-unsubstituted, 3-substituted indoles from acetylenic precursors. One of the most efficient procedures is the cyclization of 2-ethynyltrifluoroacetanilide with aryl iodides, a reaction that is based on the aminopalladation/reductive elimination protocol (Eq. 11,[100] Fig. 1, disconnection a+d, Scheme 3). The major problem in this cyclization process is the formation of coupling derivative **23**, which is a significant side product or even the main product observed when using a variety of phosphine ligands. In addition, depending on reaction conditions, a competing cyclization to give product **24** is observed. Very likely, this cyclization arises from the nucleophilic attack of the carbonyl oxygen at the internal carbon atom of the acetylenic fragment. Both the nature of the solvent and the catalyst system have a strong influence on the *N*-/*O*-cyclization ratio. The highest yields of the desired 3-substituted indoles are obtained by using $Pd_2(dba)_3$ as the palladium(0) source, DMSO as the solvent, K_2CO_3 (or Cs_2CO_3) as the base, and omitting phosphine ligands.



(Eq. 11)

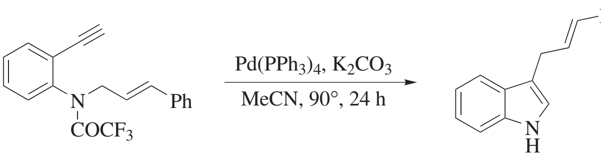
23 **24**

Indoles containing polycyclic substituents at C(3) are prepared from 2-iodo-*N*-propargylanilides through a cascade process (Fig. 1, disconnection c).[32,101] An example of this construction is shown in Eq. 12.[32] The reaction proceeds through an intramolecular carbopalladation step, followed by capture of norbornene to give a σ-alkylpalladium(II) intermediate that does not contain β-hydrogens aligned for the elimination of HPd species and undergoes an intramolecular Mizoroki–Heck reaction.



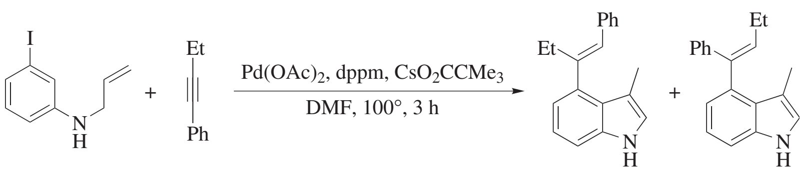
(45%) (Eq. 12)

Examples of acetylenic precursors that afford 3-substituted indoles have also been described starting from *N*-allylic 2-ethynyltrifluoroacetanilides[102] (Eq. 13; Fig. 1, disconnection a+d) and *N*-mesyl-2-ethynylaniline.[103] *N*-allylic 2-ethynyltrifluoroacetanilides are converted into the corresponding 3-allylic indoles through the aminopalladation/reductive elimination mechanism. *N*-mesyl-2-ethynylaniline affords a 3-substituted indole through a tandem process that entails an intramolecular aminopalladation, an olefin insertion, and a protonolysis step. The indole product, however, is isolated in low yield.



(49%) (Eq. 13)

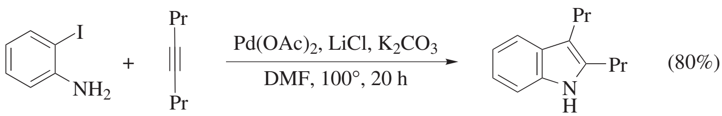
Recently, an additional approach to 3-substituted indoles starting from 3-iodo-*N*-allylaniline and internal alkynes has been described.[104] The reaction proceeds through carbopalladation, vinylic to aryl palladium migration, and intramolecular Heck reaction. Indole products are isolated in moderate yields. However, this indole synthesis is interesting in that the formation of the pyrrole ring containing a substituent at the C(3) position is accompanied by the introduction of a substituted olefinic system at the C(4) position (Eq. 14).



dppm = bis(diphenylphosphino)methane (45%) 10:1 (Eq. 14)

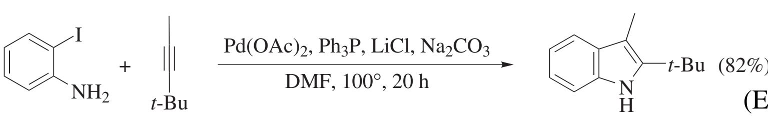
2,3-Disubstituted Indoles. Indole syntheses based on the annulation of internal alkynes with 2-haloanilines or their *N*-substituted derivatives[30,31] (Fig. 1, disconnection a+c; Scheme 4) and those based on the aminopalladation/reductive elimination of 2-alkynyltrifluoracetanilides with aryl or vinyl halides or triflates, alkyl halides, and allylic carbonates[7,105–108] (Fig. 1, disconnection a+d; Scheme 3) are some of the most powerful methods for the construction of this class of compounds.

From Internal Alkynes and 2-Haloanilid(n)es. The annulation of internal alkynes with 2-haloanilines was initially developed using 2-iodoanilines and their N-substituted derivatives.[30,31] The best results were obtained using an excess of the internal alkyne in the presence of sodium or potassium carbonate as bases, LiCl or Bu_4NCl as additives, and occasionally adding Ph_3P at 100° in DMF. Under these conditions 2,3-disubstituted indoles are isolated in good to excellent yields (Eq. 15).[31] An oxime-derived, chloro-bridged palladacycle, which is thermally stable and insensitive to air or moisture, has also been employed.[109]

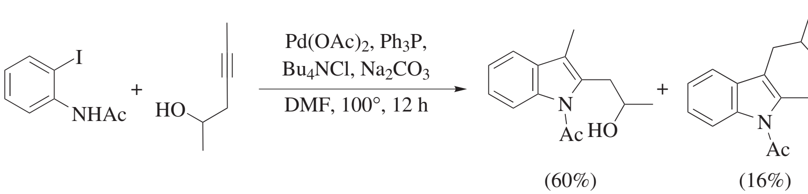


(Eq. 15)

With unsymmetrical alkynes, the regiochemical outcome is controlled by the carbopalladation step. Steric and coordinating effects are the main controlling factors. These effects follow the general trend observed in related reactions involving a carbopalladation step.[110,111] Steric effects tend to control the conversion of the π-alkyne–σ-organopalladium intermediate formed initially (**9**, Scheme 4) into the carbopalladation adduct **10**, preferentially directing the palladium moiety to the more hindered end of the carbon–carbon triple bond (Eq. 16).[31] Coordinating effects influence the formation of vinylic adducts in a way that the added palladium ends up close to the coordinating group (Eq. 17).[31] Electronic factors are believed to play a minor role; however, they must have some influence on the catalytic process. For example, the site selectivity decreases significantly for the annulation with electron-deficient anilines.[112]

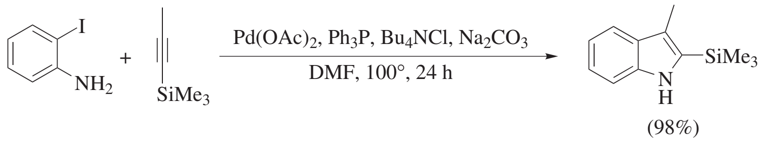


(Eq. 16)

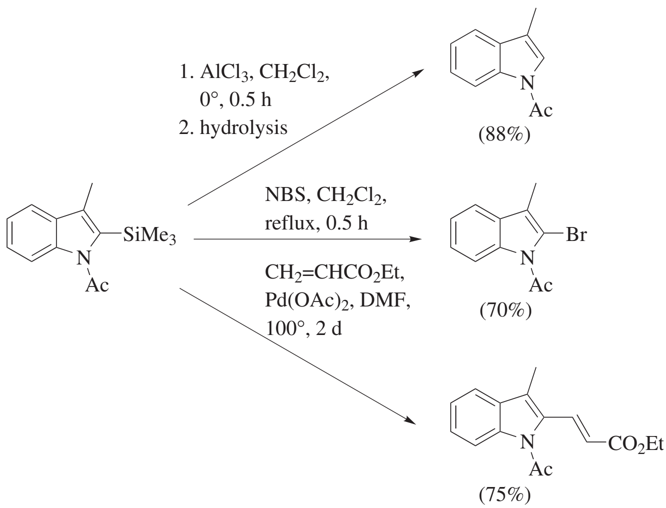


(Eq. 17)

The major drawback of this procedure is that it relies on substantially different steric bulk between the two substituents on the ends of the alkyne. For example, the direct annulation of a diaryl acetylene usually results in a mixture of two products. Consequently, some of the most successful syntheses based on this annulation protocol involve the reaction of 2-iodoanilines or 2-iodoanilides with alkynes containing a bulky silyl group at one of the acetylenic termini. Indeed, the reaction is highly site selective, with silylalkynes providing 3-substituted-2-silylindoles (Eq. 18),[31] which are versatile intermediates for the synthesis of a vast array of indole derivatives (Eq. 19).[112–121]

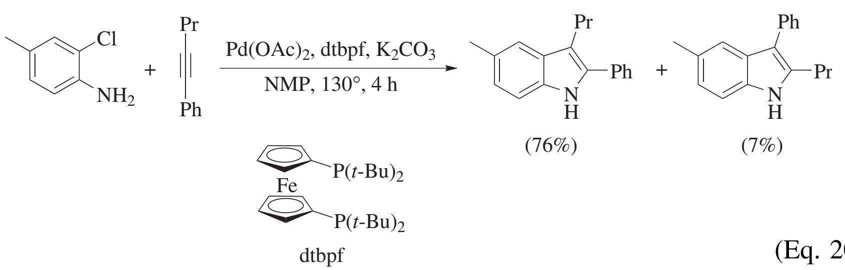


(Eq. 18)



(Eq. 19)

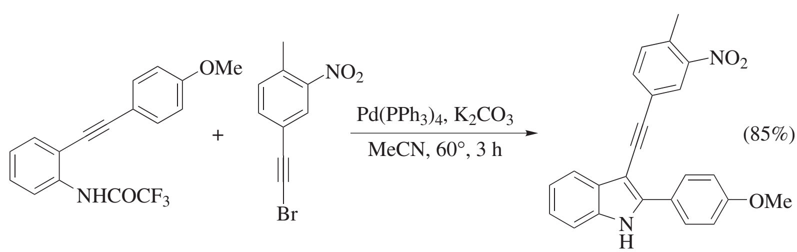
To overcome drawbacks associated with this process, such as the high cost and low stability of 2-iodoanilines, a procedure has been developed in which they are replaced by the much cheaper bromo or chloro derivatives.[122] As the oxidative insertion usually requires an electron-rich palladium species with these substrates, the phosphine-free protocol frequently adopted in the reaction of 2-iodoanilines is not applicable. Several types of highly active phosphine ligands have been examined. The best results, even in terms of site selectivity, are obtained using dtbpf under the conditions shown in Eq. 20 for the reaction of a 2-chloroaniline.[122]



(Eq. 20)

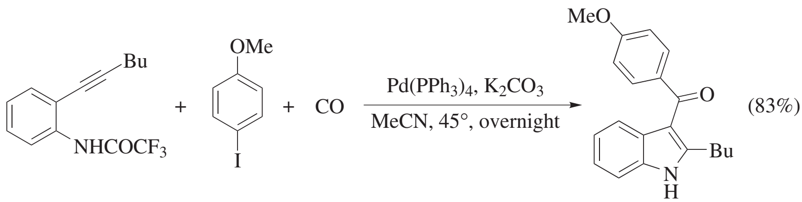
From 2-Alkynyltrifluoroacetanilides and C_{sp^3}, C_{sp^2}, and C_{sp} Donors. The aminopalladation/reductive elimination protocol allows for the preparation of a broad range of symmetrical and unsymmetrical 2,3-disubstituted indoles from 2-alkynyltrifluoroacetanilides and a wide range of cyclization partners such as aryl or heteroaryl iodides,[106,123,124] bromides,[105,106] chlorides[107] and triflates,[105,106,123] vinylic triflates,[106,123,124] allylic esters,[102,106] alkyl iodides and bromides,[106,125] and alkynyl bromides.[108] When unsymmetrical 2,3-disubstituted indoles are the target products, this method provides the remarkable advantage that formation of constitutional isomers is excluded. The site selectivity follows from the sequence of events and is unambiguous. Substituents close to the oxidative addition site usually do not hamper the reaction. 2-Alkynyltrifluoroacetanilides containing alkyl, vinylic, electron-withdrawing, and electron-donating substituents on the alkyne moiety have been successfully employed. 2-Alkynylanilines and 2-alkynylacetanilides provides unsatisfactory results, suggesting that the acidity of the nitrogen–hydrogen bond plays a key role in this cyclization reaction and that organopalladium complexes are less effective than $PdCl_2$ in activating the carbon–carbon triple bond toward intramolecular nucleophilic attack. Indeed, a variety of cyclizations of alkynes containing proximal amino[123–125] and amido[23,49,50,70,126–132] groups under catalysis by palladium(II) salts have been described. Notably, the trifluoroacetyl group is readily removed during the reaction and/or the workup to allow for the formation of free indoles (NH) thus avoiding deprotection steps.

Carbonates (Na_2CO_3, K_2CO_3, Cs_2CO_3) are better bases than Et_3N, and MeCN or THF is typically used as the solvent for these aminopalladation/reductive elimination reactions. Depending on the cyclization partner, reaction temperatures range from room temperature for vinyl triflates to 120° for aryl chlorides. As to the phosphine ligands, the popular $Pd(PPh_3)_4$ is an efficient precatalyst with aryl or heteroaryl iodides,[106,123,124] bromides,[105,106] and triflates,[105,106,123] vinylic triflates,[106,123,124] allylic carbonates[102,106] (in stepwise and one-pot protocols), and 1-bromo-2-arylalkynes.[108] Its use is exemplified in Eq. 21[108] with the preparation of 2-aryl-3-alkynylindoles.



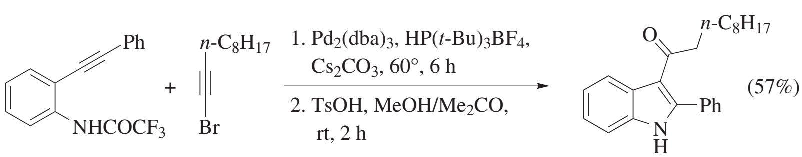
(Eq. 21)

The aminopalladation/reductive elimination reaction performed under an atmosphere of carbon monoxide affords 2-substituted 3-acylindoles in good to high yields. With neutral, electron-rich, and slightly electron-poor aryl iodides and vinylic triflates, this three-component reaction may be carried out using $Pd(PPh_3)_4$ as the palladium(0) source under a balloon of carbon monoxide (Eq. 22).[106,124] With electron-deficient aryl iodides, good results can be obtained with $(2\text{-tol})_3P$ and $Pd(dba)_2$ or by using anhydrous acetonitrile and a higher pressure of carbon monoxide.



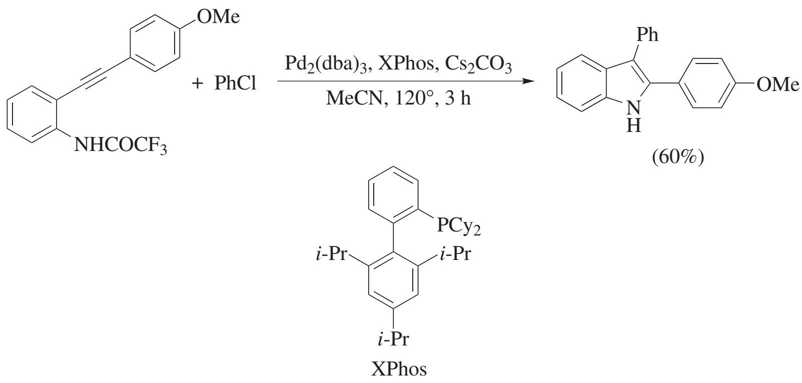
(Eq. 22)

The reaction of 1-bromoalkynes with 2-alkynyltrifluoroacetanilides affords 2-substituted 3-alkynylindoles.[108] Reactions are usually carried out using $Pd(PPh_3)_4$ and Cs_2CO_3 or K_2CO_3 in MeCN. With 1-bromoalkynes containing alkyl groups bound to the alkyne fragment, the use of $(t\text{-Bu})_3P$ (added to the reaction mixture as the tetrafluoroborate salt)[133] and $Pd_2(dba)_3$ can produce a significant increase in the yields. 2-Substituted 3-alkynylindoles represent useful intermediates for the synthesis of 2-substituted 3-acylindoles. The latter can be prepared from 2-alkynyltrifluoroacetanilides and 1-bromoalkynes via a one-pot cyclization/hydration protocol, omitting the isolation of 2-substituted 3-alkynylindoles (Eq. 23).[108]



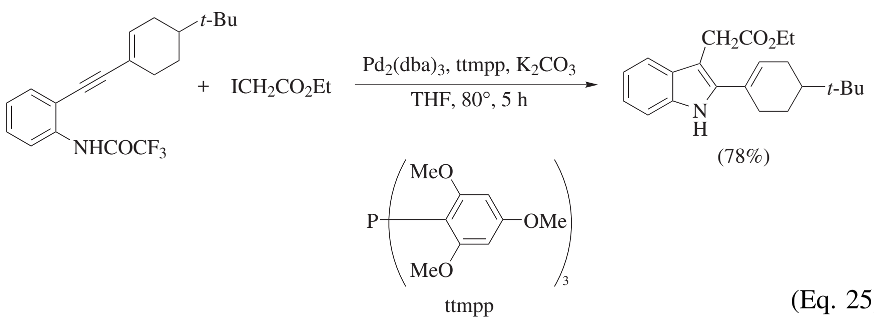
(Eq. 23)

Aryl chlorides are more reluctant to undergo oxidative addition to palladium(0) and require the use of XPhos (Eq. 24), one of the biaryl monophosphines that enhance the rate of the oxidative addition of aryl chlorides to palladium(0) species.[134–136] The use of this ligand solves one of the major problems in realizing this type of indole synthesis with relatively unreactive precursors of organopalladium complexes, namely the competitive formation of simple 2-substituted indoles, the formation of which does not involve the aryl halide partner.



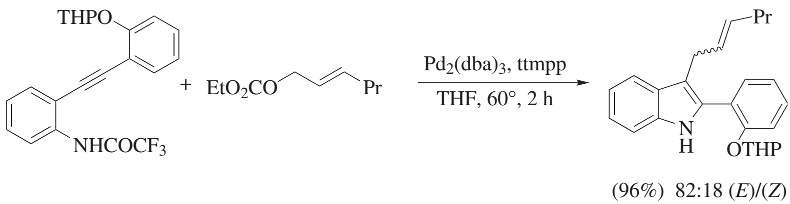
(Eq. 24)

Even with ethyl iodoacetate and benzyl bromides[106,125] a more active phosphine ligand is required for the oxidative addition to palladium(0). Indolylcarboxylate esters and 2-substituted 3-benzylindoles are isolated in good to high yields in the presence of the electron-rich, sterically-encumbered ligand tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp) and $Pd_2(dba)_3$ (Eq. 25).[125]



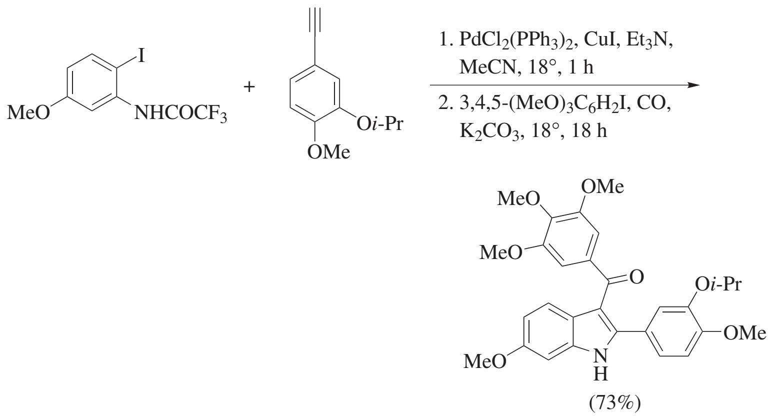
(Eq. 25)

The ttmpp ligand also provides remarkable site selectivity in the reaction of 2-alkynyltrifluoroacetanilides with allylic carbonates where steric differences between the two allylic termini are small.[102] The use of ttmpp in these reactions leads to the formation of products that bear the indole unit located almost exclusively on the less substituted terminus of the allylic system (Eq. 26).[102] The process is accompanied by some isomerization of the olefin. 2-Substituted 3-allylindoles can also be prepared through stepwise and one-pot protocols.[102] The stepwise protocol involves the *N*-allylation of 2-alkynyltrifluoroacetanilides [$Pd_2(dba)_3$, dppb, THF, 60°] followed by an aminopalladation/reductive elimination step [$Pd(PPh_3)_4$, K_2CO_3, MeCN, 90° or $Pd_2(dba)_3$, ttmpp, DME, 100°]; the one-pot synthesis is carried out by treating 2-alkynyltrifluoroacetanilides with allylic carbonates and $Pd(PPh_3)_4$ in THF at 60° until their disappearance and then adding K_2CO_3 and raising the reaction temperature to 80°.

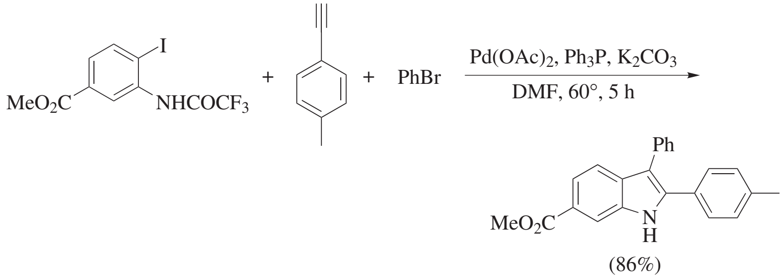


(Eq. 26)

On the whole, the aminopalladation/reductive elimination route to indoles entails three basic steps: (1) acylation of 2-haloanilines with trifluoroacetic anhydride, (2) cross-coupling of terminal alkynes with 2-halotrifluoroacetanilides, (3) indole formation by aminopalladation/reductive elimination. To make this process more practical, one-pot (Eq. 27)[137,138] and one-pot tandem (Eq. 28)[139] protocols (Fig. 1, disconnection a+c+d) have been developed.



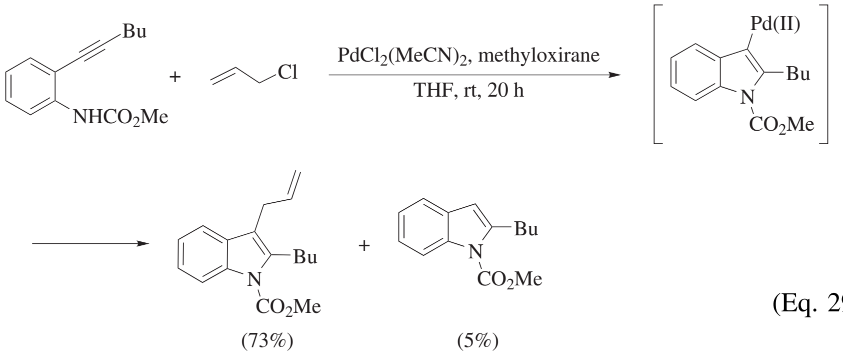
(Eq. 27)



(Eq. 28)

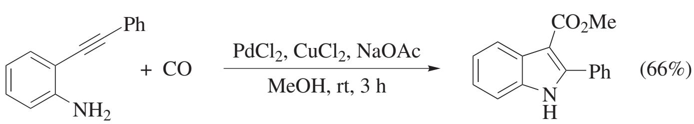
From 2-Alkynylanilid(n)es and Allylic Halides, Alkenes, and CO/MeOH. The preparation of 2,3-disubstituted indoles via the palladium(II)-catalyzed cyclization of 2-alkynylanilines and -anilides is based on the observation that σ-indolylpalladium intermediates **2** (Scheme 1) can be trapped by suitable reagents so that the cyclization step may be combined with the functionalization of the indole nucleus at C(3) (Fig. 1, disconnection a+d). The potential of this trapping approach to the synthesis of indole derivatives has not gone unnoticed and tandem processes that employ this strategy have been developed.

In the tandem allylative cyclization of 2-alkynyl-*N*-methoxycarbonylanilides (Eq. 29),[70] the reaction proceeds through a site-selective attack of the σ-indolylpalladium intermediate on the γ position of allyl chlorides. The use of the unprotected amine or the acetamido derivative give unsatisfactory results and lack of control of the olefin geometry is observed in reactions using a substituted allylic chloride. A large excess of the allyl chloride (allyl chloride/alkyne 10:1) is needed to obtain the best results. The presence of methyloxirane as the proton scavenger is crucial for minimizing the competitive protonation of the σ-indolylpalladium intermediate leading to 3-unsubstituted, 2-substituted indoles.

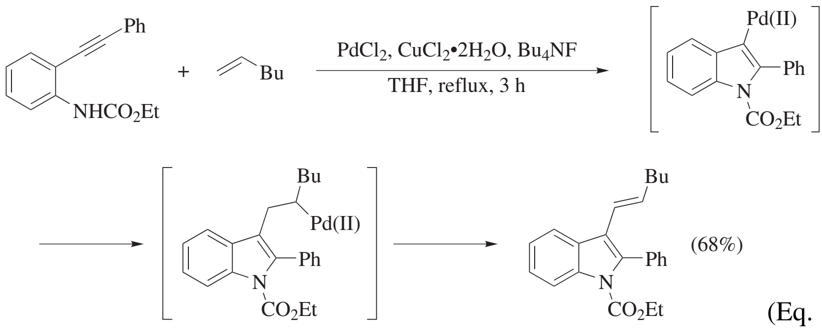


(Eq. 29)

σ-Indolylpalladium intermediates can be trapped by carbon monoxide or alkenes to give indole products incorporating carbon monoxide,[128,129] vinylic,[130,131] or alkyl groups at the C(3) position.[103] In the first case, treatment of a 2-alkynylaniline with $PdCl_2$ in methanol under an atmosphere of carbon monoxide affords a σ-acylpalladium derivative which reacts with methanol to give an indolylcarboxylate ester (Eq. 30).[128,129] Palladium(0) species formed in this step are oxidized to the active palladium(II) species by $CuCl_2$; the use of 1,4-benzoquinone, disodium peroxysulfate, or molecular oxygen met with failure. Similar conditions are used to develop a domino cyclization/Heck reaction producing 2-substituted 3-vinylic indoles with alkenes containing electron-withdrawing groups.[130] Modified conditions ($PdCl_2$, excess amounts of Bu_4NF and $CuCl_2{\bullet}H_2O$ as a reoxidant) are necessary to extend the reaction to alkenes lacking the activation of an electron-withdrawing group (Eq. 31).[131] $Cu(OAc)_2$, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), and pyridine 1-oxide fail to give the desired products.

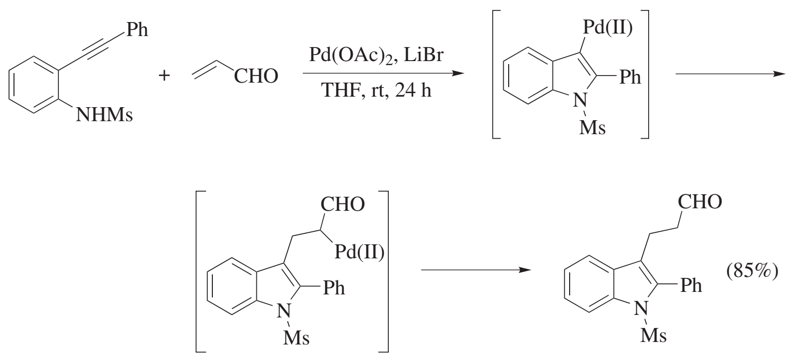


(Eq. 30)



(Eq. 31)

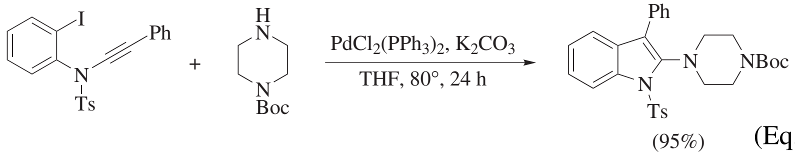
The reaction of 2-alkynylanilides with α,β-enals and -enones in the presence of LiBr affords 2-substituted, 3-alkylindoles via a tandem palladium(II)-catalyzed aminopalladation that entails addition of the resultant σ-indolylpalladium(II) intermediate to the α,β-unsaturated carbonyl compound, followed by protonolysis of the carbon−palladium bond with regeneration of the palladium(II) species (Eq. 32).[103] The addition of LiBr is crucial to inhibit β-elimination in the carbopalladation intermediate **25**. This remarkable halide effect is accounted for by assuming that the bromide anion inhibits the β-hydride elimination by occupancy of the free coordination sites. Also, electron donation from the bromide anion to palladium results in a highly polarized carbon−palladium bond that is readily cleaved via protonolysis.



(Eq. 32)

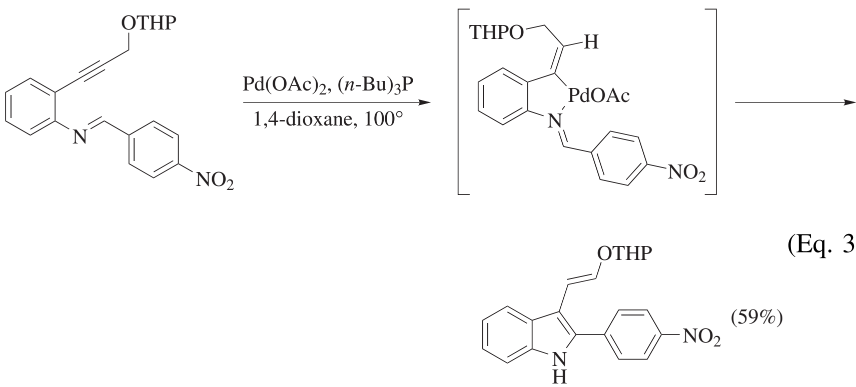
25

From N-Alkynyl-2-haloanilides. The cyclization of *N*-alkynyl-2-haloanilides with primary and secondary amines (Fig. 1, disconnection c+e) provides a convenient entry to 2-amino-3-substituted indoles, a class of compounds that is otherwise difficult to obtain. Typical reaction conditions are shown in Eq. 33,[29] although Cs_2CO_3 can also be used. THF is more suitable than DMF or toluene as the solvent. Higher yields are obtained when $PdCl_2(PPh_3)_2$ is used as the precatalyst; $Pd(PPh_3)_4$ is less effective, most probably because of the higher phosphine content, which reduces the activity of the actual palladium(0) catalyst.



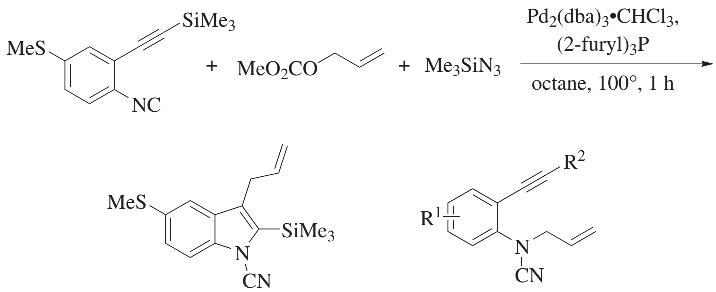
(Eq. 33)

From 2-Alkynyl-N-alkylideneanilines. The cyclization of 2-alkynyl-*N*-alkylideneanilines bearing an aryl substituent on the alkylidene fragment (Fig. 1, disconnection b) affords 2-aryl- and 2-heteroaryl-3-(1-alkenyl)indoles in good yields (Eq. 34).[33] The reaction involves the addition of a HPdOAc species to the carbon−carbon triple bond followed by a cyclization step. HPdOAc is formed by the oxidative addition of AcOH to palladium(0). Reaction of (n-Bu)$_3$P with Pd(OAc)$_2$ forms Ac$_2$O and palladium(0), and in situ hydrolysis of the Ac$_2$O provides the AcOH. The preparation of alkyl-substituted imines tends to fail due to their instability, hence, 2-alkylindoles are best prepared in a one-pot procedure. The formation of imines from 2-alkynylanilines and benzaldehyde or secondary aliphatic aldehydes followed by in situ cyclization proceeds without problems.



(Eq. 34)

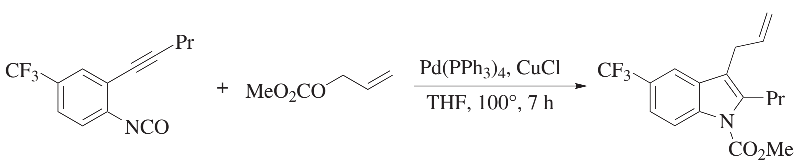
From 2-Alkynylisocyanobenzenes. 2-Alkynylisocyanobenzenes are converted into 2-substituted, 3-allyl-*N*-cyanoindoles in good to acceptable yields by a three-component reaction with allyl methyl carbonate and trimethylsilyl azide in the presence of Pd$_2$(dba)$_3$•CHCl$_3$ and (2-furyl)$_3$P at 100° (Eq. 35; Fig. 1, disconnection a+d).[26] At lower temperature (up to 40°) the reaction affords *N*-allyl cyanamides **26**. (2-Furyl)$_3$P gives the best results when combined with the Pd$_2$(dba)$_3$•CHCl$_3$ complex but other monodentate phosphine ligands such as Ph$_3$P, (2-tol)$_3$P, and (4-FC$_6$H$_4$)$_3$P can afford satisfactory results. In contrast, bidentate phosphine ligands such as 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp), and 1,4-bis(diphenylphosphino)butane (dppb) are ineffective. Toluene or THF can also be used as solvent. However, in polar solvents such as DCE, MeCN, or DMF only small amounts of the indole product are formed.



26

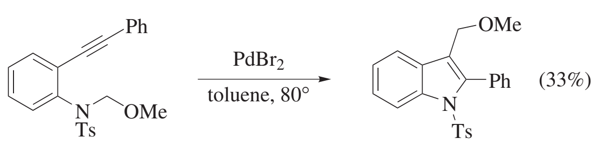
(Eq. 35)

From 2-(Alkynyl)phenylisocyanates. The reaction of 2-(alkynyl)phenylisocyanates with allyl carbonates gives 2-substituted 3-allyl-N-(alkoxycarbonyl) indoles in the presence of $Pd(PPh_3)_4$ and CuCl (Eq. 36; Fig. 1, disconnection a+d).[27,28] Copper(I) chloride affords higher yields than CuBr and is far superior to other copper salts such as CuI, CuOAc, $(CuOTf)_2$•benzene, or $CuCl_2$. Zinc chloride is also usable as a partner for palladium. The combinations $Pd(OAc)_2$/Ph_3P, $Pd_2(dba)_3$•$CHCl_3$/dppe, and $Pd_2(dba)_3$•$CHCl_3$/(2-furyl)$_3$P are less effective than $Pd(PPh_3)_4$. THF is the solvent of choice whereas toluene, MeCN, and DMF give the desired indole product in lower yield. Longer reaction times are required when a bulky substituent is bound to one of the alkyne termini. With an alkynyl *tert*-butyl group, no allylindole is obtained and the sole product is a 2-alkynyl-N-allylaniline derivative. Electronic effects of the substituents *para* to the isocyanate group and the bulk of the alcoholic fragment of the allylic carbonates do not seem to exert a significant influence on the reaction outcome.

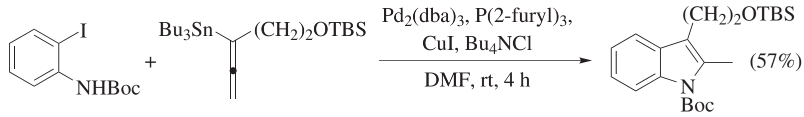


(Eq. 36)

From 2-Alkynylphenyl N,O-Acetals and from 2-Iodoanilides and 1-(Tributylstannyl)-1-substituted Allenes. A few examples of intramolecular cyclizations of 2-alkynylphenyl N,O-acetals (Eq. 37)[140] and of one-step syntheses of 2-methyl-3-substituted indoles from N-acyl-2-iodoanilines and 1-(tributylstannyl)-1-substituted allenes (Eq. 38)[141] are also known.



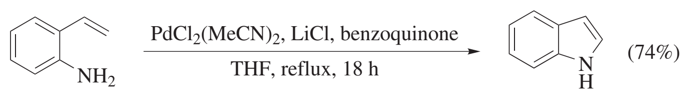
(Eq. 37)



(Eq. 38)

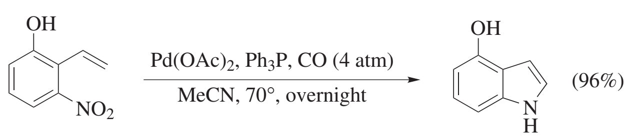
Indole Formation from Alkenes

Unsubstituted Indoles. 2-Vinylaniline[142] and its *N*-substituted derivatives, including 2-vinyl-*N*-tosylanilides,[143–146] 2-vinylacetanilides,[147] and 2-vinyl-*N*-alkylanilines,[148] undergo palladium-catalyzed cyclization to give unsubstituted indoles (Fig. 2, disconnection a). Palladium chloride and $PdCl_2(MeCN)_2$ are typically employed as precatalysts in the presence of benzoquinone or $CuCl/O_2$ as reoxidants and LiCl as an additive. An example is depicted in Eq. 39.[142] Perhaps the main limitation of this approach is that the requisite 2-vinylanilines require lengthy syntheses[145,149–152] and that more direct syntheses often proceed in only moderate yield.[145,153]



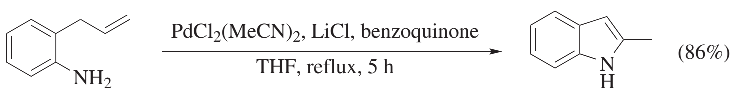
(Eq. 39)

2-Nitrostyrenes have been used as precursors for unsubstituted indoles through a reductive *N*-heterocyclization process (Fig. 2, disconnection a). The involvement of 2-nitrostyrenes as substrates in the palladium-catalyzed synthesis of indoles was first observed as a side reaction of treating 2-bromonitrobenzenes with ethylene in the presence of palladium acetate to prepare 2-nitrostyrenes.[147] In some cases, significant amounts of indole products were formed in addition to the expected Mizoroki–Heck products, most probably via the in situ reduction of the nitro group of the 2-nitrostyrenes. Subsequent studies developed this side reaction into a new indole synthesis. In the presence of 20 atm of carbon monoxide, $PdCl_2(PPh_3)_2$, and an excess of $SnCl_2$ at 100°, 2-nitrostyrene gives indole in 50% yield.[154,155] Other additives such as $BF_3{\bullet}Et_2O$, $CuCl_2$, $FeCl_3$, or $SnCl_4$ are ineffective. Further improvement on these conditions have led to a protocol which involves lower temperature and pressure and does not require an added Lewis acid (Eq. 40).[156] In general, the reaction appears to be unaffected by substituents on the aromatic ring. 2-Nitrostyrenes containing either electron-withdrawing or electron-donating substituents give indoles in moderate to excellent yields.



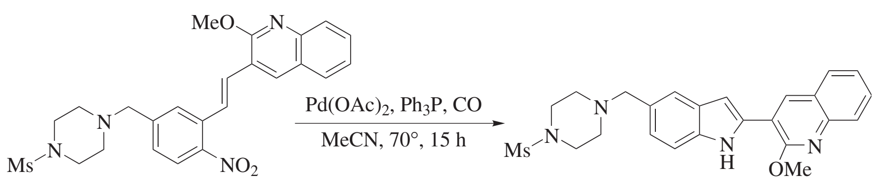
(Eq. 40)

2-Substituted Indoles. 2-Substituted indoles are prepared from 2-allylanilines, 2-nitrostyrenes (Fig. 2, disconnection a) and 2-haloanilino enamines (Fig. 2, disconnection c). 2-Allylanilines undergo palladium-catalyzed cyclization to 2-substituted indoles in the presence of $PdCl_2(MeCN)_2$ as the source of palladium(II) and benzoquinone to reoxidize palladium(0) to palladium(II) (Eq. 41).[142] Neither palladium acetate nor lithium chloropalladate is as effective. The reaction is rarely applied to the synthesis of 2,3-substituted indoles. In one of the few examples, the indole formation from properly substituted 2-allylanilines is used to prepare 2-substituted 3-alkoxyindoles.[157]

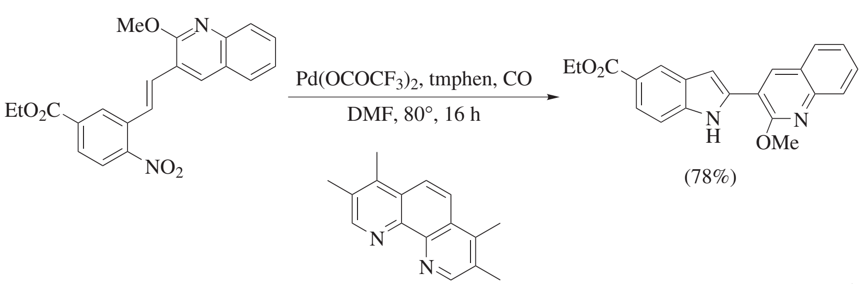


(Eq. 41)

The reductive cyclization of 2-nitrostyrenes to 2-substituted indoles can be carried out using carbon monoxide (20 atm), $PdCl_2(PPh_3)_2$, and an excess of $SnCl_2$ in dioxane at 100°.[154,155] According to an improved protocol, carbon monoxide (4 atm), $Pd(OAc)_2$, and Ph_3P in MeCN at 70° can be successfully employed (Eq. 42).[156,158–161] The configuration of the alkene moiety does not affect the reaction outcome. These improved conditions, however, require a relatively high catalyst loading [6 mol % of $Pd(OAc)_2$] and 24 mol % of Ph_3P. In some cases, chromatography may be necessary to remove both triphenylphosphine oxide and a 3,3′-bisindole derivative that can form under the reaction conditions. Further optimization with regard to catalyst, ligand, solvent, temperature, and carbon monoxide pressure has led to the following conditions: 0.1 mol % of $Pd(OCOCF_3)_2$, 0.7 mol % of tmphen, DMF, 80°, 1 atm of carbon monoxide (Eq. 43).[161] For some reactions, the combination of $Pd(OAc)_2$/phenanthroline or the preformed catalyst $phen_2Pd(BF_4)_2$ give similar results.[161]



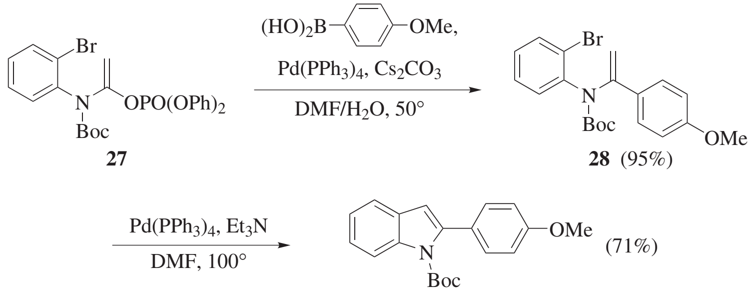
(95%) (Eq. 42)



tmphen

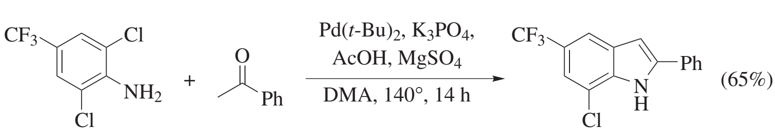
(Eq. 43)

N-Boc derivatives **28** of 2-haloanilino enamines, readily available via Suzuki–Miyaura cross-coupling of arylboronic acids with enamine derivatives **27**, provide access to 2-substituted indoles in the presence of $Pd(PPh_3)_4$ and Et_3N in DMF at 100° (Eq. 44).[162] Changing the base to $(i\text{-Pr})_2NEt$ or 1,2,2,6,6-pentamethylpiperidine (PMP) leads to dehalogenation as a significant side reaction. The entire process can also be conducted as a tandem process using $Pd(PPh_3)_4$, Cs_2CO_3, arylboronic acid, and Bu_4NBr in DMF/H_2O at 50–70°.[162]



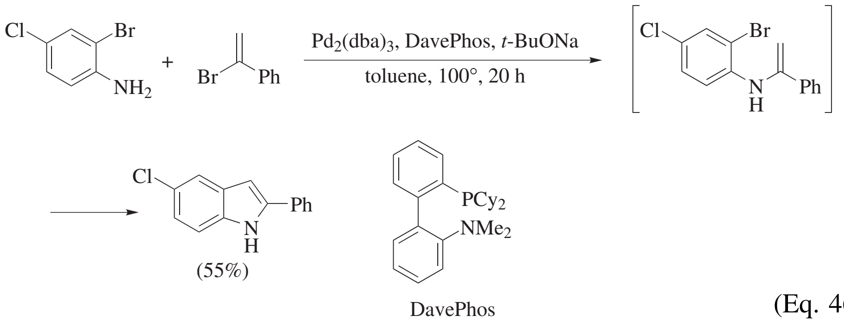
(Eq. 44)

More frequently, however, the indole formation from enamines not stabilized by conjugation with carbonyl groups is performed by processes that involve their preparation in situ followed by a cyclization step (Fig. 2, disconnection a+c). One of these procedures is based on the reaction of 2-iodo-[163] or 2-chloroanilines[164] with ketones. The latter is best conducted under the conditions shown in Eq. 45.[164] The reaction can be performed even in the presence of Cs_2CO_3 or KOAc as base, but variable amounts of side products are formed. Magnesium sulfate, presumably acting as a dehydrating agent, plays an important role in promoting the reaction.



(Eq. 45)

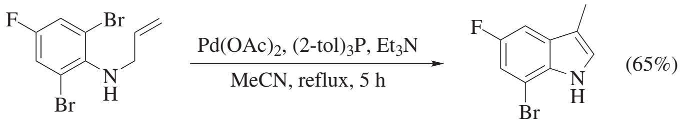
A more recent approach based on the in situ preparation of enamines takes advantage of the palladium-catalyzed reaction of 2-bromoanilines with vinyl bromides (Eq. 46).[165] The reaction is strongly dependent on the structure of the ligand. Among the ligands that have been studied—$(2\text{-tol})_3P$, BINAP, XantPhos (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene), JohnPhos (2-(biphenyl)di-*tert*-butylphosphine), DavePhos, XPhos, and the imidazolium salt HIMeCl (precursor of a carbene ligand)—DavePhos and XPhos give the best results. In particular, DavePhos is the best ligand with 2-bromoanilines, but XPhos is the ligand of choice with 2-chloroanilines. Even preformed imines have been used as precursors of indoles.[160] Very likely these cyclizations involve an isomerization step to the corresponding enamines.



(Eq. 46)

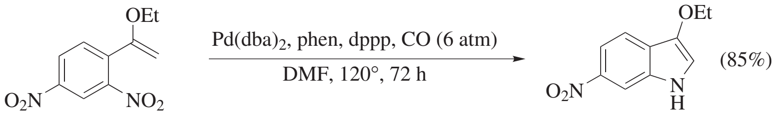
3-Substituted Indoles. Unlike the alkyne-based cyclizations to 3-substituted indoles for which there are only a few examples, the alkene-based cylizations to 3-substituted indoles are relatively abundant. 3-Substituted indoles have been synthesized from 2-halo-*N*-allylanilines and -anilides (Fig. 2, disconnection c), 2-nitrostyrenes (Fig. 2, disconnection a), and 2-haloanilino enamines (Fig. 2, disconnection c).

The cyclization of 2-halo-*N*-allylanilines and -anilides to indoles (Fig. 2, disconnection c) is based on the intramolecular Mizoroki–Heck reaction. Initial studies investigated indole formation from 2-iodo- and 2-bromo-*N*-allylacetanilides bearing an olefinic fragment conjugated to a carbonyl group in the presence of $Pd(OAc)_2$, Ph_3P, and usually TMEDA.[166] Formation of the desired indole products is accompanied by the formation of the deallylated 2-bromoacetanilide and the deallylated acetanilide (the latter derived from the reduction of the carbon–bromine bond), which in some examples are the major components of the reaction mixtures. Reaction conditions have subsequently been improved and the cyclization has been extended to a variety of activated and unactivated 2-halo-*N*-allylanilines and -anilides.[167–179] An example is shown in Eq. 47.[178] $Pd(OAc)_2$ is typically used as the source of palladium(0). The reaction can be carried out under phosphine-free conditions[167,168,171,174,175,177,179] or using Ph_3P,[166,172,173] (2-tol)$_3$P,[167,176,178] triphenylphosphine trisulfonate sodium salt (TPTTS, in MeCN/H_2O),[169] $(C_6F_{13}CH_2CH_2)_2PPh$ (in supercritical carbon dioxide),[170] $Pd(PPh_3)_4$[177] in the presence of Et_3N,[167–171,174,175,177,178] Bu_3N,[176] $NaHCO_3$,[166,179] Na_2CO_3,[168,179] K_2CO_3,[172,173] Cs_2CO_3,[173] or NaOAc[168] as bases. Tetrabutylammonium chloride[168,173,175,179] or bromide[171,174] are employed as additives, particularly under phosphine-free conditions.



(Eq. 47)

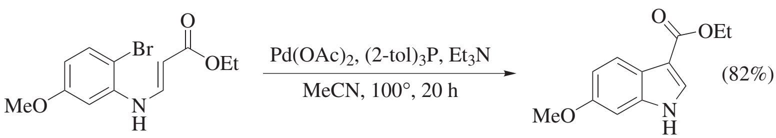
Only a few 3-substituted indoles have been prepared from 2-nitrostyrenes. Indole derivatives containing a C(3)-methyl substituent are obtained by reaction of 2-nitro-α-methylstyrenes with carbon monoxide (20 atm), $PdCl_2(PPh_3)_2$, and $SnCl_2$ in dioxane[154,155] at 100° or carbon monoxide (4 atm), $Pd(OAc)_2$, and Ph_3P in MeCN at 70°.[156] 3-Alkoxy-substituted indoles are synthesized from 2-nitro-α-alkoxystyrenes under the conditions shown in Eq. 48.[180]



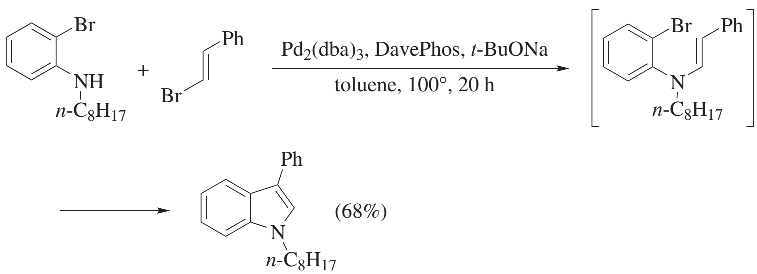
(Eq. 48)

phen = 1,10-phenanthroline

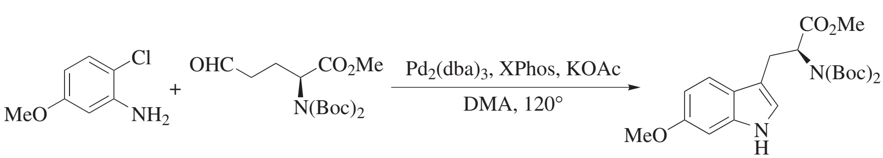
The cyclization of 2-haloanilino enamines to 3-substituted indoles has received more attention than their formation from 2-nitrostyrenes. A number of 3-substituted indoles are prepared from preformed 2-haloanilino enamines, stabilized by conjugation with keto or ester groups (Eq. 49).[181,182] Enamines not stabilized by conjugation with carbonyl groups are generated in situ from *trans*-1,2-disubstituted bromoalkenes and 2-bromoanilines (Eq. 50)[165] and from 2-haloanilines and aldehydes.[183] In the latter process, coupling of 2-iodoanilines with aldehydes is realized under mild, phosphine-free conditions ($Pd(OAc)_2$, DABCO, DMF, 85°), whereas XPhos is found to be the ligand of choice with 2-bromo- and 2-chloroanilines (Eq. 51).[183] As shown in Eq. 51, chiral aldehydes can participate in this process without racemization. The reaction also tolerates a variety of 2-haloanilines with different electronic properties.



(Eq. 49)



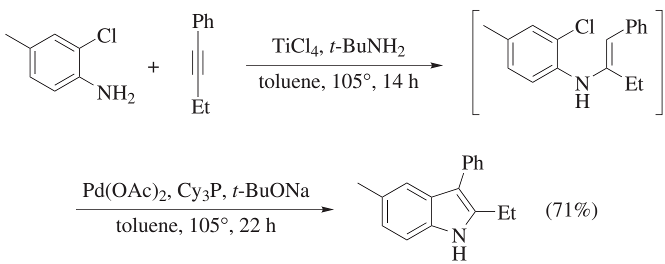
(Eq. 50)



(73%) (Eq. 51)

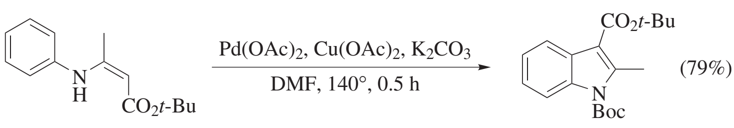
2,3-Disubstituted Indoles. The formation of 2,3-disubstituted indoles from 2-nitrostyrenes (Fig. 2, disconnection a), 2-allylanilines (Fig. 2, disconnection a), and 2-haloanilino enamines (Fig. 2, disconnection c) is performed under the same conditions described for the formation of other substituted indoles from the same substrates. Thus, 2-nitrostyrenes are cyclized in the presence of carbon monoxide (20 atm), $PdCl_2(PPh_3)_2$, and $SnCl_2$ in dioxane[155] or carbon monoxide (4 atm), $Pd(OAc)_2$, and Ph_3P in MeCN.[156] The cyclization of 2-allylanilines is typically performed using $PdCl_2(MeCN)_2$ and Na_2CO_3 or K_2CO_3, with or without LiCl in THF.[157] 2-Haloanilino enamines give indoles in the presence of $Pd(OAc)_2$ and Ph_3P in DMF using Pr_3N or $NaHCO_3$ as bases.[45,46]

Recently, 2-haloanilino enamines have been prepared in situ from 2-bromo- or 2-chloroanilines and internal alkynes via site selective titanium-catalyzed intermolecular hydroamination. The enamine formation is followed by a palladium-catalyzed cyclization step (Eq. 52).[184] The high site selectivity observed in the hydroamination step enables the synthesis of a variety of functionalized indoles with a site selectivity that is complementary to that obtained when using the palladium-catalyzed reaction of 2-haloanilines or their *N*-substituted derivatives with internal alkynes (Eqs. 16–18).[30,31]



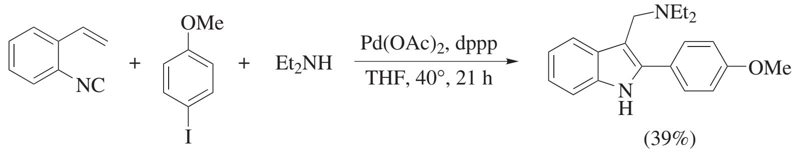
(Eq. 52)

Functionalized indoles have been prepared by palladium-catalyzed intramolecular oxidative coupling from simple arylenamines, without the need to activate the arene fragment through the introduction of a carbon–halogen bond (Eq. 53; Fig. 2, disconnection c).[185] This indole synthesis can also be carried out in a one-pot sequence from anilines and 3-oxo esters.[185]

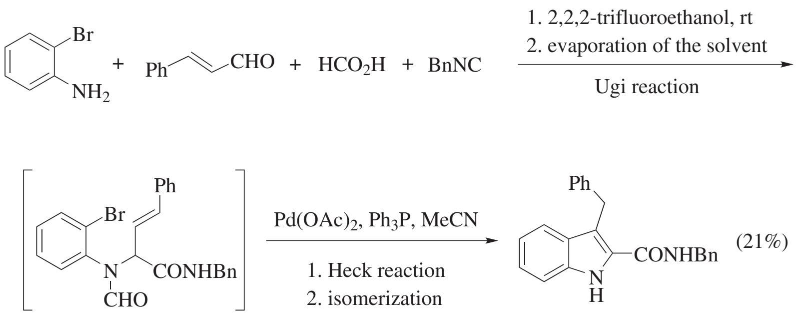


(Eq. 53)

Other novel alkene-based routes to 2,3-disubstituted indoles include a palladium-catalyzed three-component coupling of aryl iodides, 2-isocyanovinylbenzene and Et_2NH (Eq. 54; Fig. 2, disconnection b+h),[186] and a one-pot, two-step, four-component reaction of cinnamaldehydes, bromoanilines, formic acid, and isocyanides, a process that relies on an Ugi reaction followed by an intramolecular Heck reaction (Eq. 55).[187] Both reactions proceed with low to moderate yields.



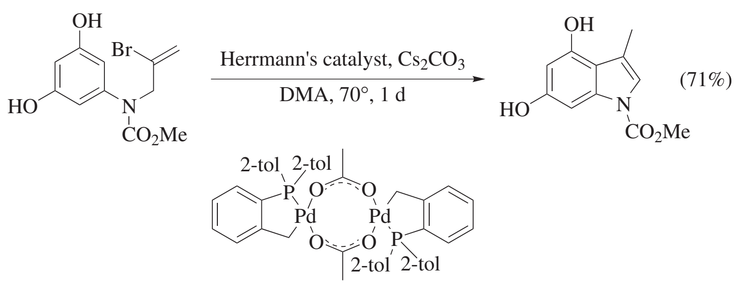
(Eq. 54)



(Eq. 55)

Indoles via Arene Vinylation

The palladium-catalyzed intramolecular reaction of a vinylic halide fragment with an arene unit has a limited synthetic scope. This strategy has been applied to the preparation of a few 3-methylindoles from aniline carbamates containing a bromopropenyl fragment bound to the nitrogen atom (Fig. 3).[47] However, it is interesting that the oxidative addition site is located in a vinylic fragment tethered to the benzenoid ring unlike the majority of the cyclization procedures described in this chapter, where the site of the oxidative addition of the carbon−X bond to the palladium(0) species is located on the benzenoid ring. Optimum yields are obtained by using Herrmann's catalyst. Cleavage of the allylic side chain is observed as a side reaction. Cyclization at both the *ortho* and *para* positions with respect to the hydroxy group can occur to generate mixtures of indole derivatives. This can be avoided by blocking one of the positions with a substituent or using a symmetrical phenol such as shown in Eq. 56.[47]



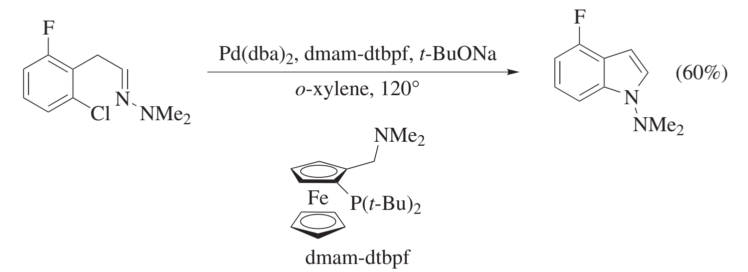
Herrmann's catalyst

(Eq. 56)

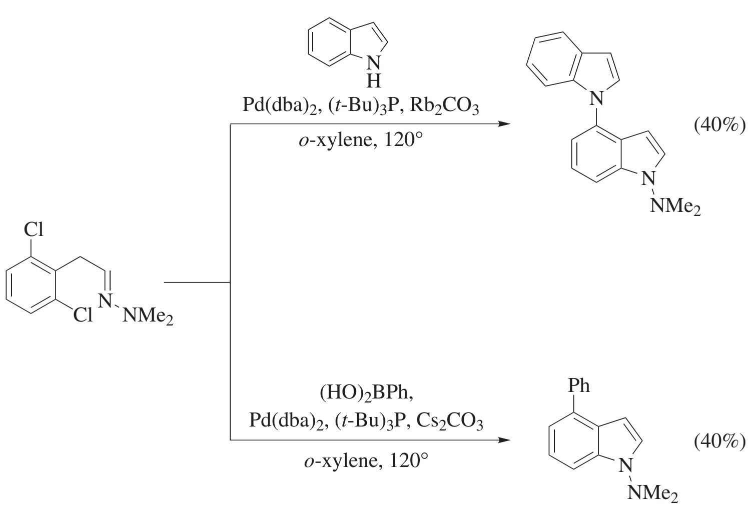
Recently, the arene vinylation based indole synthesis has been applied to *N*-methylanilines bearing bromopropenyl fragments bound to the nitrogen atom.[188] However, best results have been obtained when the propenyl moiety is part of a cyclic system. The indole product was isolated in low yield with an acyclic bromopropenyl fragment.

Indoles via *N*-Vinylation and *N*-Arylation

Unsubstituted Indoles. The first extension of the carbon–nitrogen bond forming reaction[15–22] to the direct formation of indole rings involves the palladium-catalyzed cyclization of 2-chloroarylacetaldehyde *N*, *N*-dimethylhydrazones to give 1-aminoindole derivatives (Fig. 4, disconnection g). The best results are obtained under the conditions shown in Eq. 57 for the synthesis of a fluoroindole derivative.[189] In some reactions, the use of the bulky, electron-rich ligand $(t\text{-Bu})_3P$ gives satisfactory results; Cs_2CO_3 and Rb_2CO_3 can also be used as bases. Yields of chloroindoles are lower than those of unsubstituted indoles or fluoroindoles because competitive oxidative addition of the product chloroindoles to palladium(0) species takes place under the reaction conditions. Because indole derivatives bearing chloro substituents could be useful substrates for increasing the molecular complexity of the indole products, a tandem process has been developed that involves a palladium-catalyzed intramolecular cyclization to chloroindoles followed by palladium-catalyzed functionalization of their carbocyclic rings (Eq. 58).[189]



(Eq. 57)



(Eq. 58)

Unsubstituted indoles have also been prepared from benzenoid precursors that do not incorporate the nitrogen atom required for the final ring-closing indole-forming event. Thus, 2-(2-haloalkenyl)aryl halides are converted into indoles via palladium-catalyzed reaction with nitrogen nucleophiles (Fig. 4, disconnection a+g).[190–192] Introducing an external nitrogen unit is particularly useful for the preparation of *N*-functionalized indoles, including indoles with sterically demanding *N*-substituents.[191] A palladium(0) source ($Pd_2(dba)_3$) along with a variety of phosphine ligands such as DPEPhos, PhXPhos, SPhos (Fig. 5), DavePhos (see Eq. 46), and $HP(t\text{-}Bu)_3BF_4$ are used. Sodium *tert*-butoxide is usually employed as the base (Eq. 59), although Cs_2CO_3 gives good results in some examples.[190] Alkene partners have been used successfully as a (Z) and (E) mixture of isomers. In several examples, the (Z)/(E) ratio is low and sometimes the (E) isomer dominates, suggesting that both geometrical isomers can be converted into the indole products. As control experiments revealed that no isomerization of the vinyl halide substrates takes place, it is likely that the funneling of the isomer mixtures to a single indole product is due to the isomerization of an initially formed enamine. By careful choice of the substrate, i.e., introducing a suitable second halide leaving group, it is possible to develop one-pot (Eq. 60)[190] or tandem processes to introduce further amine functionality via a third carbon–nitrogen bond formation in the benzenoid ring.[190]

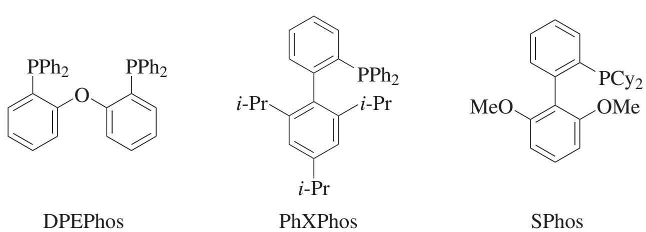
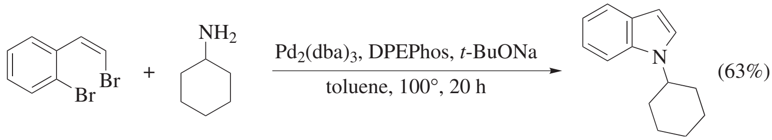
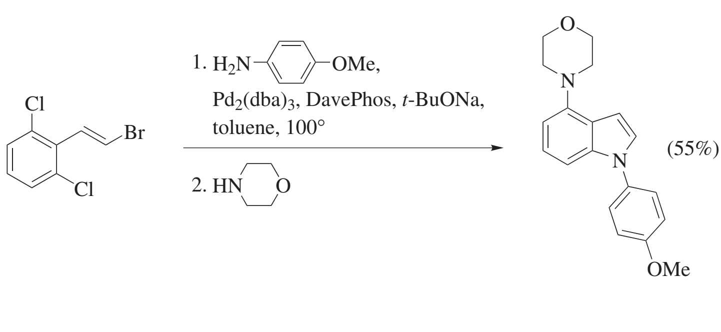


Figure 5. Three of the phosphine ligands examined in the synthesis of indoles from 2-(2-haloalkenyl)aryl halides and amines.

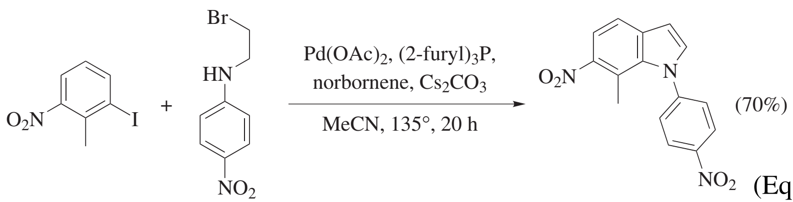


(Eq. 59)



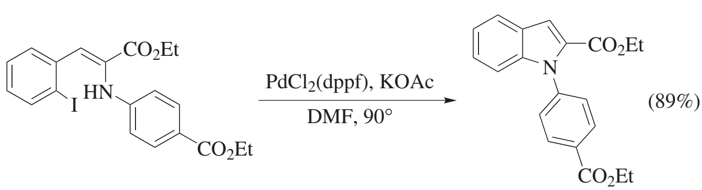
(Eq. 60)

Formation of unsubstituted indoles from 3-nitro-2-methyliodobenzene via a process that usually leads to indoline products entails a tandem intermolecular alkylation/intramolecular amination (Eq. 61; Fig. 4, disconnection c+g).[193] Norbornene is suggested to enter the catalytic cycle favoring the alkylation of the aromatic ring. This alkylation involves carbopalladation, C_{Ar}–H activation, oxidative addition, and reductive elimination steps followed by the extrusion of norbornene. The condensed five-membered ring is formed via an intramolecular Buchwald–Hartwig reaction. Nevertheless, the detailed mechanism of formation of the pyrrole ring is uncertain. The palladium-catalyzed dehydrogenation of an indoline intermediate seems unlikely in view of the fact that indole formation is not observed with any of the other iodoarenes tested. The process is protecting-group dependent: the phenyl-protected amine also gives the corresponding indole in 53% yield, whereas the CO_2Et carbamate gives only the indoline in 20% yield.



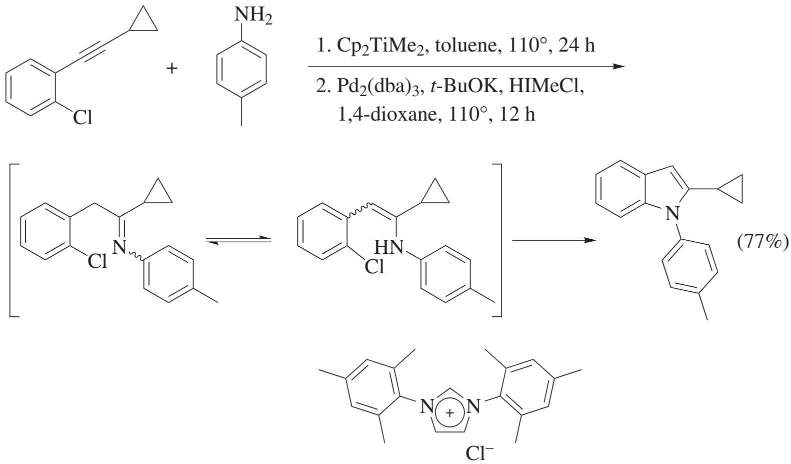
(Eq. 61)

2-Substituted Indoles. 2-Substituted indoles may be constructed through *N*-arylation (Fig. 4, disconnection g) and *N*-vinylation (Fig. 4, disconnection a) processes. In the *N*-arylation approach, 2-haloarylenamines are usually the direct precursors of indole products. An example is shown in Eq. 62 (Fig. 4, disconnection g) for the preparation of an indole-2-carboxylate from a preformed 2-iodoarylenamine.[194]



(Eq. 62)

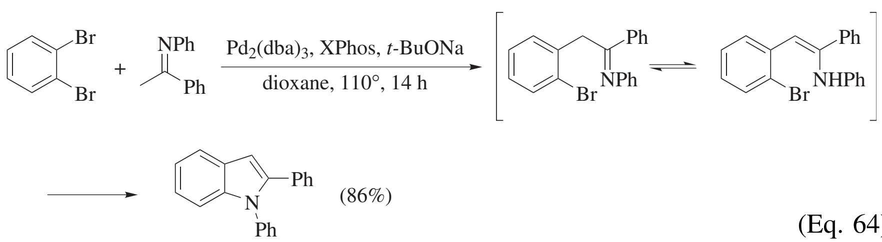
Preferably, 2-haloarylenamines are generated in situ from suitable precursors. Very likely, they are intermediates in the formation of indoles from 2-(2-haloalkenyl)aryl halides.[190] In the synthesis based on the one-pot titanium-catalyzed hydroamination of 2-(alkynyl)aryl chlorides followed by a palladium-catalyzed *N*-arylation, 2-haloarylenamines are generated via base-catalyzed isomerization of the initially formed imines (Eq. 63; Fig. 4, disconnection a+g).[195] The reaction usually affords indoles in good yields. However, the reaction of a 2-alkenyl alkyne with *tert*-butylamine gives the corresponding indole in modest yield (39%), most probably because the site selectivity of the titanium-catalyzed hydroamination of 2-alkenyl alkynes is poorer than that of 2-alkyl alkynes.



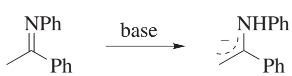
HIMeCl

(Eq. 63)

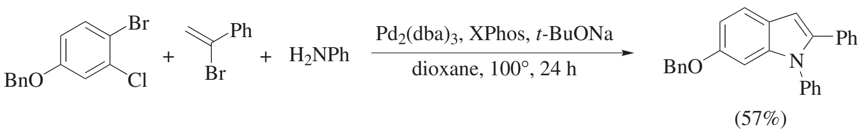
2-Haloarylenamines may also be generated in situ from imines and 1,2-dihalobenzenes or 2-chlorosulfonates to provide an indole synthesis that involves a tandem intermolecular *C*-arylation followed by an intramolecular *N*-arylation (Eq. 64; Fig. 4, disconnection c+g).[196,197] Under the basic conditions used, imines are converted into azaallylic anions (Eq. 65). Control experiments have shown that azaallylic anions are selectively arylated on carbon. With imines containing two different acidic carbon−hydrogen bonds, mixtures of constitutionally isomeric indoles are obtained. For example, the imine derived from 2-heptanone gives a 5:1 mixture of 2-substituted indole (formed via *C*-arylation of the less substituted position of the imine) and 2,3-disubstituted indole (formed via *C*-arylation of the more substituted position of the imine). The reaction has also been developed into a three-component process that provides indoles from 1,2-dihaloarenes, amines, and bromoalkenes (Eq. 66; Fig. 4, disconnection a+c+g).[196]



(Eq. 64)

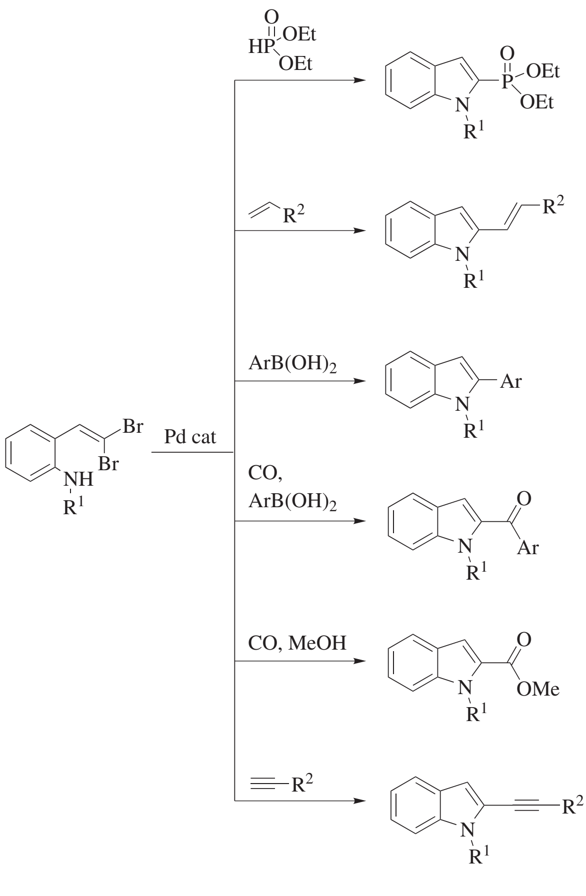


(Eq. 65)



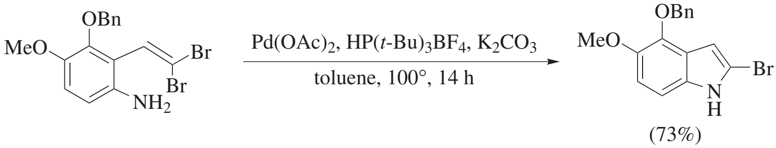
(Eq. 66)

The N-vinylation approach has been used to prepare 2-substituted indoles from *ortho-gem*-dihalovinylanilines or -anilides and involves tandem carbon$_{alkenyl}$–nitrogen bond forming processes followed by phosphonylation reactions,[198] Mizoroki–Heck reactions,[199] Suzuki–Miyaura cross-couplings,[200–202] carbonylation/Suzuki–Miyaura cross-couplings,[203] carboalkoxylation reactions,[204] or Sonogashira cross-couplings[205] (Eq. 67; Fig. 4, disconnection a+b). $Pd(PPh_3)_4$,[203] $PdCl_2(PPh_3)_2$,[204] $Pd(OAc)_2$,[198–201] $Pd_2(dba)_3$,[198] or Pd/C,[205] the latter four along with Ph_3P,[204] 1,1'-bis(diphenylphosphino)ferrocene (dppf),[198] $(2\text{-tol})_3P$,[199] SPhos,[200,201] and $(4\text{-MeOC}_6H_4)_3P$[205] as phosphine ligands, are commonly used as the source of the palladium(0) species. $EtN(i\text{-Pr})_2$,[204] $HN(i\text{-Pr})_2$,[205] $K_3PO_4\bullet H_2O$,[199–201] K_2CO_3,[203] or Et_3N[198,199] are used as bases and THF/MeOH,[204] toluene,[198–201,205] or dioxane[203] as solvents. In some cases, beneficial effects are obtained using additives such as Me_4NCl.[199]



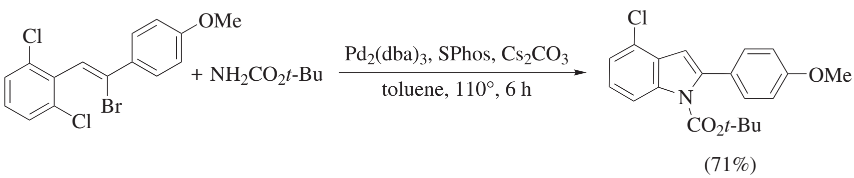
(Eq. 67)

A tandem intermolecular N-vinylation followed by an intramolecular C-arylation (Fig. 4, disconnection a+c)[165,206] is involved in the reaction of 2-bromoanilines with vinylbromides.[165] The N-vinylation approach (Fig. 4, disconnection a) has also been used to prepare 2-bromoindoles from 2-(2,2-dihaloalkenyl)anilines in the presence of $Pd(OAc)_2$, $HP(t\text{-}Bu)_3BF_4$, and K_2CO_3 in toluene at 100° (Eq. 68).[207] The use of $P(t\text{-}Bu)_3$, generated in situ from the $HP(t\text{-}Bu)_3BF_4$ salt, appears to be necessary to prevent inhibition of the catalyst by facilitating reversible oxidative addition into the product carbon−bromine bond.



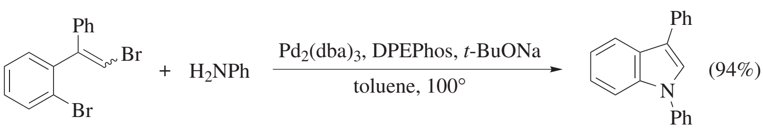
(Eq. 68)

2-Substituted monochloroindoles have been prepared from trihalogenated alkenylbenzenes and carbamates through a process that is based on two sequential palladium-catalyzed amination reactions, the first intermolecular, the second intramolecular (Eq. 69; Fig. 4, disconnection a+g).[192]



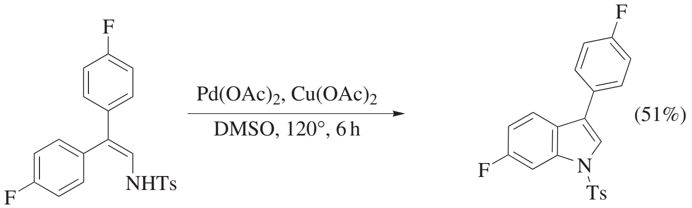
(Eq. 69)

3-Substituted Indoles. The preparation of 3-substituted indoles via carbon−nitrogen bond forming reactions has received much less attention than that of 2-substituted indoles. These materials are prepared from 1-bromoalkenes and 2-haloanilines (Fig. 4; disconnection a+c)[165] and from properly substituted 2-(2-haloalkenyl)aryl halides and amines (Eq. 70; Fig. 4, disconnection a+g).[190,191] Reactions are carried out using $Pd_2(dba)_3$/DPEPhos or $Pd(OAc)_2/HP(t\text{-}Bu)_3BF_4$ in the presence of t-BuONa in toluene.



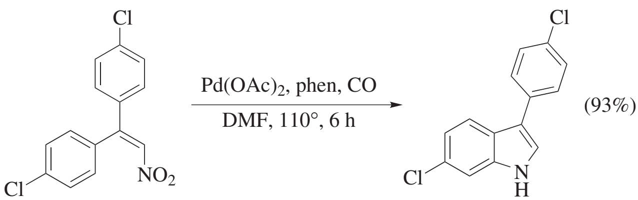
(Eq. 70)

A new approach to 3-substituted indoles from arylenamines that do not contain an aryl halide fragment was subsequently developed (Eq. 71; Fig. 4, disconnection g).[208] The reaction proceeds through a palladium-catalyzed carbon−hydrogen activation followed by an intramolecular amination. Mixtures of indole products are isolated from enamines containing different aromatic rings, suggesting that an E/Z isomerization occurs rapidly during this process.



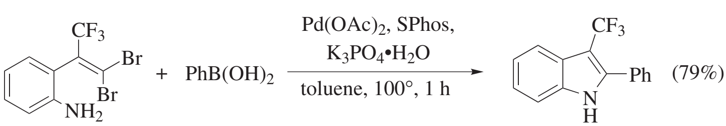
(Eq. 71)

Recently, 2,2-diaryl nitroalkenes have been converted into 3-arylindoles via reductive cyclization under 1 atmosphere of carbon monoxide in the presence of $Pd(OAc)_2$ and 1,10-phenanthroline in DMF at 110° (Eq. 72).[209] The reaction proceeds through direct amination of aromatic C_{sp^2}–H bonds without requiring a functionalized coupling fragment (e.g., an aryl halide or triflate fragment). Both regioisomers of the indole products are obtained with *meta*-substituted 2,2-nitroalkenes. However, a 2,2-dinaphthyl nitroalkene derivative produce only one regioisomer.

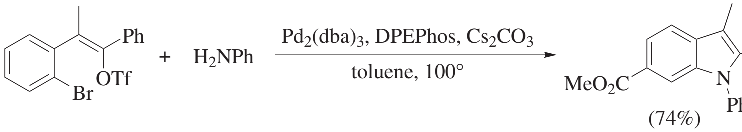


(Eq. 72)

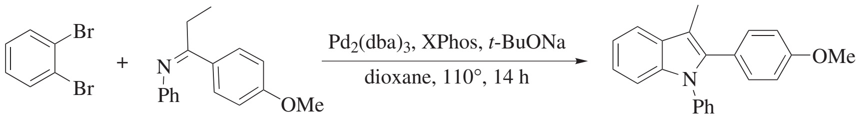
2,3-Disubstituted Indoles. The pyrrole ring of 2,3-disubstituted indoles can be generated in many ways: (1) from *ortho*-*gem*-dihalovinylanilines via a formal tandem intramolecular carbon–nitrogen bond forming reaction followed by an intermolecular carbon–carbon cross-coupling reaction with boronic acids (Eq. 73; Fig. 4, disconnection a+b),[200,202] (2) from (2-haloaryl)vinylic triflates via a tandem N-vinylation and N-arylation process (Eq. 74; Fig. 4, disconnection a+g),[210] (3) from ketimines and 2-dihalobenzenes via the intermediacy of azaallylic anions (Eq. 75; Fig. 4, disconnection c+g),[196,197] and (4) from α-aryloxime O-pentafluorobenzoates[211] or substituted enamines[212] (Fig. 4, disconnection g). The cyclization of α-aryloxime O-pentafluorobenzoates[211] is supposed to proceed via intramolecular aromatic carbon–hydrogen amination of a vinyl nitrene–palladium intermediate. In the synthesis of indoles from enamines (Eq. 76),[212] the cyclization step is suggested to proceed through an electrophilic attack of palladium(II) on an aromatic ring. Most probably, the role of $Cu(OAc)_2$ is to reoxidize palladium(0).



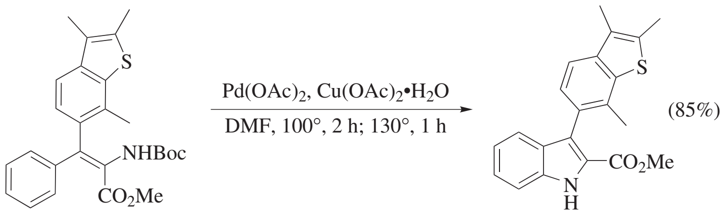
(Eq. 73)



(74%) (Eq. 74)



(66%) (Eq. 75)



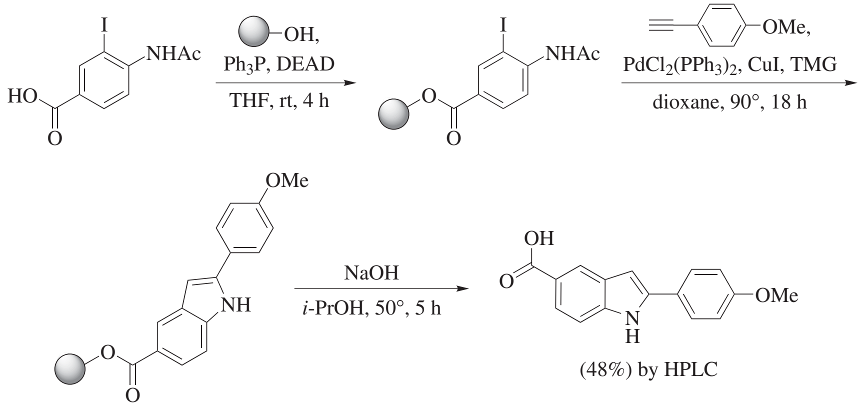
(Eq. 76)

Solid-Phase Synthesis

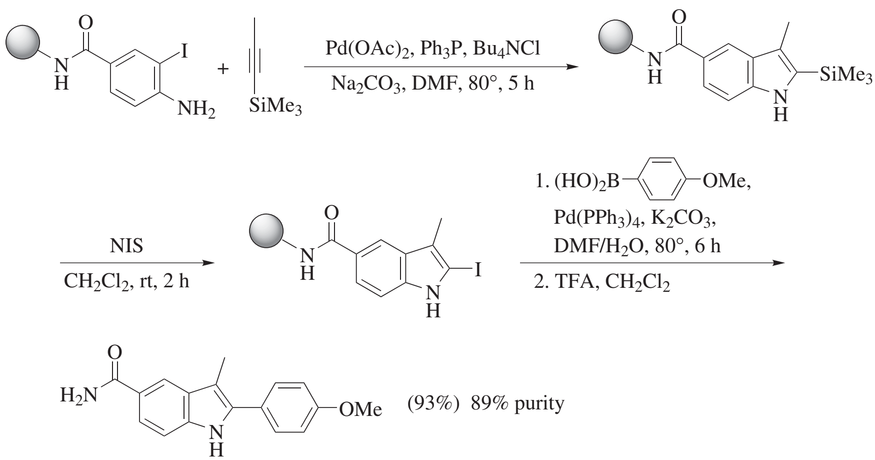
Solid-phase synthesis is particularly attractive for the generation of libraries of small organic molecules[213–220] and a few very efficient applications of this method to the de novo construction of the indole ring via palladium-catalyzed processes have been introduced.[221] These processes rely on palladium-catalyzed cyclization of properly substituted polymer-bound benzenoid precursors. Described below are indole formations from alkyne and alkene derivatives through carbon–carbon and carbon–carbon/carbon–nitrogen bond forming reactions and the indolization of enamine derivatives via carbon–nitrogen bond forming reactions.

Indole Formation from Alkynes. Palladium-catalyzed, solid-phase syntheses of indoles from alkynes are based on the cyclization of 2-alkynylanilines or -anilides (typically prepared from terminal alkynes and 2-iodoanilines or -anilides via Sonogashira cross-coupling) (Fig. 1, disconnection a), on the intermolecular annulation of 2-iodoanilides with internal alkynes[30,31] (Fig. 1, disconnection a+c), and on the aminopalladation/reductive elimination process[7,9] (Fig. 1, disconnection a+d).

Ester[222,223] and amide[224–226] linkers at the benzene moiety are frequently used as resin attachment points, as shown in the examples in Schemes 7 and 8. In Scheme 7,[222] 1,1,3,3-tetramethylguanidine (TMG) plays a key role in promoting the one-pot coupling/cyclization reaction, with the only byproducts observed arising from an incomplete cyclization step. For the Suzuki–Miyaura cross-coupling shown in Scheme 8,[225] it was found that $Pd(PPh_3)_4$ in DMF/H_2O provides better yields than $Pd_2(dba)_3$ in DMF. Solution-phase conditions can often be successfully applied to solid-phase synthesis. It is interesting to note that K_2CO_3 gives



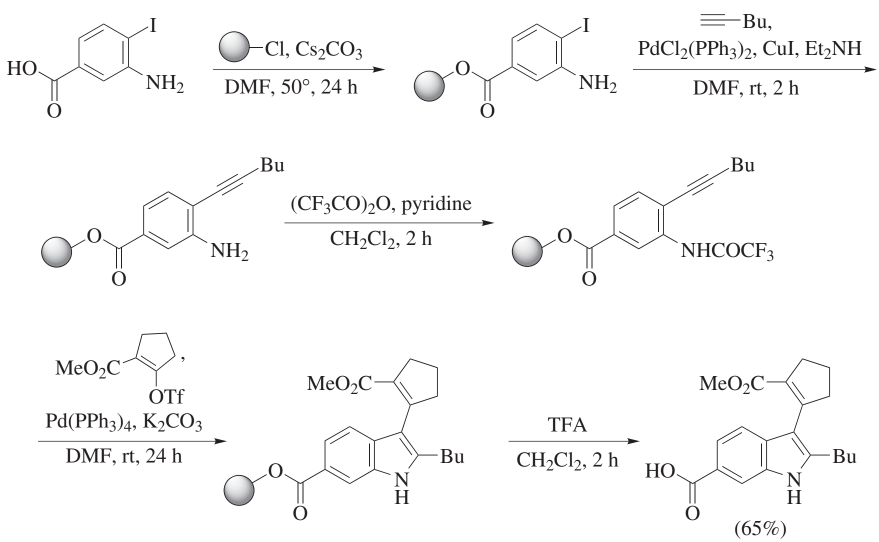
Scheme 7. Synthesis of 2-substituted indoles via tandem Sonogashira cross-coupling/cyclization on the solid phase.



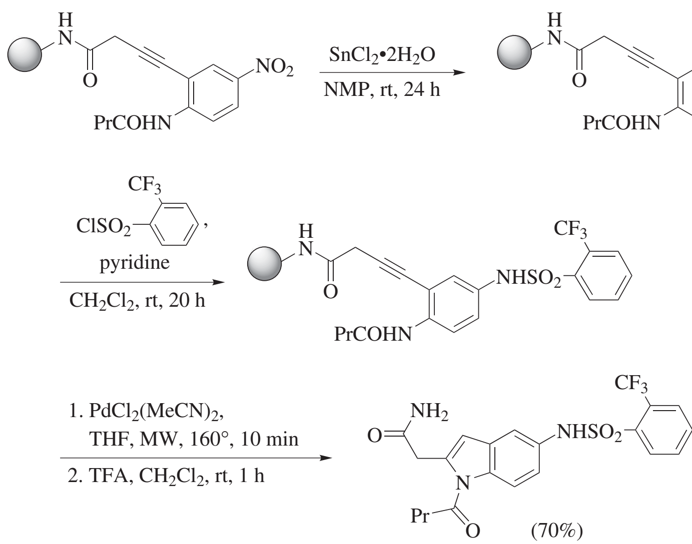
Scheme 8. Synthesis of 3-substituted 2-arylindoles via annulation of internal alkynes with 2-iodoanilines and Suzuki-Miyaura cross-coupling reactions on the solid phase.

better results than Et_3N in both the solution-[123] and solid-phase[223] synthesis of 2,3-disubstituted indoles according to the aminopalladation/reductive elimination protocol, despite the expectation that a soluble base would be necessary for a solid-phase reaction (Scheme 9).[223] In fact, little product is obtained when Et_3N is used as the base.[223]

Amide linkers at the pyrrole nucleus are also employed. This approach is exemplified by the palladium-catalyzed cyclization of resin-bound 2-alkynylanilides performed under microwave-assisted conditions (Scheme 10).[227] Because



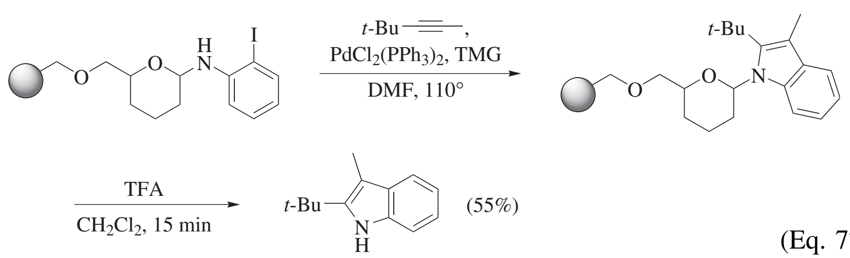
Scheme 9. Synthesis of 2,3-disubstituted indoles via aminopalladation/reductive elimination on the solid phase.



Scheme 10. Synthesis of 2-substituted indoles via cyclization of 2-alkynylanilides on the solid phase.

of their heterogeneous nature, solid-phase syntheses often suffer from long reaction times and/or incomplete conversion of the starting materials. In the latter case, impurities may accumulate on the polymeric surface and lower the purity of compound libraries. Thus, accelerating organic reactions by using microwave conditions appears ideally suited for solid-phase combinatorial synthesis. Indole products are obtained in 65–82% overall yields and with 95–99% purities. Replacement of THF with NMP in the cyclization step decreases both the yield and the purity of the indole products.

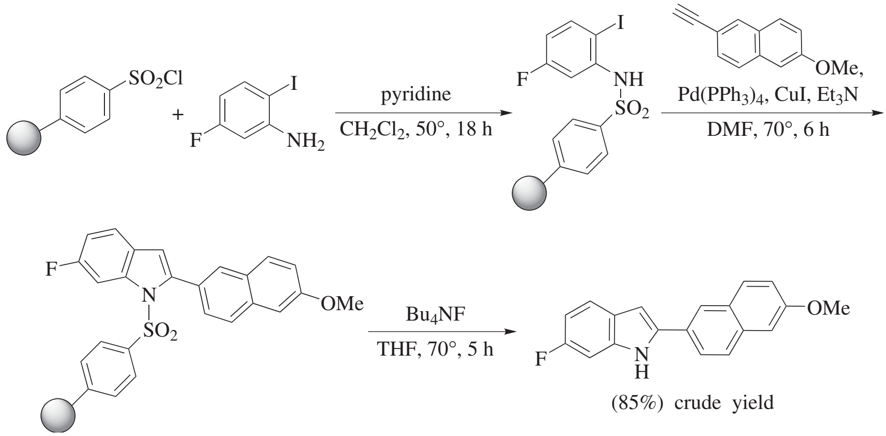
All the linkers mentioned above remain as substituents in the final indole derivatives and extraneous substituents such as CO_2H and $CONH_2$ remaining in the final product after cleavage may be undesirable. This may represent a limitation to the scope of the solid-phase approach to the synthesis of indole products and has led to the development of procedures that use traceless linkers. This approach uses the nitrogen–hydrogen bond that will be incorporated into the pyrrole ring to graft the indole precursor on the resin. Cleavage at the end of the synthetic process gives the free indole. In one of the procedures that is based on this strategy, the NH group is attached to the resin via an aminal linkage with a resin-bound 3,4-dihydro-2*H*-pyran residue (Eq. 77).[228] Resin cleavage with trifluoroacetic acid gives the free indole products. Solution-phase conditions are not particularly successful in this case, with incomplete reaction and large quantities of multiple acetylene insertion products being observed. Optimum yields are obtained with $PdCl_2(PPh_3)_2$, TMG, and resubjection of the reaction mixture to the reaction conditions to drive reactions to completion.



(Eq. 77)

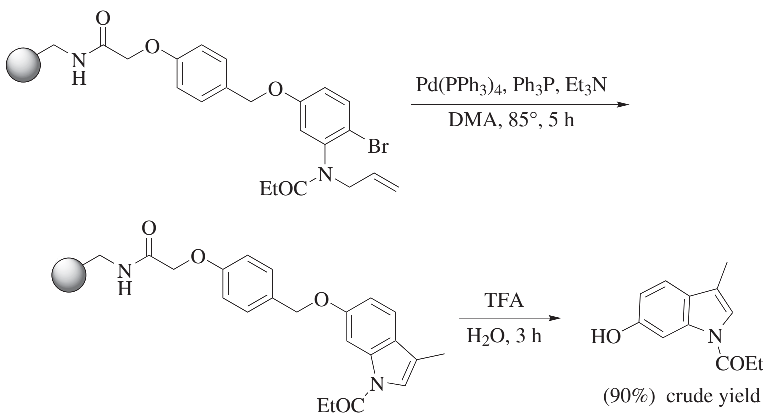
N-Sulfonyl linkers represent a convenient alternative.[225,229,230] The sulfonyl group plays two significant roles: it serves as an activating group to facilitate the cyclization step that occurs under relatively mild conditions and, after indole formation, facilitates the cleavage step, which can be performed under mild conditions (Scheme 11).[229] This should allow the synthesis of diverse indole derivatives bearing either base- or acid-sensitive functional groups. Potassium *tert*-butoxide as the base provides excellent results in some cases.[229,230]

Indole Formation from Alkenes. Palladium-catalyzed solid-phase syntheses of indoles from alkenes are based on the use of an ether linker at the benzene moiety[231] and amide[232] and ester[233–235] linkers at the pyrrole moiety. In these examples, functionalized pyrrole rings are constructed via carbon–carbon bond forming reactions (Fig. 2, disconnection c). Cyclizations have been performed with polymer-bound 2-bromo-*N*-allylanilides (Eq. 78),[231] 2-haloanilino enamines (Eq. 79),[233,234] and 3-(2-iodoanilino)crotonic acid amides (Scheme 12).[232]

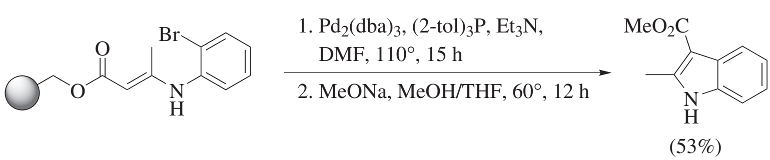


Scheme 11. Traceless linker based synthesis of 2-substituted indoles via tandem Sonogashira cross-coupling/cyclization on the solid phase.

In the latter synthesis, *N*-alkylated indoles are used because of their higher stability under TFA-cleavage conditions as compared to the free NH counterparts; TFA is reported[236] to induce dimerization of indole-3-acetic acids or their methyl esters.

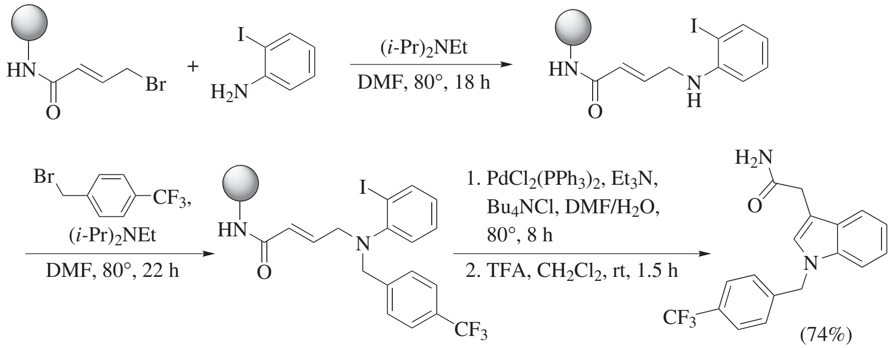


(Eq. 78)



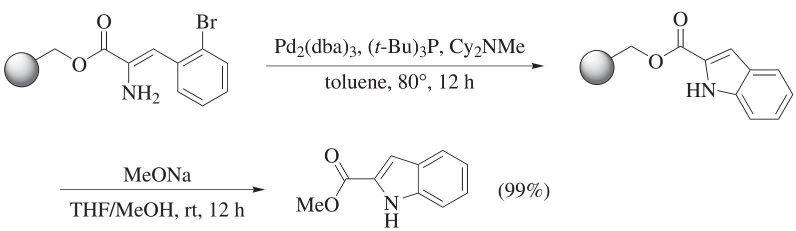
(Eq. 79)

Indole Formation via *N*-Vinylation and *N*-Arylation. The cyclization of 2-(2-halophenyl)amino acrylates (immobilized via ester linkers) to methyl 2-indolecarboxylates[234,235] provides examples of solid-phase syntheses of indoles

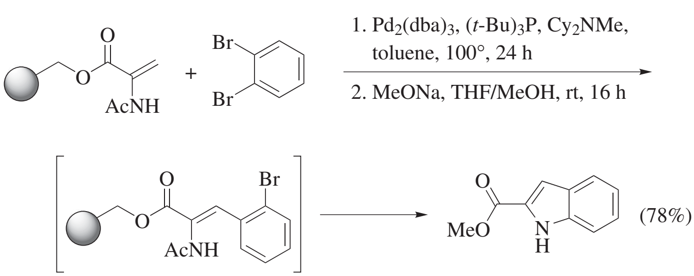


Scheme 12. Indole synthesis via cyclization of 3-(2-iodoanilino)crotonic acid amides on the solid phase.

via the carbon–nitrogen bond forming reaction. The *N*-arylation is carried out in the presence of $Pd_2(dba)_3$, $(t\text{-Bu})_3P$, and $(c\text{-}C_6H_{11})_2NMe$ in toluene at 80° when it involves the substitution of the carbon–nitrogen bond for a carbon–bromine bond (Eq. 80)[234] and in the presence of $Pd_2(dba)_3$, the air stable $HP(Bu\text{-}t)_3BF_4$, and $(c\text{-}C_6H_{11})_2NMe$ in DME at 100° when the reaction involves the substitution of the carbon–nitrogen bond for a carbon–triflate bond. This reaction can be conducted as a tandem process that relies on the Mizoroki–Heck reaction of solid-supported *N*-acetyldehydroalanine with 1,2-dibromobenzenes, followed by in situ intramolecular cyclization of the 2-acetamido-3-(2-bromophenyl)acrylate intermediates (Eq. 81).[234] 1,2-Dibromobenzene gives better results than 1-bromo-2-iodobenzene and 2-bromophenyltriflate.



(Eq. 80)



(Eq. 81)

COMPARISON WITH OTHER METHODS

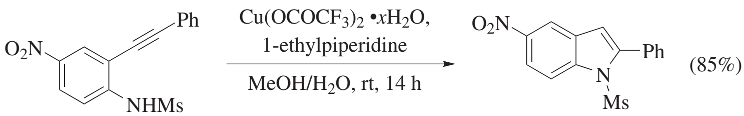
The construction of the indole ring from benzenoid precursors has been performed using a variety of other transition metals. Copper-, gold-, indium-, iridium-, molybdenum-, platinum-, rhodium-, ruthenium-, titanium-, and zinc-catalyzed cyclizations are the most synthetically useful. However, as indicated by the number of approaches developed, the impact of palladium chemistry on indole synthesis has been extraordinary. Although other transition metals can provide better results than palladium in some specific applications, the versatility, flexibility, and substrate scope of palladium-catalyzed reactions are unique. Indole syntheses based on palladium catalysis have incorporated the many advances in catalyst efficiency and allow significant variations in reaction conditions. Despite their importance and utility for the field, indole syntheses based on the other transition metals play a secondary role.

In some cases, and although the same class of indole products is formed, the functionalized pyrrole ring is constructed via bond-forming sequences that are different from those involved in palladium-catalyzed cyclizations. Often, only a few examples are reported so that the substrate scope of the method cannot be critically evaluated. In view of the limited data available, comparisons could be made only on a speculative basis, making it preferable to simply describe the main attributes of the other methods presented in this section. In general, and like the palladium-catalyzed cyclizations to indoles, methods based on the use of stoichiometric amounts of transition metals are not treated and only synthetic procedures where transition metal catalysis is directly involved in the pyrrole ring construction event are discussed. Furthermore, transition-metal-catalyzed reactions producing indole-related compounds such as azaindoles, indazoles, indolines, oxindoles, bis(indolyl)methanes, and related systems or condensed polycyclic compounds such as carbolines, carbazoles, indoloquinolines, indoloquinazolines, and related systems are not treated.

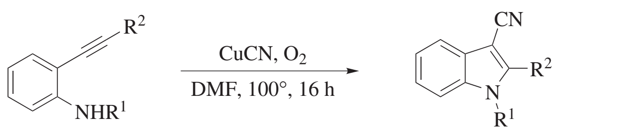
Copper-Catalyzed Indole Formation

The use of copper catalysis is attractive in comparison to palladium-based methods because of its economic advantages and its potential in large-scale reactions. As with palladium, alkynes are the substrates that have been most used with copper to perform cyclizations to indoles. The synthesis of indoles from alkenes, particularly from 2-alkenylphenyl isocyanides, have also been explored. Other synthetic approaches to indoles rely on copper-catalyzed *N*-arylations or *N*-vinylations and carbon–carbon bond forming reactions.

Indole Formation from Alkynes. Typically, alkyne-based, copper-catalyzed indole syntheses rely on 2-alkynylanilines and their *N*-substituted derivatives as direct precursors of 2-substituted indoles. In general, these substrates are prepared via Sonogashira cross-coupling of terminal alkynes with 2-haloanilines or -anilides. Their cyclization into the corresponding indole ring is carried out in the presence of both copper(I) and copper(II) salts. In particular, the cyclization of 2-alkynylanilines and their *N*-substituted derivatives to indoles has been performed in the presence of CuCl in DMF at 70°,[237] $Cu(OAc)_2$ or $Cu(OTf)_2$ in refluxing 1,2-dichloroethane,[66,238] and $Cu(OCOCF_3)_2{\bullet}xH_2O$ in $MeOH/H_2O$ at room temperature (Eq. 82).[69] Free NH indoles can be obtained from 2-alkynyltrifluoroacetanilides in the presence of CuI and 1,2-*trans*-cyclohexanediamine or PPh_3.[239] When the reaction of 2-alkynyltrifluoroacetanilides is carried out in the presence of CuCN, free NH 2-substituted 3-cyanoindoles are obtained through a direct cyclization/cyanation reaction (Eq. 83).[240] With their *N*-tosyl analogues, *N*-tosyl or free NH or a mixture of free NH and *N*-tosyl indole derivatives have been obtained depending on the nature of the substrates (Eq. 83).[240] Tandem Sonogashira cross-coupling of terminal alkynes with 2-haloanilines followed by cyclization to indoles that have been suggested to involve copper catalysis in the cyclization step have also been described.[65,68]



(Eq. 82)



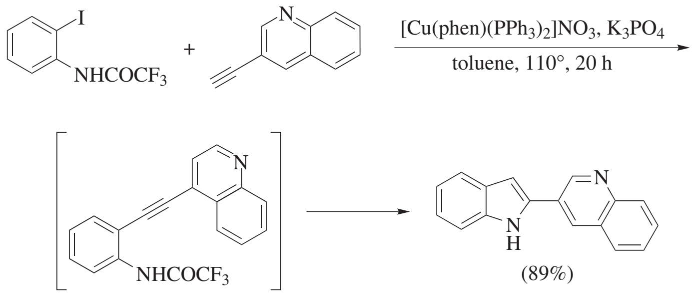
(Eq. 83)

$R^1 = COCF_3$; $R^2 = n\text{-}C_5H_{11}$ — $R^1 = H$; $R^2 = n\text{-}C_5H_{11}$ (73%)

$R^1 = Ts$; $R^2 = Ph$ — $R^1 = Ts$; $R^2 = Ph$ (74%)

The copper-catalyzed construction of indole rings from 2-alkynylanilid(n)es has also found its place in solid-phase synthesis. Taking advantage of microwave irradiation, *N*-acyl-[241] and free NH[242] 2-substituted 5-arenesulfamoylindoles have been prepared from resin-bound 2-alkynylanilides.

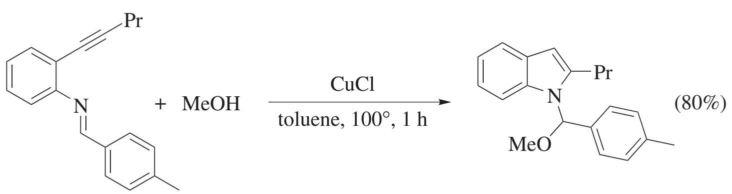
A notable advance in the alkyne-based, copper-catalyzed route to indoles is the demonstration that copper catalysis can be used both in the formation of 2-alkynylanilides via reaction of terminal alkynes with 2-haloanilides and in the subsequent cyclization to indoles.[239] 2-Iodotrifluoroacetanilide and terminal alkynes can be converted into the corresponding free 2-substituted indoles (NH) through a tandem process that gives the best results in the presence of $[Cu(phen)(PPh_3)_2]NO_3$ and K_3PO_4 in toluene or dioxane at 110° (Eq. 84).[239] In some cases, the tandem coupling/cyclization process can be carried out successfully using a CuI/Ph_3P combination. Like the related palladium-based tandem processes, the reaction tolerates a wide range of functionalized 1-alkynes, including those containing ether, amide, aldehyde, ester, nitro, and heterocyclic groups. Among the alkynes that have been investigated, a sluggish coupling step that limits the efficiency of the tandem process is observed only with 1-hexyne. No such limitation is observed in the cross-coupling of 1-hexyne with 2-iodotrifluoroacetanilide under Sonogashira conditions.[123,124] The tandem coupling/cyclization procedure was also performed using a catalytic system made of $Cu(PPh_3)NO_3$ as the copper source and a 1,10-phenanthroline immobilized on a polystyrene/divinylbenzene solid support.[243] The cyclization step was not as efficient as with $[Cu(phen)(PPh_3)_2]NO_3$. However, the catalytic system could be reused three times.



(Eq. 84)

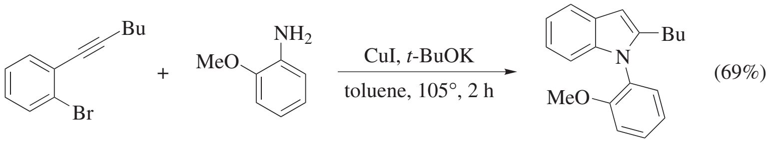
The tandem copper-catalyzed coupling/cyclization process has been subsequently extended to 2-bromoalkynyltrifluoroacetanilides using CuI and L-proline as the ligand.[244] Notably, the amino acid ligand allows for running the reaction of the less reactive 2-bromoalkynyltrifluoroacetanilides under conditions milder than those employed with the corresponding iodo derivatives.

The reaction of 2-alkynyl-*N*-arylideneanilines with alcohols in the presence of catalytic amounts of CuCl affords *N*-(alkoxybenzyl)indoles (Eq. 85).[245] Other transition metal complexes such as $[(\eta^3\text{-}C_3H_5)PdCl]_2$, $[IrCl(cod)]_2$, and $[RuCl(cod)]_2$ exhibit catalytic activity, but copper catalysts are the most convenient to use and CuCl gives the best results. Since the *N*-(alkoxybenzyl)indoles are formed from aldehydes, 2-iodoanilines, terminal alkynes, and alcohols, a wide variety of indole derivatives can be prepared using this protocol.



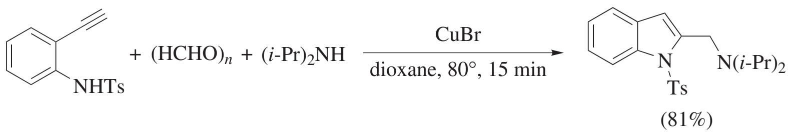
(Eq. 85)

An alternative to the synthesis of indoles from 2-alkynylanilines and their *N*-substituted derivatives is the tandem copper-catalyzed reaction of 2-alkynylhaloarenes with primary amines (Eq. 86).[86] Indoles are formed via a carbon–nitrogen bond forming reaction followed by a cyclization step. This reaction is similar to the palladium-catalyzed reaction (Eq. 3),[86,246] with the main differences being the use of K_3PO_4 or an imidazolium salt (HIPrCl) as a precursor to a carbene ligand for palladium.



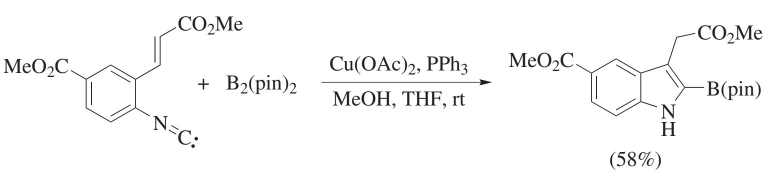
(Eq. 86)

The recently described synthesis of 2-(aminomethyl)indoles through copper(I)-catalyzed, tandem three-component coupling/cyclization (Eq. 87),[247,248] which has been applied to the synthesis of a variety of indole derivatives,[249−251] has its counterpart in the palladium-catalyzed reaction of 3-(2-trifluoroacetamidophenyl)-1-propargyl carbonate esters with amines (Eq. 8).[34] The copper-catalyzed process, however, allows for the construction of the functionalized pyrrole ring through the formation of carbon−nitrogen and carbon−carbon bonds that are different from those involved in the related palladium-catalyzed process (compare with Fig. 1, disconnection a+f). Steric effects influence the reaction outcome with secondary amines in the palladium-catalyzed cyclization (for example, a moderate yield is obtained with diisopropylamine), whereas they appear to play a minor role, if any, in the copper-catalyzed process. In addition, the palladium-catalyzed process forms free indoles (NH) while the copper-catalyzed reaction forms *N*-tosyl indoles.



(Eq. 87)

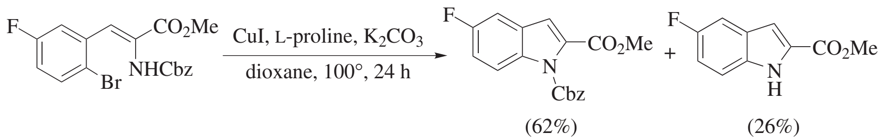
Indole Formation from Alkenes. The use of alkene-based copper-catalyzed synthesis of indoles is still rare. An example of this chemistry has recently been reported and involves the preparation of 2-boryl- (Eq. 88) and 2-silylindoles by copper-catalyzed borylative and silylative cyclization of 2-alkenylaryl isocyanides.[252]



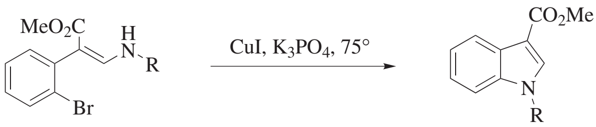
(Eq. 88)

Indole Formation via *N*-Vinylation and *N*-Arylation. The potential of the palladium-catalyzed *N*-arylation and *N*-vinylation approach to the construction of the pyrrole ring has been demonstrated through several applications. This synthetic approach has been quickly applied to the copper-catalyzed construction of the pyrrole ring incorporated into the indole system. Basically, indoles have been prepared through two main synthetic strategies: the cyclization of 2-haloarylenamid(n)es, and the cyclization of 2-(bromovinyl)anilid(n)es.

Preformed 2-haloarylenamid(n)es have been converted into the corresponding indoles by using the CuI/L-proline precatalyst system (Eq. 89)[253] or under the conditions shown in Eq. 90.[254] Similarly, enehydrazid(n)es and enehydroxylamines have been converted into *N*-aminoindole and *N*-alkoxyindole derivatives, respectively.[255]



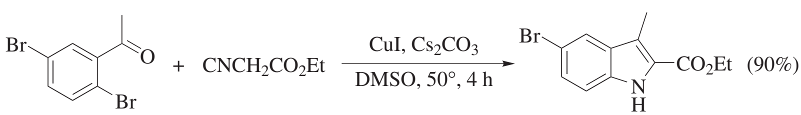
(Eq. 89)



(Eq. 90)

R	Conditions	
4-$MeOC_6H_4$	ethylene glycol, 2-propanol, 6 h	(89%)
Bn	ethylene glycol, DMF, 15 h	(91%)
c-C_6H_{11}	DMF, 20 h	(57%)

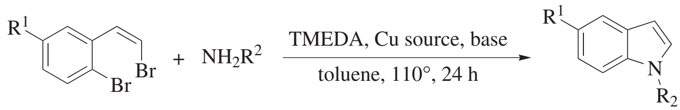
Indoles have also been synthesized from 2-haloarylenamid(n)es prepared in situ. An example of this chemistry is provided by the synthesis of indole-2-carboxylates from 2-haloaryl aldehydes or ketones and ethyl isocyanoacetate (Eq. 91).[256] The reaction is suggested to proceed through a tandem condensation/coupling/deformylation process. It is performed at room temperature or 50° with iodo- and bromo-containing substrates. With chloride-substituted substrates a higher reaction temperature (80°) is required. CuI and CuBr display a similar catalytic activity whereas CuCl, Cu_2O, and $CuSO_4$ are less active. 2-Haloarylenamid(n)es are also generated in situ in the synthesis of indole-2-carboxylic esters from 2-bromoaryl aldehydes and ethyl acetamidoacetate in the presence of CuI and Cs_2CO_3 in DMSO at 80°.[257]



(Eq. 91)

The copper-catalyzed reaction of 2-(2-bromoalkenyl)bromoarenes with carbamates, amides, and anilines allows the preparation of *N*-functionalized indoles through a tandem amination/cyclization process.[258] In the presence of *N*,*N*-dimethylethylenediamine, CuI, CuOAc, and CuTC (copper thiophene-2-carboxylate) can be successfully employed, and K_2CO_3, K_3PO_4, and Cs_2CO_3 are effective bases (Eq. 92).[258] The range of *N*-coupling partners that can be used complements that achievable using palladium catalysis. The major advantage of employing the copper system is the successful preparation of *N*-acyl indoles, which could not be effectively prepared using the palladium-catalyzed process.[259] Conversely, the copper chemistry is less efficient in couplings employing simple amines. A related approach to the construction of the indole ring has been used to prepare 2-bromoindole intermediates in a one-pot synthesis of pyrimido[1,6-*a*]indol-1(2*H*)-ones by a nucleophilic addition/Cu-catalyzed *N*-arylation/Pd-catalyzed

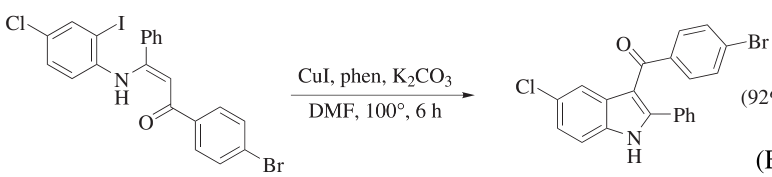
C–H activation sequential process.[260]



R^1	R^2	Cu Source	Base	
Br	*t*-$BuCO_2$	CuOAc	Cs_2CO_3	(53%)
H	*n*-C_5H_{11}	CuTC	K_2CO_3	(87%)
H	Ph	CuI	K_2CO_3	(80%)

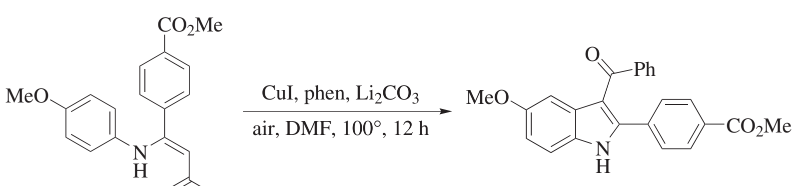
(Eq. 92)

Indole Formation via Arene Vinylation. Some approaches to the contruction of the indole skeleton have been based on the ability of copper to catalyze the formation of carbon–carbon bonds. In particular, this strategy has been applied to the preparation of indoles from *N*-(2-haloaryl)-[261,162] and *N*-(aryl)enaminones.[263] *N*-(2-Haloaryl)enaminones have been converted into the corresponding 2-substituted 3-acylindoles through a process that involves the copper-catalyzed substitution of the carbon–carbon bond for the carbon–halogen bond (Eq. 93).[261] The synthesis of indoles from *N*-(aryl)enaminones is based on the formation of carbon–carbon bonds through selective catalytic activation of aryl carbon–hydrogen bonds (Eq. 94).[263] This reaction reflects the current interest in minimizing substrate preactivation in indole synthesis,[264,265] taking advantage of carbon–carbon bond forming processes that do not rely on preactivation of the starting materials, an inherently wasteful requirement since the installation of activating groups (commonly halogens) may require multiple steps while none appear in the final products.



(92%)

(Eq. 93)

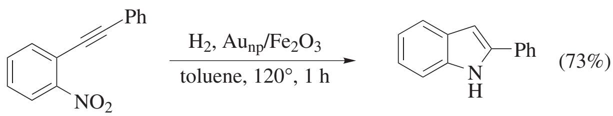


(66%)

(Eq. 94)

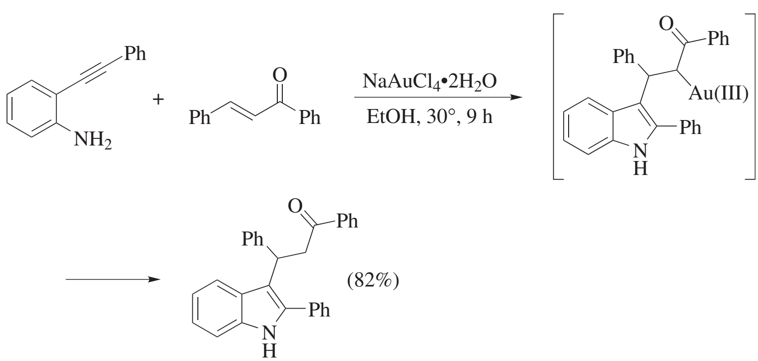
Gold-Catalyzed Indole Formation

Alkynes are the typical substrates even for gold-based indole syntheses. In particular, 2-alkynylanilines[70,266,267] and their *N*-substituted derivatives[70] are converted into 2-substituted indoles using $NaAuCl_4$ in THF,[70] EtOH, or EtOH–H_2O mixtures,[266] and $AuCl_3$ in EtOH.[267] Gold-catalyzed cyclizations to indoles may be carried out using a polystyrene-silica-gel-supported gold(III) catalyst[268] or with water[269] or ionic liquids[270] as the reaction medium. In the latter case, cyclization of 2-alkynylanilines with $NaAuCl_4 \cdot H_2O$ in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) affords 2-substituted indoles in high yields. The catalyst system is best recycled using Bu_4NAuCl_4.[270] The related synthesis of 2-substituted indoles from 2-alkynylnitroarenes proceeds through a one-pot, one-step (Eq. 95) or one-pot, two-step hydrogenation/hydroamination process catalyzed by gold nanoparticles supported on Fe_2O_3.[271]



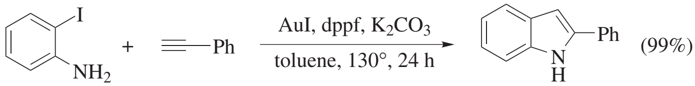
(Eq. 95)

The gold-catalyzed hydroamination of 2-alkynylanilines has been combined with a C-3 functionalization step to provide a general entry into 2,3-disubstituted indoles.[272–274] An example of this approach to 2,3-disubstituted indoles is shown in Eq. 96.[272] The reaction involves the conjugate addition to α,β-enones of indolylgold intermediates formed in situ. Both the cyclization reaction and the conjugate addition reaction are completely inhibited when the nitrogen nucleophilicity is decreased as with 2-alkynylacetanilides. In these cases, a competitive addition of water to the triple bond is observed. Both gold(III)[275–278] and gold(I)[279] species are known to catalyze the hydration of alkynes. A related palladium-catalyzed cyclization of aryl alkynes containing *ortho* nitrogen nucleophiles with α,β-enals and -enones has been described.[103] However, the reaction fails to give the desired 2-substituted 3-alkylindoles using anilines, requiring the use of 2-alkynylanilides to give the best results.

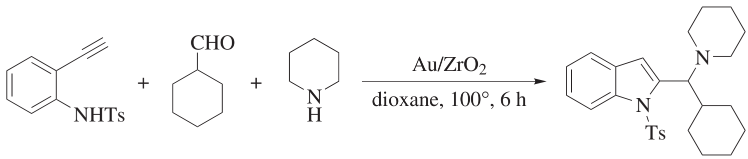


(Eq. 96)

Some procedures that involve the in situ preparation and cyclization of 2-alkynylanilines to 2-substituted indoles have been developed. Terminal alkynes and 2-iodoaniline have been converted into 2-substituted indoles through a gold-catalyzed coupling/cyclization sequence (Eq. 97).[280] N-Boc, N-Ts, N-Ms, and N-acetyl 2-iodoanilines are also suitable coupling/cyclization partners. However, no indole formation is observed with 2-bromoaniline. Recently, a three-component coupling/cyclization of N-Ts ethynylaniline, aldehydes, and amines has been described (Eq. 98).[281] The reaction occurs in the presence of a heterogeneous catalyst based on gold supported on nanocrystalline ZrO_2.

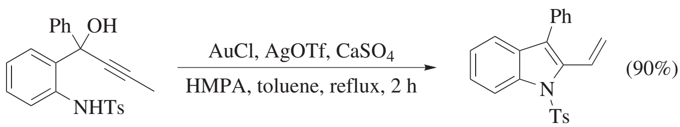


(Eq. 97)



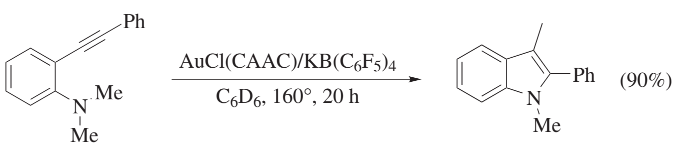
(Eq. 98)

In addition to 2-alkynylanilid(n)es, 2-tosylaminophenylprop-1-yn-3-ols have been shown to be useful precursors of indole derivatives (Eq. 99).[282]



(Eq. 99)

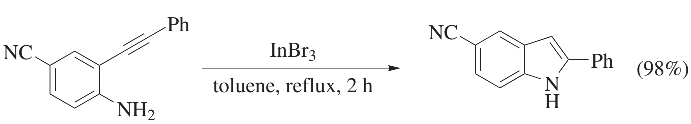
All the above-mentioned alkyne-based gold-catalyzed indole syntheses involve a hydroamination reaction, that is, the addition of a nitrogen–hydrogen bond across a carbon–carbon triple bond. Recently, a synthetic approach that is based on the quite rare carboamination of alkynes[7,102,140,283] (i.e., the addition of a carbon–nitrogen bond to a carbon–carbon triple bond) has been developed. In particular, 2-substituted 3-methylindoles are formed from 2-alkynyl-*N*,*N*-dimethylanilines through an intramolecular methylamination catalyzed by AuCl(CAAC) (CAAC = cyclic (alkyl)(amino)carbene) (Eq. 100).[284] In the same paper, cationic gold(I) complexes supported by CAAC ligands were shown to promote the formation of indole derivatives via an intramolecular hydroammoniumation reaction.



(Eq. 100)

Indium-Catalyzed Indole Formation

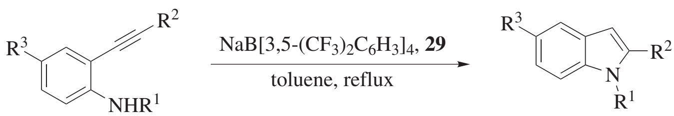
Indium(III) bromide has been reported to catalyze the intramolecular hydroamination of 2-ethynylanilines having an alkyl or aryl group on the alkyne to selectively afford 2-substituted indole derivatives (Eq. 101).[285,286] Interestingly, using substrates with a trimethylsilyl group or no substituents on the triple bond exclusively gives quinoline derivatives.



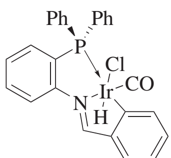
(Eq. 101)

Iridium-Catalyzed Indole Formation

The combination of iridium complex **29** with NaB[3,5-$(CF_3)_2C_6H_3$]$_4$ provides a catalyst system that can be used for the synthesis of 2-substituted indoles from 2-alkynylanilines (Eq. 102).[287] High to excellent yields are obtained with neutral and electron-donating substituents on the aromatic ring and/or the nitrogen whereas indoles are isolated in very low yields when either the aromatic ring or the nitrogen atom bears electron-withdrawing substituents. The number of examples investigated is relatively limited in comparison with the large number of related palladium(II)-catalyzed hydroaminations and there is room for further improvement. Nevertheless, the substrate scope of the palladium(II)-catalyzed processes is wider. Indeed, a number of successful palladium(II)-catalyzed hydroaminations to indoles have been performed using aryl alkynes containing *ortho* nitrogen nucleophiles with electron-withdrawing substituents both on the aromatic ring and/or the nitrogen atom.



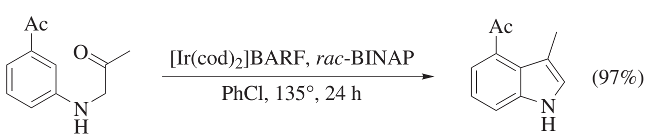
(Eq. 102)



29

R^1	R^2	R^3	Time (h)	
H	H	H	24	(10%)
H	*n*-Bu	H	6	(96%)
H	*n*-Bu	Cl	24	(84%)
H	*n*-Bu	NO_2	24	traces
H	*n*-Bu	Me	6	(96%)
Ac	*n*-Bu	H	24	(21%)
H	Ph	H	12	(95%)
H	Ph	Cl	24	(27%)
H	Ph	NO_2	24	(16%)
H	Ph	Me	24	(96%)

Several types of 4-acetylindoles have been selectively obtained through directed cyclodehydration of α-arylamino ketones catalyzed by a cationic iridium–BINAP complex (Eq. 103).[288] The acetyl group at the *meta* position plays a key directing role and enables carbon–iridium bond formation at the congested *ortho* position, which is followed by an intramolecular 1,2-addition to a carbonyl moiety and a dehydration step.

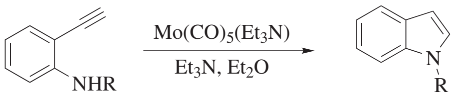


(Eq. 103)

BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

Molybdenum-Catalyzed Indole Formation

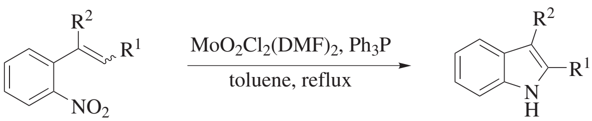
Molybdenum catalysis has been applied to a few alkyne-based indole syntheses. In particular, the Boc derivative of 2-ethynylaniline, a terminal alkyne, can be converted into the corresponding indoles in the presence of the $Mo(CO)_5(Et_3N)$ complex (Eq. 104).[289] Interestingly, the cyclization of 2-ethynylaniline provides the desired product in high yield under molybdenum-catalyzed conditions, whereas a poor yield is obtained using an iridium complex (Eq. 102).[287]



(Eq. 104)

R = H (79%)
R = Boc (50%)

An alkene-based route to indoles has also been investigated using molybdenum complexes as catalysts. In particular, 2-nitrostyrenes provide access to 2-substituted and 2,3-disubstituted indoles by molybdenum-catalyzed reductive cyclization with $MoO_2Cl_2(DMF)_2$ and Ph_3P (Eq. 105).[290] Toluene is the most suitable solvent and the use of an inert atmosphere leads to a better conversion, probably due to the oxidation of Ph_3P in air. Both the *cis* and *trans* isomers react, although a slightly higher yield is obtained from the former. In comparison to palladium-catalyzed methods,[154–156,158–161,180] no carbon monoxide is required. To make the procedure more practical, the dioxomolybdenum-catalyzed reductive cyclization of 2-nitrostyrenes to indoles can be carried out using a polymer-bound triphenylphosphine.[290] Under these conditions, reaction times are a bit longer, but the isolation of the product by simple filtration to remove the solid-supported phosphine is much easier.

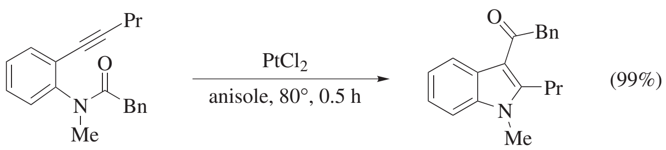


(*E*)/(*Z*)	R^1	R^2	
4:1	Me	H	(77%)
1:0	CO_2Et	H	(75%)
0:1	CO_2Et	Me	(84%)
1:2.3	n-C_5H_{11}	H	(80%)
1:2	Ph	H	(73%)
10:1	Ph	H	(64%)
1.5:1	Ph	H	(80%)

(Eq. 105)

Platinum-Catalyzed Indole Formation

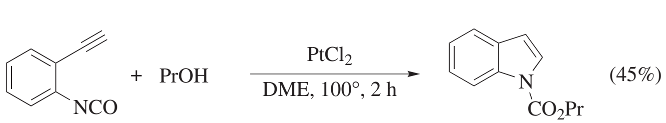
2-Alkynylanilides also are the typical indole precursors in the platinum-catalyzed cyclizations. However, some of the alkyne-based, platinum-catalyzed cyclizations provide routes to indoles that do not have a palladium counterpart. Furthermore, some of the acetylenic substrates that afford indoles under platinum-catalyzed conditions do not undergo indole formation using palladium. This divergence is the case with the platinum-catalyzed synthesis of 2-substituted-3-acyl indoles (Eq. 106),[283] where $PtCl_2$ gives the best results. Slightly lower yields are obtained with other platinum(II) precatalysts, such as $PtCl_2(MeCN)_2$ and $PtBr_2$, whereas $Pt(PPh_3)_4$ does not afford the products at all. Palladium catalysts such as $Pd(PPh_3)_4$ and $PdCl_2$ do not exhibit useful catalytic activity. 2-Substituted 3-acyl indoles can be accessed using palladium catalysis by the reaction of 2-alkynyltrifluoroacetanilides with aryl iodides or vinyl triflates under an atmosphere of carbon monoxide.[124] This protocol allows for the synthesis of indoles containing aryl and vinylic units bound to the carbonyl group at C(3) but no alkyl substituents can be introduced. In contrast, the synthesis of 2-substituted 3-acylindoles containing alkyl substituents bound to the carbonyl group at C(3) can be readily accomplished by the platinum-catalyzed process.



(Eq. 106)

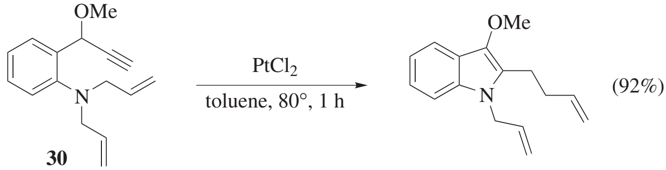
The platinum-catalyzed cyclization of 2-alkynylanilides to indoles has been combined with the reaction of the latter with electron-poor alkynes such as ethyl propiolate and dimethyl acetylenedicarboxylate to give 2,3-disubstituted indoles.[291] The composition of the products is largely influenced by the substituents on the indoles as well as the amount of alkyne used.

A few 2-(alkynyl)phenylisocyanates have been converted into 2-substituted *N*-(alkoxycarbonyl)indoles using $PtCl_2$, although most of the 2-(alkynyl)phenylisocyanates investigated have been converted into the corresponding indoles with Na_2PdCl_4.[28] In some cases, platinum catalysis affords better results than palladium catalysis. For example, an isocyanate having a terminal acetylenic group gives the corresponding indole derivative in 45% yield with $PtCl_2$ and *n*-propanol (Eq. 107)[28] whereas the use of Na_2PdCl_4 results in the formation of a complex mixture of unidentified products. Longer reaction times are needed with increasing bulk of the alcohols. With *tert*-butyl alcohol, $PtCl_2$ shows higher catalytic activity than Na_2PdCl_4, and only the use of $PtCl_2$ allows reaction of an internal alkyne with allyl alcohol for formation of the desired 2-substituted indole.[28] Recently, 2-(alkynyl)phenylisocyanates have been prepared via a Hofmann-type rearrangement of 2-(alkynyl)benzamides promoted by $PhI(OAc)_2$ and cyclized in situ to 2-substituted indoles with $PtCl_2$ through a tandem procedure.[292,293]



(Eq. 107)

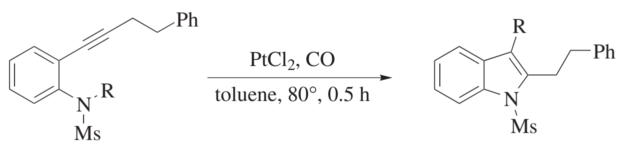
The preparation of 2,3-disubstituted indoles and particularly 3-alkoxyindoles from aniline **30** (Eq. 108)[294] is another platinum-catalyzed reaction without a palladium counterpart. It can be carried out even using proton catalysis.



30

(Eq. 108)

The cyclization of precursor **31** to give the 2-substituted indole derivative **32** has numerous related palladium-based analogs and the conversion of precursor **33** into indole **34** (Eq. 109)[295] resembles the related palladium-catalyzed reaction of 2-alkynyl-*N*-allyltrifluoroacetanilides.[102] These are the only examples reported. However, unlike the palladium-based version, the platinum-catalyzed reaction requires the presence of carbon monoxide (its presence has been shown to accelerate certain $PtCl_2$-catalyzed skeletal rearrangements).[296] This reaction is performed with anilides, thus forming *N*-protected indoles, whereas free indoles (NH) are obtained in the palladium-catalyzed cyclization. Furthermore, the two methods differ mechanistically in that the palladium-based reaction relies on a redox palladium(0)–palladium(II) cycle, whereas the platinum-based one does not. This feature may be of interest when working with substrates that contain additional sites prone to oxidative addition.



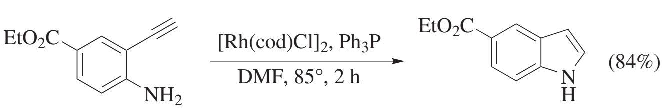
(Eq. 109)

	R	
31	H	**32** (93%)
33	$CH_2CH{=}CH_2$	**34** (59%)

2-Propargyl anilines can give indoles through a platinum-catalyzed cycloisomerization that can occur under acid-catalyzed or even uncatalyzed conditions.[297]

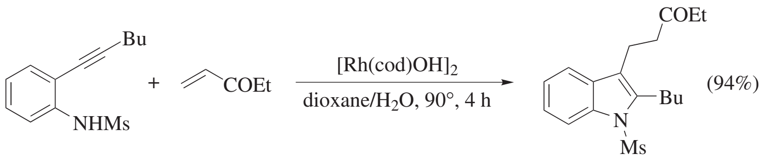
Rhodium-Catalyzed Indole Formation

The rhodium-catalyzed synthesis of indoles[298] provides interesting alternatives to palladium-based processes. Unprotected 2-ethynylanilines have been converted into parent indoles through a cycloisomerization process catalyzed by $[Rh(cod)Cl]_2$ in the presence of Ph_3P (Eq. 110) or $(4\text{-}FC_6H_4)_3P$.[299] The reaction is suggested to involve a rhodium-vinylidene intermediate. Thus, only terminal alkynes can serve as substrates for indole formation. The synthesis of parent indoles from the cyclization of unprotected 2-ethynlanilines distinguishes this process from other metal-catalyzed cyclization methods.



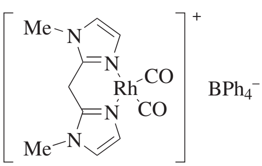
(Eq. 110)

One of the advantages of using cycloisomerisation to synthesize indoles is that the cyclization step affords metalloindoles that can be trapped using suitable reagents, allowing for the design of processes in which several sequential transformations occur. Such a strategy has been applied to the rhodium-catalyzed synthesis of 2,3-disubstituted indoles from 2-alkynylanilides and alkenes (Eq. 111)[300] or alkynes.[301] The reaction outcome is dependent on the catalyst used. With $Rh(CO)_2acac$, the major pathway is the protodemetallation to generate the corresponding 2-substituted indole product. With $[Rh(cod)OH]_2$, the tandem reaction is favored.



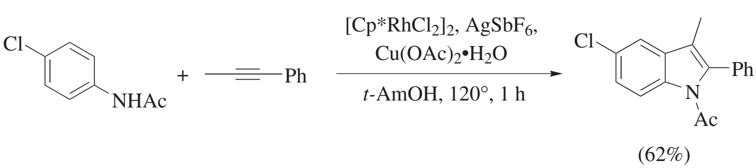
(Eq. 111)

The rhodium complex **35** can catalyze the hydroamination of 2-alkynylanilines to indoles. Specifically, 2-ethynylaniline and 2-(phenylethynyl)aniline are converted into indole and 2-phenylindole, respectively, in acetone at 55°.[302]

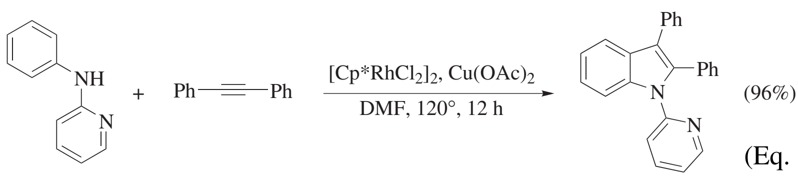


35

Following a current trend aimed at minimizing substrate preactivation in indole synthesis to reduce cost and increase the breadth of readily available starting materials,[263–265] new approaches based on the rhodium-catalyzed oxidative coupling of alkynes with *N*-acetyl anilines (Eq. 112)[303,304] and *N*-aryl-2-aminopyridine (Eq. 113)[305] have been realized.

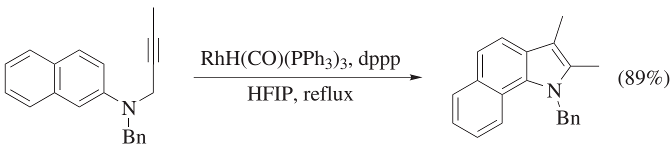


(Eq. 112)



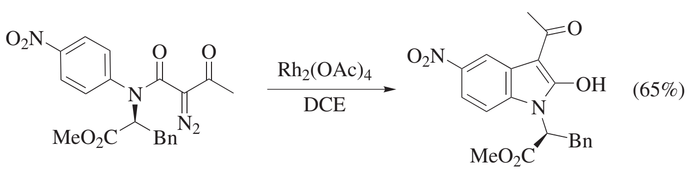
(Eq. 113)

N-Propargylanilines have been converted into 2-substituted and 2,3-disubstituted indoles in the presence of $RhH(CO)(PPh_3)_3$ or $[Rh(cod)_2]OTf$ in hexafluoroisopropyl alcohol (HFIP) (Eq. 114).[306,307] The cyclization proceeds via the corresponding 2-allenylaniline intermediates, which are generated by the rhodium(I)-catalyzed amino-Claisen rearrangement of *N*-propargylanilines. The reaction was also developed into a one-pot synthesis of indoles by reacting *N*-alkylaniline with propargyl bromide.



(Eq. 114)

3-Acetyl-2-hydroxyindoles have been prepared via rhodium(II)-catalyzed decomposition of α-diazoanilides.[308−310] The course of this type of reaction is highly dependent on the substituents surrounding the diazo group. Eq. 115 illustrates an interesting example in which the exclusive alkylation of the nitrophenyl group takes place.[310] Frequently, in similar substrates, insertion of the carbenoid into an aliphatic carbon−hydrogen bond tends to compete with the alkylation of the aryl group. No related palladium-catalyzed reactions have been developed.

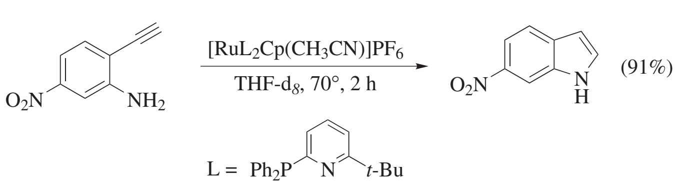


(Eq. 115)

A variety of 2,3-disubstituted indoles have been synthesized by $Rh_2(O_2CCF_3)_4$ catalyzed isomerization of 2-aryl-2*H*-azirines.[311]

Ruthenium-Catalyzed Indole Formation

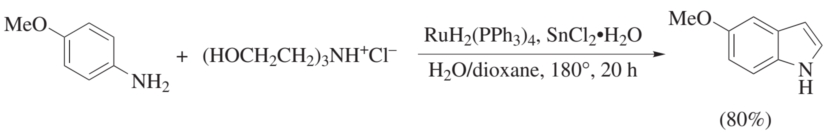
A few examples of indole synthesis via ruthenium-catalyzed, intramolecular hydroamination of an acetylenic precursor have been described. By subjecting 2-ethynylaniline to $Ru_3(CO)_{12}$ in diglyme for 4 hours at 110° under an argon atmosphere, indole is isolated in 54% yield.[312] 2-Ethynylanilid(n)es have been converted into the corresponding indoles in the presence of $[RuL_2Cp(MeCN)]PF_6$ (Eq. 116).[313,314] No reaction is observed with 2-(phenylethynyl)aniline whereas parent indole is isolated in 84% yield after 400 hours using 2-(trimethylsilylethynyl)aniline as the starting alkyne. The reaction has been developed into a one-pot cyclization/hydration process to give indoles containing a C-6 acetaldehyde group.[313,314]



(Eq. 116)

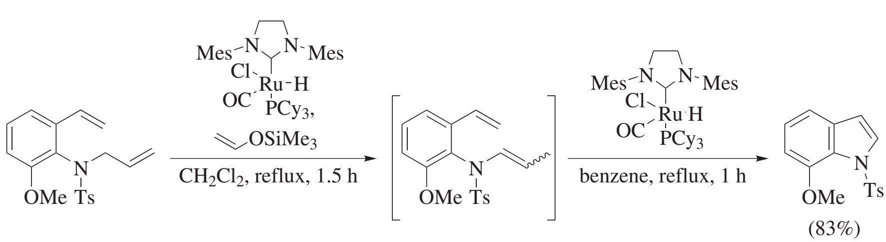
Another ruthenium-catalyzed indole formation is based on the functionalization of benzylic carbon–hydrogen bonds of 1,2-disubstituted isocyanates.[315] In one example, heating a solution of 2,6-xylyl isocyanide and $RuH_2(dmpe)_2$ at 140° in benzene-d_6 for 24 hours results in the formation of 7-methylindole in 98% yield as determined by NMR spectroscopy.

More attention has been paid to the preparation of indoles from anilines and alcohol derivatives. Anilines and 1,2-diols are converted into indole products with $RuCl_2(PPh_3)_2$ at 180° in dioxane[316] or $RuCl_3 \bullet xH_2O$ and Ph_3P or XantPhos at 170°.[317] The reaction of anilines with trialkanolamines[318] and trialkanolammonium chorides[319,320] (Eq. 117) also provides access to indoles. 2,3-Unsubstituted,[315,316,318,319] 2-methyl-,[319] and 2,3-dimethylindoles[315] have been prepared using these methods. The alcoholic components act as two-carbon donors in the construction of the pyrrole ring. In this sense, the reaction is reminiscent of the synthesis of indoles via palladium-catalyzed annulation of 2-haloanilines or their derivatives with internal alkynes.[30,31] The palladium-catalyzed reactions, however, are more versatile.



(Eq. 117)

N-Allyl-2-vinylanilides are converted into indoles through a ruthenium-catalyzed isomerization to enamines in the presence of vinyloxytrimethylsilane followed by a ruthenium-catalyzed ring-closing metathesis which is performed on the crude isomerization mixture after evaporation of the volatile materials (Eq. 118).[321,322] The aromatic enamide/ene methatesis has been subsequently applied to the synthesis of indomethacins.[323]

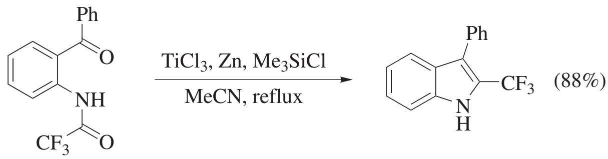


(Eq. 118)

The cyclization reaction of diallylanilines containing an ethynyl group at the *ortho* position of the aromatic ring in the presence of $CpRuCl(PPh)_3$ or CpRuCl(dppe) is accompanied by an aza-Claisen rearrangement, causing an allyl group migration to give substituted indole compounds. This cyclization can also be performed by using the $AuCl(PPh_3)/AgSbF_6$ combination.[324]

Titanium-Catalyzed Indole Formation

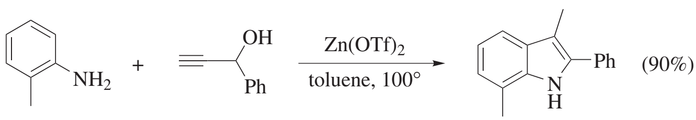
Indoles have been obtained through titanium-catalyzed reductive coupling of carbonyl compounds, a reaction that is based on the high reducing ability and pronounced oxophilicity of low-valent titanium (Eq. 119).[325] Heating oxoamides with catalytic amounts of $TiC1_3$, Zn dust as the stoichiometric reducing agent, and an excess of R_3SiCl in MeCN or DME affords indole derivatives in yields comparable to those obtained in stoichiometric reactions.[326,327]



(Eq. 119)

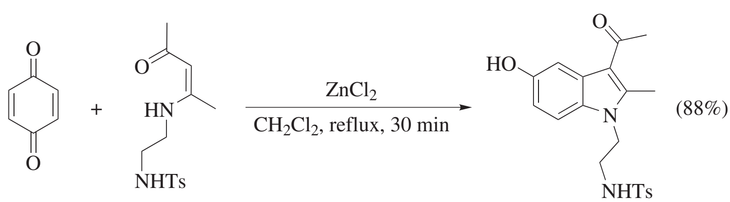
Zinc-Catalyzed Indole Formation

Zinc-catalyzed hydroamination of 2-alkynyl-*N*-tosylanilides (with Et_2Zn)[328] and 2-alkynylanilines (with $ZnBr_2$ or ZnI_2)[329] to the corresponding 2-substituted indole derivatives have been described. A different alkyne-based zinc-catalyzed indole synthesis involves the reaction of propargyl alcohols with anilines in toluene without additives (Eq. 120).[330] The mechanism has been elucidated and the reaction proceeds through a 1,2-nitrogen shift catalyzed by $Zn(OTf)_2$.



(Eq. 120)

Zinc catalysis has also been proven to favor the synthesis of 5-hydroxyindoles from benzoquinone and enaminones.[331,332] An example of this chemistry is shown in Eq. 121.[332]



(Eq. 121)

Fischer indole synthesis has taken advantage of zinc catalysis. Particularly, triethylene glycol with a catalytic quantity of zinc chloride has been described as an efficient reaction medium for the difficult Fischer synthesis of sensitive indoles.[333]

EXPERIMENTAL CONDITIONS

Both palladium(II) salts and palladium(0) complexes have been used in the construction of the indole ring. Commercial samples are normally used without further purification. $PdCl_2$ and $Pd(OAc)_2$ are the most commonly used palladium(II) salts, but the use of $Pd(OCOCF_3)_2$ has also been described. Very often palladium(II) salts (particularly $PdCl_2$, which has a low solubility in water and organic solvents) are used as complexes of the type PdX_2L_2 such as $PdCl_2(PPh_3)_2$, $Pd(OAc)_2(PPh_3)_2$, and $PdCl_2(MeCN)_2$. Complexes containing phosphine ligands are frequently formed in situ by combining palladium(II) salts with the phosphine ligands.

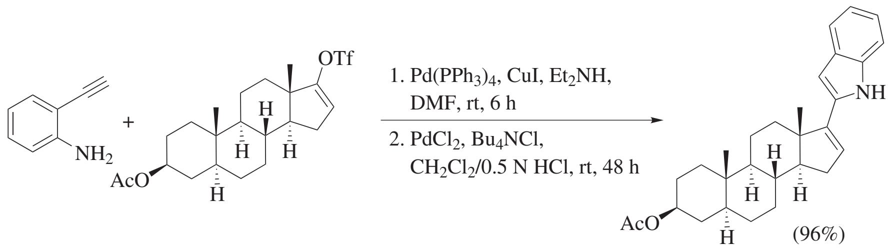
The commercially available $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ are two of the most commonly used sources of palladium(0) species. $Pd(PPh_3)_4$ is unstable in air and light sensitive whereas $Pd_2(dba)_3$ is much easier to store and manipulate. Palladium on charcoal, or other supported palladium metal catalysts, are also employed as a source of palladium(0). As an alternative to the use of preformed palladium(0) complexes, palladium(0) species can be formed in situ by reduction of palladium(II) species by several reagents such as alkenes, terminal alkynes, carbon monoxide, alcohols, amines, formate anions, metal hydrides, butyllithium, or phosphines. Reactions involving palladium(0) catalysis are usually carried out in an inert atmosphere of argon or nitrogen.

The efficiency of palladium catalysts is dependent on the nature of the ligands and on the ratio of the ligand to palladium. For example, with the coordinatively saturated palladium(0) complex $Pd(PPh_3)_4$, the dissociation of two Ph_3P is necessary to generate the coordinatively unsaturated $Pd(PPh_3)_2$, which allows for the coordination of the reactants to palladium. Although a number of reactions have been carried out under phosphine-free conditions, phosphines are usually required to generate soluble palladium catalysts and to modulate the reactivity of palladium complexes. The recent development of several indole syntheses involving the oxidative addition of carbon–bromine or carbon–chlorine bonds to palladium employ biarylmonophosphines[134–136] because these bonds are usually reluctant to undergo oxidative addition with other commonly used ligands. Carbene ligands have also been employed.[86]

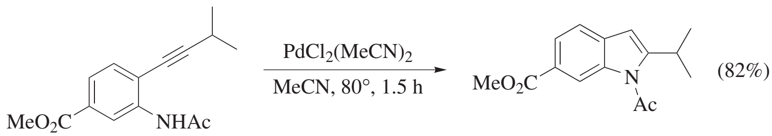
Palladium(II) salts reduced in situ to palladium(0) species or commercially available palladium(0) compounds (particularly $Pd_2(dba)_3$) are frequently used to prepare palladium–phosphine complexes in situ via a ligand exchange reaction. Such an exchange reaction has been carried out with a vast range of monodentate and bidentate phosphines and some carbene ligands and represents a convenient entry into the generation of "tailor-made" catalyst systems.

In addition to phosphine and carbene ligands, additives (mostly halide additives such as LiCl, LiBr, Bu_4NCl, or BuN_4Br), bases, and solvents play an important role in controlling the outcome of palladium-catalyzed reactions. Chloride anions stabilize palladium species and provide more efficient catalytic cycles.[31,334,335] Bromide anions control the vinylic substitution/conjugate addition-type ratio in the reaction of 2-alkynylanilides with α,β-enals and -enones.[103] In general, and apart from some important rationalizations, the specific role of all these factors, which may change from one type of reaction to another, is not always well understood. They combine to afford a toolbox of tunable reaction conditions that make palladium chemistry extraordinarily flexible. Therefore, it is advisable that a variety of ligands, solvents, bases, and additives be investigated in the initial search for optimal conditions.

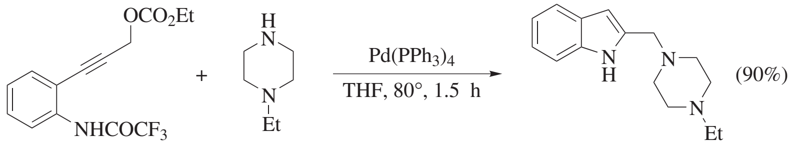
EXPERIMENTAL PROCEDURES



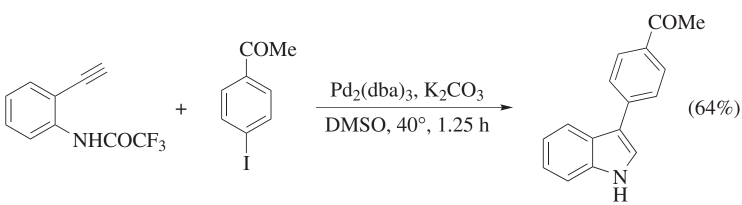
2-(3α-Acetoxyandrost-16-en-17-yl)-1*H*-indole [One-Flask Synthesis of a 2-Substituted Indole from 2-Ethynylaniline].[71] To a stirred solution of 3α-acetoxyandrost-16-en-17-yl triflate (0.230 g, 0.49 mmol) in DMF (0.5 mL) and Et_2NH (2 mL) were added 2-ethynylaniline (0.058 g, 0.49 mmol), $Pd(PPh_3)_4$ (0.011 g, 0.009 mmol), and CuI (0.004 g, 0.020 mmol). The reaction mixture was stirred for 6 h at rt under a nitrogen atmosphere, and then evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (13 mL) and 0.5 N HC1 (5 mL), and $PdCl_2$ (0.05 g, 0.028 mmol) and Bu_4NCl (0.015 g, 0.051 mmol) were added. The reaction mixture was stirred at rt for 48 h under nitrogen, then poured into a separatory funnel containing Et_2O and saturated, aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel chromatography, eluting with 20% EtOAc/*n*-hexane to give 0.205 g (96%) of the title product: mp 119–121°; IR (KBr) 3400, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.16 (br s, 1H), 7.55 (d, $J = 8.2$ Hz, 1H), 7.31–7.01 (m, 3H), 6.53 (d, $J = 1.6$ Hz, 1H), 5.95 (br s, 1H), 5.03 (br s, 1H), 2.05 (s, 3H), 1.03 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.8, 146.7, 136.0, 134.1, 129.0, 124.9, 122.1, 120.4, 119.8, 110.3, 99.9, 70.1; EIMS m/z (relative intensity): M$^+$ 431 (100), 372 (46).



***N*-Acetyl-2-isopropyl-6-carbomethoxyindole [Preparation of a 2-Substituted Indole from a 2-Alkynylacetanilide].[49]** To a solution of *N*-acetyl-2-(3-methylbutyn-l-yl)-5-carbomethoxyaniline (0.107 g, 0.413 mmol) in MeCN (4 mL) was added $PdCl_2(MeCN)_2$ (11 mg, 0.041 mmol) and the mixture was heated at 80° for 1.5 h. The solvent was removed in vacuo and the resulting oil was purified by column chromatography on silica gel (17% EtOAc/n-hexane) to yield 0.088 g (82%) of the title product as a white, crystalline solid: mp 67.5–68.5°; IR ($CHCl_3$) 1711, 1554, 1462, 1313, 1304, 1297, 1255, 1108 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.41 (d, J = 1.4 Hz, 1H), 7.89 (dd, J = 1.4, 8.1 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 6.50 (s, 1H), 3.92 (s, 3H), 3.72 (hept, 1H), 2.84 (s, 3H), 1.30 (d, J = 6.8 Hz, 6H). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61. Found: C, 69.40; H, 6.61.

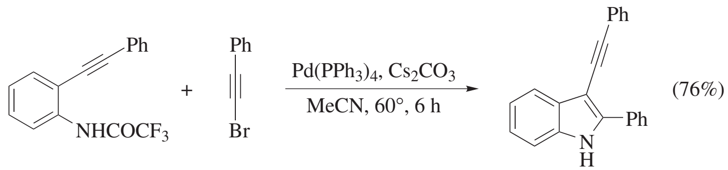


2-[(4-Ethylpiperazin-1-yl)methyl]indole [Synthesis of a 2-Substituted Indole through an Intramolecular Heterocyclization/Intermolecular Nucleophilic Attack on a π-Allylpalladium Intermediate].[34] A Carousel Tube Reactor (Radley Discovery Technology) equipped with a magnetic stirrer was charged with ethyl 3-(2-trifluoroacetamidophenyl)-1-propargyl carbonate (0.050 g, 0.159 mmol), N-ethylpiperazine (0.055 g, 0.477 mmol), and $Pd(PPh_3)_4$ (0.009 g, 0.00795 mmol) in 1.0 mL of anhydrous THF under argon. The mixture was warmed at 80° and stirred for 1.5 h. After cooling, the reaction mixture was concentrated under reduced pressure and the residue was purified by chromatography (Al_2O_3, 50 g; 30% EtOAc/n-hexane) to give 0.035 g (90%) of the title product as an oil: IR (neat) 3404, 2935, 2816, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.64 (br s, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.16–7.07 (m, 2H), 6.37 (s, 1H), 3.67 (s, 2H), 2.54–2.41 (m, 10H), 1.09 (t, J = 8.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 136.2, 135.8, 128.4, 121.6, 120.2, 119.6, 110.7, 101.7, 55.9, 53.3, 52.8, 52.3, 12.0. Anal. Calcd for $C_{15}H_{21}N_3$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.01; H, 8.68; N, 17.25.

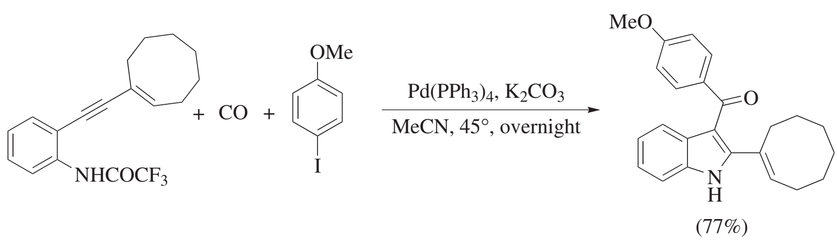


3-(4-Acetylphenyl)indole [Synthesis of a 2-Unsubstituted 3-Arylindole via the Aminopalladation/Reductive Elimination Pathway].[100] To a stirred solution of 2-ethynyltrifluoroacetanilide (0.260 g, 1.22 mmol) and 4-iodoacetophenone (0.200 g, 0.81 mmol) in DMSO (3.0 mL) was added $Pd_2(dba)_3$ (0.019 g, 0.020 mmol) and K_2CO_3 (0.168 g, 1.22 mmol) under argon. The reaction mixture was heated at 40° for 1.25 h. Ethyl acetate was added and the resulting solution was washed with a saturated aqueous NaCl solution, dried over

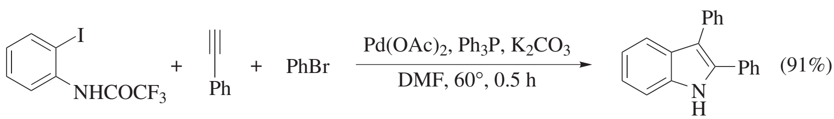
Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 40 g; 30% EtOAc/*n*-hexane) to give 0.120 g (64%) of 3-(4-acetylphenyl)indole: mp 127–128°; IR 3345, 1663, 744 cm^{-1}; ^{1}H NMR δ 8.73 (br s, 1H), 8.05–7.96 (m, 3H), 7.75 (d, J = 8.2 Hz, 2H), 7.43–7.40 (m, 2H), 7.3–7.23 (m, 2H) 2.63 (s, 3H); ^{13}C NMR δ 198.2, 141.0, 136.8, 134.3, 129.1, 126.8, 125.3, 123.2, 122.7, 120.8, 119.7, 116.9, 111.8, 26.6; MS m/z (relative intensity): M$^+$ 235 (88), 220 (100), 192 (44), 165 (30). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.67; H, 5.57; N, 5.96. Found: C, 81.57; H, 5.59; N, 5.95.



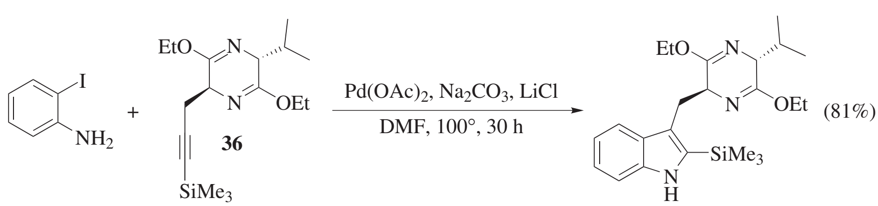
2-Phenyl-3-(phenylethynyl)indole [Synthesis of a 2,3-Disubstituted Indole from a 2-Alkynyltrifluoroacetanilide and a 1-Bromoalkyne].[108] In a Carousel Tube Reactor (Radley Discovery Technology), a solution of 2-phenylethynyl-trifluoroacetanilide (0.100 g, 0.346 mmol) in 2 mL of MeCN was treated with 1-bromophenylacetylene (0.075 g, 0.415 mmol), $Pd(PPh_3)_4$ (0.020 g, 0.017 mmol), and Cs_2CO_3 (0.169 g, 0.519 mmol). The reaction mixture was stirred at 60° for 6 h. After cooling, the reaction mixture was diluted with EtOAc, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; 10% EtOAc/*n*-hexane) to give 0.077 g (76%) of 2-phenyl-3-(phenylethynyl)indole: mp 81–83°; IR (KBr) 3407, 3057, 2201 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.41 (s, 1H), 8.08 (d, J = 7.4 Hz, 2H), 7.88–7.84 (m, 1H), 7.63–7.51 (m, 4H), 7.43–7.26 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 139.5, 135.4, 131.7, 131.3, 130.4, 129.0, 128.5, 128.3, 127.6, 126.6, 124.4, 123.6, 121.0, 120.2, 111.0, 96.1, 93.6, 84.1. Anal. Calcd for $C_{22}H_{15}N$: C, 90.07; H, 5.15; N, 4.77. Found: C, 89.91; H, 5.17; N, 4.74.



2-(Cyclooct-1-enyl)-3-(4-methoxybenzoyl)indole [Synthesis of a 2-Substituted-3-Carbonylated Indole via a Carbonylative Three-Component Cyclization].[124] To a solution of 2-(cyclooct-1-enyl)ethynyltrifluoroacetanilide (0.180 g, 0.56 mmol) in MeCN (6 mL) were added 4-iodoanisole (0.157 g, 0.67 mmol), K_2CO_3 (0.387 g, 2.80 mmol), and $Pd(PPh_3)_4$ (0.032 g, 0.028 mmol). The flask was purged with carbon monoxide for a few seconds and connected to a balloon of carbon monoxide. The reaction mixture was stirred at 45° overnight and poured into a separatory funnel containing 0.1 N HC1 and EtOAc. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by silica gel chromatography, eluting with 20% EtOAc/n-hexane to give 0.155 g (77%) of the title product: mp 72–76°; IR 3250, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.45 (br s, 1H), 7.82 (AA′ part of an AA′BB′ system, $J = 8.9$ Hz, 2H), 7.71–7.64 (m, 1H), 7.40–7.34 (m, 2H), 7.25–7.08 (m, 2H), 6.88 (BB′ part of an AA′BB′ system, $J = 8.9$ Hz, 2H), 6.06 (t, $J = 8.2$ Hz, 1H), 3.87 (s, 3H), 2.38–2.27 (m, 2H), 2.21–2.08 (m, 2H), 1.46 (br s, 8H); ^{13}C NMR ($CDCl_3$) δ 192.5, 162.7, 145.9, 134.8, 134.4, 133.6, 133.2, 131.9, 128.5, 122.6, 121.4, 120.9, 113.2, 112.6, 111.0, 55.4; MS m/z (relative intensity): M^+ 359 (51), 135 (60). Anal. Calcd for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.77; H, 7.12; N, 4.56.

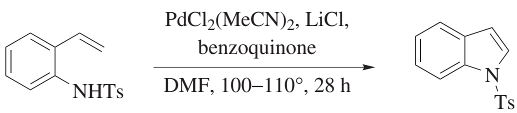


2,3-Diphenylindole [Synthesis of a 2,3-Disubstituted Indole via a One-Pot Tandem Cross-Coupling/Aminopalladation/Reductive Elimination Process].[139] A 10 mL 3-neck flask equipped with a magnetic stirring bar, a thermocouple, and an argon inlet was charged with 2-iodotrifluoroacetanilide (0.5 g, 1.54 mmol), $Pd(OAc)_2$ (17.3 mg, 0.08 mmol), Ph_3P (80.9 mg, 0.154 mmol), and K_2CO_3 (0.851 g, 6.16 mmol), followed by addition of 5 mL of anhydrous DMF. Phenylacetylene (0.189 g, 1.85 mmol) and bromobenzene (0.290 g, 1.85 mmol) were added to the reaction mixture with stirring at rt. The reaction mixture was heated at 60° for 0.5 h. The mixture was quenched with water, and the aqueous solution was extracted three times with EtOAc. The organic solution was washed with saturated aqueous NaCl solution, and dried over Na_2SO_4. The product was purified by column chromatography to give 0.453 g (91%) of 2,3-diphenylindole as an off-white solid: mp 108–110°; ^1H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 7.46–6.90 (m, 14H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.9, 135.1, 134.1, 132.7, 130.2, 128.8, 128.7, 128.5, 128.2, 127.7, 126.2, 122.7, 120.4, 119.7, 115.1, 110.9; LC-MSD (API-ES, positive) m/z: ($M + H^+$) 270.



(2*R*, 5*S*)-3,6-Diethoxy-2-isopropyl-5-[2-(trimethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine [Synthesis of a 2,3-Disubstituted Indole via

Heteroannulation of an Internal Alkyne with 2-Iodoaniline].[112] In a 100 mL round-bottom flask equipped with a stirring bar were placed 2-iodoaniline (200 mg, 0.91 mmol), compound **36** (322 mg, 1 mmol), $Pd(OAc)_2$ (8 mg, 0.036 mmol), LiCl (39 mg, 0.91 mmol), Na_2CO_3 (193 mg, 1.8 mmol), and DMF (12 mL). The reaction mixture was degassed and then heated at 100° under argon until the starting iodoaniline was no longer detected on analysis by TLC (30 h). The DMF was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 (50 mL). The suspension that resulted was passed through a Celite pad to remove the insoluble solids. The solution was concentrated under vacuum and the product was purified by silica gel column chromatography (2% EtOAc/*n*-hexane) to afford 301 mg (81%) of the title product as an oil: IR (NaCl) 3415, 2952, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDC1_3$) δ 7.93 (br s, 1H), 7.72 (d, $J = 7.9$ Hz, 1H), 7.32 (d, $J = 8.1$ Hz, 1H), 7.13 (t, $J = 8.0$ Hz, 1H), 7.05 (t, $J = 7.9$ Hz, 1H), 4.14 (m, 5H), 3.87 (t, 1H), 3.54 (dd, $J = 3.6$, 14.2 Hz, 1H), 2.88 (dd, $J = 9.6$, 14.2 Hz, 1H), 2.27 (m, 1H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.19 (t, $J = 7.1$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.67 (d, $J = 6.8$ Hz, 3H), 0.41 (s, 9H); ^{13}C NMR (75.5 MHz, $CDC1_3$) δ 164.2, 163.3, 138.7, 134.4, 130.1, 123.4, 122.6, 121.0, 119.1, 111.1, 61.2, 61.0, 59.1, 32.4, 19.7, 17.1, 14.9, 14.8, 14.6; EIMS m/z (relative intensity): M^+ 413 (4), 202 (100), 186 (18), 169 (36), 160 (11); exact mass calcd for $C_{23}H_{35}N_3O_2Si$, 413.2499; found, 413.2473.



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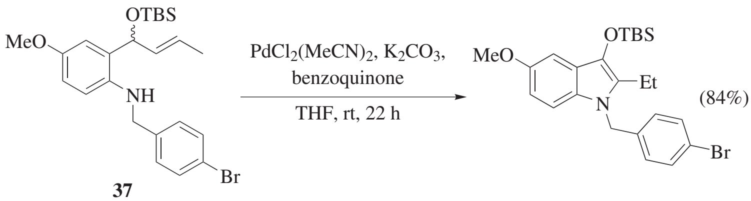
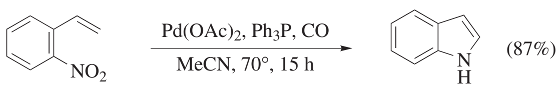
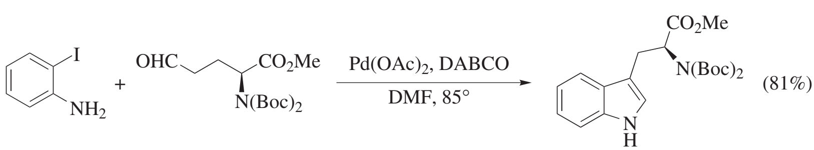
***N*-Tosylindole [Synthesis of a 2,3-Unsubstituted Indole via Cylization of a 2-Vinylanilide].**[145] 2-Vinyl-*N*-tosylaniline (273 mg, 1.00 mmol) was dissolved in 5 mL of DMF. The system was flushed with argon, and $PdCl_2(MeCN)_2$ (26 mg, 0.10 mmol), benzoquinone (216 mg, 2.0 mmol), and LiCl (445 mg, 10 mmol) were added. The mixture was heated at 100–110° for 28 h, cooled, diluted with 25 mL each of Et_2O and water, and filtered through Florisil. The Florisil was washed with 100 mL of Et_2O and the combined filtrates were washed with 50 mL each of water and saturated aqueous NaCl. After drying (Na_2SO_4), the solution was concentrated in vacuo and the residue was purified by silica gel chromatography to yield *N*-tosylindole as a colorless solid that rapidly decomposed to a red oil upon exposure to air: IR ($CDC1_3$) 3010, 2960, 1585, 1435, 1370 cm^{-1}; ^1H NMR ($CDC1_3$) δ 7.95 (br d, $J = 9$ Hz, 1H), 7.78 (d, $J = 9$ Hz, 2H), 7.58 (d, $J = 4$ Hz, 1H), 7.50 (d, $J = 2$ Hz, 1H), 7.29 (d, $J = 9$ Hz, 1H), 7.27 (d, $J = 9$ Hz, 2H), 6.58 (d, $J = 4$ Hz, 1H), 2.35 (s, 3H).



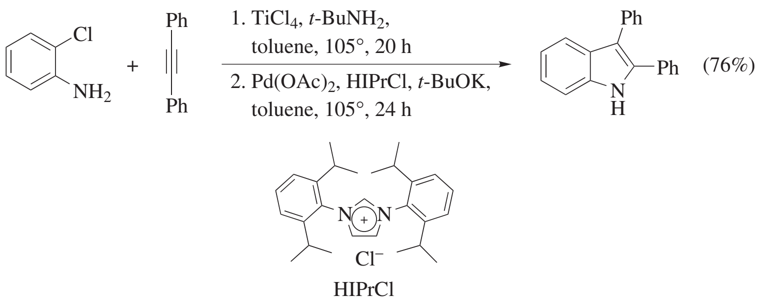
***N*-(4-Bromobenzyl)-2-ethyl-3-(*tert*-butyldimethylsilyloxy)-5-methoxyindole [Synthesis of a 2,3-Substituted Indole via Cyclization of a 2-Allylaniline].[157]** To a degassed suspension of K_2CO_3 (414 mg, 3 mmol), benzoquinone (162 mg, 1.5 mmol), and $PdCl_2(MeCN)_2$ (52 mg, 0.2 mmol) in THF (10 mL) was added a degassed solution of precursor **37** (462 mg, 10 mmol) in THF (5 mL) under nitrogen. The mixture was stirred at rt for 22 h. The THF was evaporated under vacuum and the residue was dissolved in Et_2O and purified by silica gel chromatography to give 389 mg (84%) of the title product: ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.44 (dd, $J = 6.6$, 1.8 Hz, 2H), 7.15 (d, $J = 8.8$ Hz, 1H), 6.93 (d, $J = 2.4$ Hz, 1H), 6.87 (d, 1H), 6.68 (dd, $J = 8.8$, 2.5 Hz, 1H), 5.30 (s, 2H, $C\underline{H}_2$Ph), 3.78 (s, 3H, OMe), 2.27 (s, 3H), 1.09 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (100.6 MHz, CD_3COCD_3) δ 158.7, 143.5, 136.5, 135.7, 134.1, 133.0, 127.8, 127.0, 125.2, 115.7, 114.9, 104.0, 59.8, 50.4, 30.4, 22.9, 13.5, 5.8, 0.2. Anal. Calcd for $C_{23}H_{30}BrNO_2Si$: C, 59.99; H, 6.57; N, 3.04. Found: C, 59.89; H, 6.73; N, 2.99.



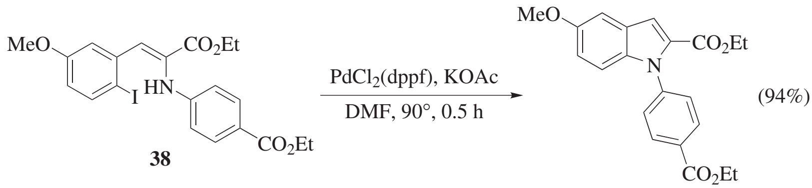
Indole [Cyclization of 2-Nitrostyrene].[156] To an oven-dried, threaded ACE glass pressure tube was added 2-nitrostyrene (298 mg, 2.00 mmol), $Pd(OAc)_2$ (26 mg, 0.12 mmol), Ph_3P (124 mg, 0.48 mmol), and 4 mL of MeCN. The tube was fitted with a pressure head, the solution was saturated with CO (four cycles to 4 atm of CO), and the reaction mixture was heated to 70° (oil bath temperature) under CO (4 atm) until all starting material was consumed (15 h) as judged by TLC. The reaction mixture was diluted with 10% aqueous HCl (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with 10% aqueous HCl (10 mL) and dried ($MgSO_4$), and the solvent was removed to give the crude product which was purified by chromatography (10% EtOAc/*n*-hexanes) to give 203 mg (87%) of indole as white crystals. The spectroscopic data matched those found in the *Aldrich Library of Spectra*: FT-IR spectra **2**, 653 A;^{1}H and ^{13}C NMR spectra **3**, 121 A.



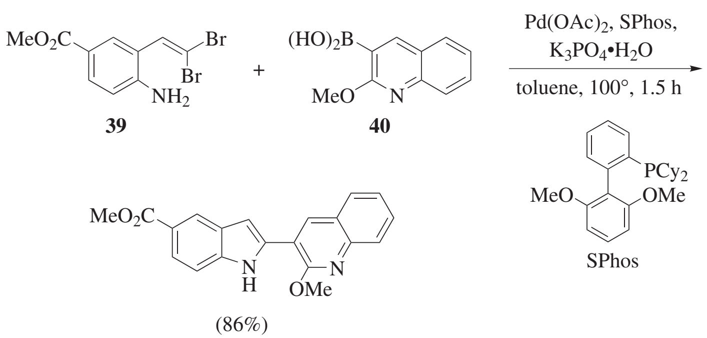
(L)-*N*,*N*-Di-*tert*-butoxycarbonyltryptophan Methyl Ester [Synthesis of a 3-Substituted Indole via Cyclization of an in Situ Generated 2-Haloanilinoenamine].[336] A solution of 2-iodoaniline (73.0 mg, 0.33 mmol), (*S*)-methyl 2-(bis(*tert*-butoxycarbonyl)amino)-5-oxopentanoate (104.0 mg, 0.30 mmol), DABCO (101.0 mg, 0.9 mmol), and $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) in anhydrous DMF (1.5 mL) was degassed. The reaction mixture was heated to 85° until the reaction was complete (usually 8–12 h). The reaction mixture was cooled to rt and diluted with H_2O. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Purification of the crude product by silica gel chromatography (20% EtOAc/heptane) provided 101 mg (81%) of the title product as a yellow oil: $[\alpha]_D^{23}$ −60.0 (*c* 1.0, $CHC1_3$); IR ($CHC1_3$) 3348, 2980, 2359, 1782, 1741, 1457, 1369, 1273, 1140, 1092, 852 cm^{-1}; ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.45 (br s, 1H), 7.58 (d, $J = 7.7$ Hz, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.15 (dt, $J = 1.2$, 7.7 Hz, 1H), 7.09 (dt, $J = 1.2$, 7.9 Hz, 1H), 6.98 (d, $J = 2.1$ Hz, 1H), 5.20 (dd, $J = 4.7$, 10.3 Hz, 1H), 3.77 (s, 3H), 3.62 (dd, $J = 4.7$, 14.9 Hz, 1H), 3.40 (dd, $J = 10.3$, 14.9 Hz, 1H), 1.28 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 151.5, 136.3, 127.5, 123.2, 121.7, 119.2, 118.5, 111.2, 82.8, 58.9, 52.1, 27.6 (6C), 25.8; MS (ESI) *m/z*: [M + Na] 441; HRMS (ESI) *m/z*: [M + Na] calcd for $C_{22}H_{30}N_2O_6Na$, 441.2002; found, 441.1975.



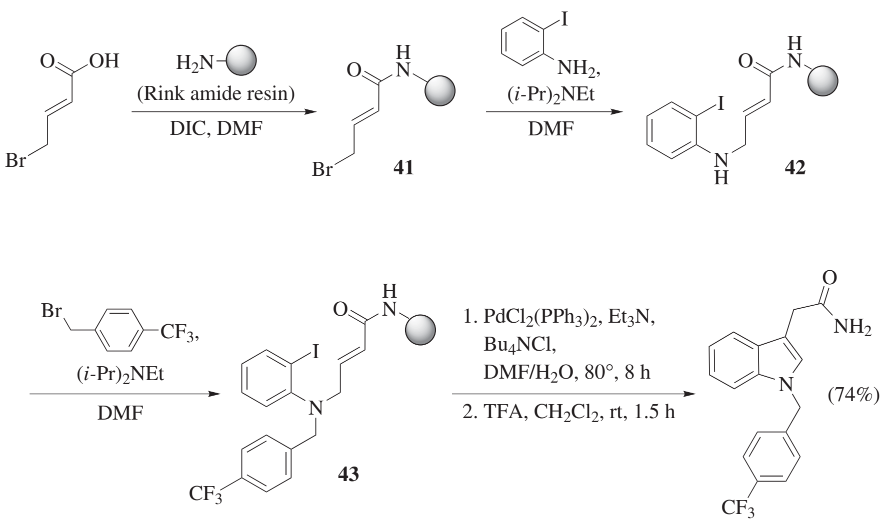
2,3-Diphenylindole [Synthesis of a 2,3-Disubstituted Indole through a One-Pot Hydroamination/Cyclization Process].[184] 2-Chloroaniline (610 mg, 4.76 mmol) and diphenylacetylene (1.02 g, 5.70 mmol) were added to a solution of $TiCl_4$ (0.05 mL, 0.47 mmol) and *t*-$BuNH_2$ (0.30 mL, 2.86 mmol) in toluene (5 mL) and the resulting mixture was stirred for 20 h at 105°. The solvent was partially removed and *t*-BuOK (1.60 g, 14.0 mmol), HIPrCl (202 mg, 0.48 mmol), and $Pd(OAc)_2$ (106 mg, 0.48 mmol) were added. The mixture was stirred at 105° for 24 h. CH_2Cl_2 (75 mL) and aqueous 2 M HCl (50 mL) were added to the cold suspension. The separated aqueous phase was washed with CH_2Cl_2 (2 × 75 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl (50 mL). Drying with $MgSO_4$ and purification by silica gel chromatography (5% → 10% → 20% Et_2O/*n*-pentane) yielded 974 mg (76%) of 2,3-diphenylindole as an off-white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (br s, 1H), 7.67 (d, $J = 7.8$ Hz, 1H), 7.45–7.12 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.9, 135.1, 134.1, 132.7, 130.2, 128.8, 128.7, 128.5, 128.2, 127.7, 126.2, 122.7, 120.4, 119.7, 115.2, 110.9; EIMS *m/z* (relative intensity): M^+ 269 (100), 254 (4), 239 (5), 165 (11), 134 (6), 127 (4); HRMS (EI) m/z: calcd for $C_{20}H_{15}N$, 269.1204; found, 269.1198.



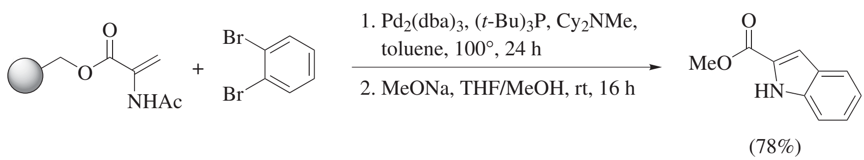
***N*-(4-Ethoxycarbonylphenyl)-2-ethoxycarbonyl-5-methoxyindole [Synthesis of a 2-Substituted Indole Based on an Intramolecular *N*-Arylation Process].[194]** To a solution of precursor **38** (148 mg, 0.3 mmol) in DMF (5 ml) under nitrogen at rt was added KOAc (95 mg, 1 mmol) and $PdCl_2$(dppf) (14 mg, 6 mol %). The mixture was heated to 90° for 30 min, and then partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was separated and the organic phase was washed with water (4 × 25 mL), saturated aqueous NaCl (30 mL), dried ($MgSO_4$), filtered, and the solvent was removed in vacuo to give a brown oil. Column chromatography (20% EtOAc/*n*-hexane) gave 111 mg (94%) of the title product as a clear oil: IR (film) 2982, 1710, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.2 Hz, 2H), 7.42 (s, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 2.1 Hz, 1H), 7.02 (d, J = 9.1 Hz, 1H), 6.95 (dd, J = 2.2, 9.1 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 161.5, 155.7, 143.1, 136.1, 130.8, 130.5, 130.3, 129.6, 128.3, 127.1, 117.5, 112.5, 112.2, 103.0, 61.6, 61.0, 56.1, 14.8, 14.5; MS (ESI$^+$, 70 V) m/z: [MH$^+$] 368.



Methyl 2-(2-Methoxyquinolin-3-yl)indole-5-carboxylate [Synthesis of a 2-Substituted Indole through a Tandem Carbon–Nitrogen/Suzuki–Miyaura Coupling].[201] A 5 mL round-bottomed flask was charged with **39** (0.1675 g, 0.5 mmol), **40** (0.1523 g, 0.75 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), SPhos (12.3 mg, 0.03 mmol), and K_3PO_4•H_2O (0.58 g, 2.5 mmol). The solid mixture was purged with argon for 10 min followed by addition of toluene (2.5 mL). The resulting mixture was stirred at rt for 2 min, then heated at 100° for 1.5 h. The mixture was diluted with EtOAc (10 mL) and H_2O, and the organic phase was separated and dried over Na_2SO_4. The crude material was purified by chromatography with 20% EtOAc/*n*-hexane to afford 0.143 g (86%) of the title product as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.74 (s, 1H), 8.31 (s, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.84–7.77 (m, 2H), 7.70 (dd, J = 7.0, 1.3 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.50 (dd, J = 6.9, 1.2 Hz, 1H), 7.32 (d, J = 1.3 Hz, 1H), 4.18 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.2, 158.3, 144.7, 139.4, 135.5, 134.2, 130.0, 127.8, 127.7, 126.4, 124.9, 124.8, 123.0, 122.9, 120.9, 116.5, 111.4, 104.7, 53.8, 51.7; HRMS (EI) m/z: $[M]^+$ calcd for $C_{20}H_{16}N_2O_3$, 332.1161; found, 332.1161.



2-[1-[4-(Trifluoromethyl)benzyl]indol-3-yl]acetamide [A Solid-Phase Synthesis of a 3-Substituted Indole via Cyclization of a 2-Iodo-*N*-allylaniline].[232] Rink amide resin (7.5 g, 0.48 mmol/g, 3.6 mmol) was deprotected with 20% piperidine in DMF (100 mL) at rt for 1.5 h and then filtered and washed with DMF, MeOH, and CH_2Cl_2. The deprotected resin was suspended in DMF (36 mL) and treated with 1,3-diisopropylcarbodiimide (2.73 g, 21.6 mmol), followed by 4-bromocrotonic acid (3.56 g, 21.6 mmol). The mixture was stirred at rt for 30 min, and then filtered, washed with CH_2Cl_2 and DMF. The resulting resin was retreated with DMF (36 mL), 1,3-diisopropylcarbodiimide (21.6 mmol), and 4-bromocrotonic acid (21.6 mmol) at rt for 30 min and then washed with DMF, MeOH, CH_2Cl_2, and Et_2O, and dried in vacuo to give 7.41 g of resin **41** with a loading level of 0.32 mmol/g, which was determined by cleaving an aliquot with 30% TFA in CH_2Cl_2 at rt for 80 min. Resin **41** (1.2 g, 0.38 mmol) was suspended in DMF (10 mL) and treated with $(i\text{-Pr})_2$NEt (387 mg, 3.0 mmol) followed by 2-iodoaniline (420 mg, 1.9 mmol). The reaction mixture was stirred at 80° for 18 h and then filtered, washed with CH_2Cl_2, MeOH, and CH_2Cl_2, and dried in vacuo to give 1.25 g of resin **42**. A mixture of resin **42** (230 mg, 0.070 mmol), (i-Pr)$_2$NEt (90 mg, 0.70 mmol), and 4-(trifluoromethyl)benzyl bromide (167 mg, 0.70 mmol) in DMF (2.5 mL) was stirred at 80° for 22 h and then filtered, washed sequentially with MeOH and CH_2Cl_2, and dried in vacuo to give resin **43**. The resulting resin was then suspended in DMF/H_2O (9:1, 4 mL) and treated with Bu_4NCl (29 mg, 0.11 mmol), Et_3N (21 mg, 0.21 mmol), and $PdCl_2(PPh_3)_4$ (4.9 mg, 0.007 mmol). The suspension was stirred at 80° for 8 h, at which time TLC indicated that the reaction was complete. The dark-brown reaction mixture was filtered and the solid was washed sequentially with CH_2Cl_2, MeOH, and CH_2Cl_2, and then dried in vacuo. The resulting resin was cleaved with 30% TFA in CH_2Cl_2 (8 mL) at rt for 1.5 h. The crude cleaved product obtained was dissolved in EtOAc (25 mL), and the solution was washed with H_2O (5 mL, to remove contaminated Et_3N–TFA salt), and saturated aqueous NaCl (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting product showed 85% purity by reversed-phase HPLC [2 mL/ min, 30% H_2O/MeCN (0.2% TFA), linear gradient to 5:95 in 30 min; Rf = 18.5 min]. After purification by preparative TLC using 5% MeOH/EtOAc as the eluent, 17.2 mg (74% yield for four steps, based on the loading level of resin **41**) of the title product was obtained as a colorless solid: ^{1}H NMR (CD_3OD) δ 7.61–7.56 (m, 3H), 7.31–7.25 (m, 4H), 7.13 (t, J = 7.2 Hz, 1H), 7.06 (t, J = 7.0 Hz, 1H), 5.46 (s, 2H), 3.67 (s, 2H); ^{13}C NMR (CD_3OD) δ 177.7, 144.4, 138.2, 130.8 (q, $^2J_{CF}$ = 32.3 Hz), 129.6, 128.9, 128.6, 126.7, 125.8 (q, J_{CF} = 271.9 Hz), 123.2, 120.7, 120.1, 111.0, 110.3, 50.3, 33.4; MS m/z: [MH$^+$] 333; HRMS-FAB m/z: [M + H]$^+$ calcd for $C_{18}H_{15}F_3N_2O$, 333.1215; found, 333.1165. Anal. Calcd for $C_{18}H_{15}F_3N_2O$•1.3 H_2O: C, 60.77; H, 4.99; N, 7.87; F, 16.02. Found: C, 60.45; H, 4.22; N, 7.79; F, 16.57.



Methyl 2-Indolecarboxylate [A Solid-Phase Synthesis of a 2-Substituted Indole via Tandem Heck Reaction/N-Arylation].[234] To a mixture of solid-supported N-acetyl dehydroalanine (300 mg, 0.285 mmol), 1,2-dibromobenzene (0.051 mL, 0.428 mmol), $Pd_2(dba)_3$•$CHCl_3$ (39 mg, 0.043 mmol), and (c-C_6H_{11})$_2$NMe (0.18 mL, 0.855 mmol) in toluene (3 mL) was added a 0.5 M toluene solution of (t-Bu)$_3$P (0.34 mL, 0.17 mmol) and the mixture was then heated at 100° for 24 h. The resin was collected by filtration and washed with DMF (three times), DMF/H_2O 1:1 (three times), DMF (three times), THF (three times), and MeOH (three times), and the resin was dried under reduced pressure at 40°. A mixture of the above resin and NaOMe (15 mg, 0.285 mmol) in THF (3 mL) and MeOH (1.5 mL) was agitated at rt for 16 h. The resin was separated by filtration and washed with EtOAc; the filtrate was washed with saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl, dried over Na_2SO_4, and evaporated to afford the crude product which was purified by silica gel chromatography using 20% EtOAc/*n*-hexane to afford 39 mg (78%) of methyl 2-indolecarboxylate as a colorless solid: mp 150–151° (EtOAc/*n*-hexane); IR 3330, 1696, 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.89 (br s, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.45–7.14 (m, 4H), 3.95 (s, 3H); MS m/z: M^+ 175; HRMS calcd for $C_{10}H_9HNO_2$, 175.0633; found, 175.0609.

TABULAR SURVEY

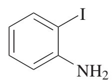
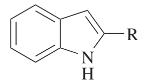
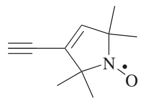
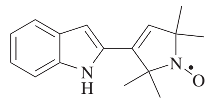
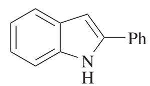
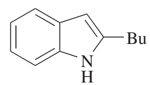
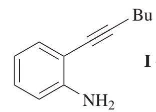
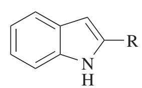
The literature has been surveyed up to the end of 2010. No attempts have been made to cover the patent literature. In general, Tables 1–15 are organized according to the sequence used in the "Scope and Limitations" section. Failed reactions have not been included in the tables. Entries in the tables are ordered by increasing carbon count of the substrates, including protecting groups. The carbon count of Tables 13–15 (solid-phase syntheses) applies only to polymer-bound benzenoid fragments, including the functional groups involved in the linkage to the solid support that remain in the indole product. Yields given for solid-phase syntheses refer to the entire synthetic process; conditions are given for the indole formation step and for the reactions that follow the indole formation step leading to the isolated products. When the numbering is different for an R group in the starting material and the product, the numbering is based on the product.

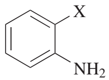
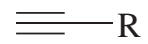
The following abbreviations are used in the tables:

addn	addition
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
bmim	1-butyl-3-methylimidazolium
CPC	cetylpyridinium chloride
DavePhos	2-(2'-*N*,*N*-dimethylaminobiphenyl)dicyclohexylphosphine
dba	dibenzylideneacetone
DIC	*N*,*N*'-diisopropylcarbodiimide
dipf	1,1'-bis(di-*iso*-propylphosphino)ferrocene
dmam-dtbpf	2-(dimethylaminomethyl)-1-(di-*tert*-butylphosphanyl)ferrocene
dmpe	1,2-bis(dimethylphosphino)ethane
DPEPhos	bis[(2-diphenylphosphino)phenyl]ether
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphoshino)ferrocene
dppm	bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
dtbpf	1,1'-bis(di-*tert*-butylphosphino)ferrocene
HIPrCl	1,3-bis(2,6-diisopropylphenyl)imidazolium chloride

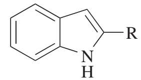
JohnPhos	2-(biphenyl)di-*tert*-butylphosphine
MW	microwave irradiation
NfO	nonafluorobutanesulfonate
NIS	*N*-iodosuccinimide
Np	naphthyl
phen	1,10-phenanthroline
PhXPhos	2-(2’,4’,6’-triisopropylbiphenyl)diphenylphosphine
PMP	1,2,2,6,6-pentamethylpiperidine
PS-PEO	polystyrene–polyethylene oxide copolymer
SBA-15	silica mesophases
$scCO_2$	supercritical carbon dioxide
SPhos	2-(2’,6’-dimethoxybiphenyl)dicyclohexylphosphine
TES	triethylsilyl
TMG	1,1,3,3-tetramethylguanidine
tmphen	3,4,7,8-tetramethyl-1,10-phenanthroline
tol	tolyl, methylphenyl
TPPTS	triphenylphosphine-3,3’,3”-trisulfonate sodium salt
ttmpp	tris(2,4,6-trimethoxyphenyl)phosphine
XantPhos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene
XPhos	2-(2’,4’,6’-triisopropylbiphenyl)dicyclohexylphosphine
))))	ultrasound irradiation

TABLE 1A. 2-SUBSTITUTED INDOLES FROM 2-HALOANILINES AND ALKYNES

2-Haloaniline	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 	≡—R	$[Pd(NH_3)_4]$/NaY zeolite, Et_3N, DMF/H_2O, 80°	 **I** R / Time (d) CMe_2OH 1 (64) Bu 1 (70) $(CH_2)_3CO_2Me$ 1 (51) Ph 0.4 (91)[a]	78
	≡—R	[Pd]/SBA-15, Et_3N, DMF/H_2O (4:1), 80°	**I** R / Time (d) $C(Me)_2OH$ 1 (93)[a] Bu 1 (62) $(CH_2)_3CO_2Me$ 1 (89) Ph 0.1 (72)	78
		$Pd(OAc)_2$, PPh_3, K_2CO_3, Bu_4NCl, DMF, 100°, 3 h	 (50)	91
	≡—Ph	Pd/C, CuI, Et_3N, DMF/H_2O (1:1), 120°, 6 h	 (72)	93
	≡—Bu	$Pd(OAc)_2$, TPPTS, Et_3N, MeCN/H_2O, 65°, 72 h	 **I** +  **II** **I** + **II** (75), **I**:**II** = 75:25	92
	≡—R	$Pd(OAc)_2$, Et_3N, DMF/H_2O, 80°, 2 d	 R CMe_2OH (78)[a] $(CH_2)_3CO_2Me$ (80)[a] Ph (75)[a]	78

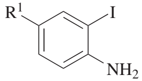
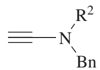
 

$PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 24 h

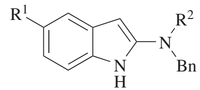


X	R	Temp	
Br	Ph	rt	(78)
I	n-C_5H_{11}	reflux	(68)
I	Ph	rt	(72)

79

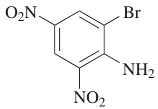
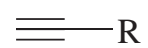
 

$Pd(OAc)_2$, PPh_3, Bu_4NOAc, DMF, 60°

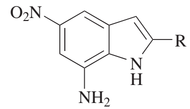


R^1	R^2	
H	Boc	(40)
H	Ts	(64)
O_2N	Ts	(26)

337

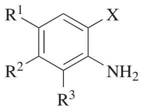
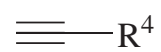
1. $PdCl_2(PPh_3)_2$, CuI, Et_2NH, DMF, 70°
2. NaOH, 140°, 2–4 h



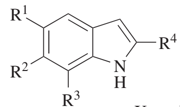
R	
Bu	(40)
n-C_5H_{11}	(50)
c-C_6H_{11}	(36)
Ph	(46)
3-ClC_6H_4	(44)
4-MeC_6H_4	(43)

338

C_{6-7}

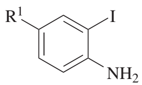
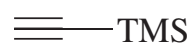
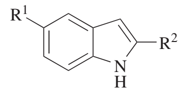
1. $PdCl_2(PPh_3)_2$, CuI, Et_2NH, DMA, rt
2. NaOH, 140°, 2–4 h

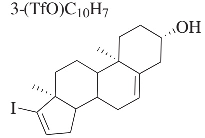


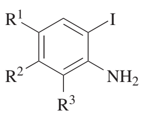
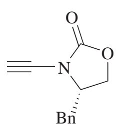
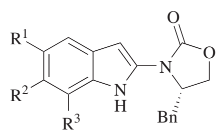
X	R^1	R^2	R^3	R^4	
I	O_2N	H	H	Bu	(89)[b]
I	Cl	H	O_2N	Bu	(55)[b]
I	O_2N	H	H	n-C_5H_{11}	(81)
I	O_2N	H	H	Ph	(84)
I	O_2N	H	H	1-cyclohexenyl	(76)
I	Cl	H	O_2N	3-ClC_6H_4	(76)[b]
Br	H	O_2N	H	n-C_5H_{11}	(47)
Br	H	O_2N	H	Ph	(60)
I	Me	H	O_2N	n-C_5H_{11}	(52)[b]
I	Me	H	O_2N	Ph	(69)

338

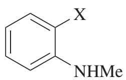
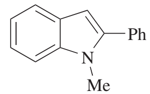
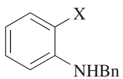
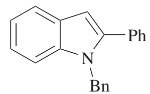
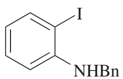
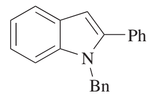
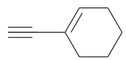
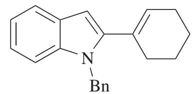
TABLE 1A. 2-SUBSTITUTED INDOLES FROM 2-HALOANILINES AND ALKYNES (*Continued*)

2-Haloaniline	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{6-8} 		1. $PdCl_2$dpp—Si, CuI, *i*-Pr_2NH, MeCN, 60°, 12 h 2. Bu_4NF on silica, 90°, 2 h 3. R^2X, 60°, time 1 4. HCl (1 N), $PdCl_2$, reflux, time 2		339

R^1	R^2	Time 1 (h)	Time 2 (h)	
H	2-IC_4H_3S	2	5	(57)
H	3-IC_5H_4N	2	45	(40)
5-Cl	PhI	2	7	(52)
H	4-IC_6H_4Br	3	5	(28)
H	3-IC_6H_4F	2	7	(59)
5-O_2N	PhI	2	7	(11)
H	3-(TfO)$C_{10}H_7$	3	6	(38)
H		20	24	(21)
5-NC	PhI	2	24	(47)
5-MeO_2C	PhI	2	7	(20)

2-Haloaniline	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$, PPh_3, Bu_4NOAc, DMF, 60°		337

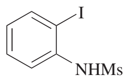
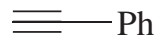
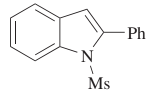
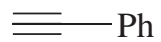
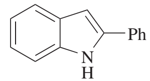
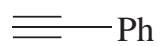
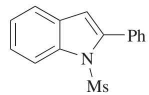
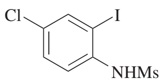
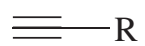
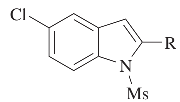
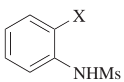
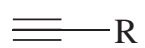
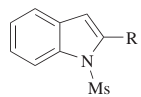
R^1	R^2	R^3	
H	H	H	(81)
Cl	H	H	(87)
H	F	H	(69)
Cl	H	F	(87)
O_2N	H	H	(31)
CF_3	H	H	(48)
NC	H	H	(38)
H	MeO_2C	H	(42)

C_7 	$\equiv$—Ph	$PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, rt, 8 h	 X: Br (82); I (80)	79
C_{13} 	$\equiv$—Ph	$PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, rt, 12 h	 X: Br (74); I (76)	79
	$\equiv$—Ph	Pd(II)/NaY zeolite, LiCl, Cs_2CO_3, DMF, 140°, 6 h	 (68)	96
		Pd(II)/NaY zeolite, LiCl, Cs_2CO_3, DMF, 140°, 6 h	 (52)	96

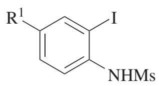
[a] The yield was determined using gas chromatography.

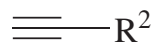
[b] The reaction was carried out under microwave irradiation.

TABLE 1B. 2-SUBSTITUTED INDOLES FROM 2-HALOANILIDES AND ALKYNES

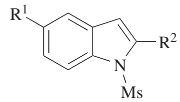
<table>
<tr><th></th><th>2-Haloanilide</th><th>Alkyne</th><th>Conditions</th><th colspan="2">Product(s) and Yield(s) (%)</th><th>Refs.</th></tr>
<tr><td>C_7</td><td></td><td></td><td>PS-PEO-CPC-Pd, ligand, $H_2N(CH_2)_2OH$, CuI, 80°</td><td></td><td><table><tr><th>Solvent</th><th>Ligand</th><th>Time (h)</th><th></th></tr><tr><td>DMA</td><td>—</td><td>4.5</td><td>(79)</td></tr><tr><td>DMA</td><td>PPh_3</td><td>3</td><td>(70)</td></tr><tr><td>H_2O</td><td>—</td><td>3</td><td>(20)</td></tr><tr><td>H_2O</td><td>PPh_3</td><td>3</td><td>(42)</td></tr></table></td><td>85</td></tr>
<tr><td></td><td></td><td></td><td>Pd, CuI, PPh_3/KF–Al_2O_3, no solvent, MW</td><td></td><td>(80)</td><td>95</td></tr>
<tr><td></td><td></td><td></td><td>$PdCl_2(MeCN)_2$, PPh_3, $H_2N(CH_2)_2OH$, CuI, 80°, 4 h</td><td></td><td>(91)</td><td>85</td></tr>
<tr><td></td><td></td><td></td><td>Pd/C, PPh_3, CuI, 2-aminoethanol, H_2O, 80°</td><td></td><td><table><tr><th>R</th><th>Time (h)</th><th></th></tr><tr><td>CH_2OH</td><td>12</td><td>(65)</td></tr><tr><td>$(CH_2)_2OH$</td><td>12</td><td>(60)</td></tr><tr><td>$C(OH)Me_2$</td><td>12</td><td>(89)</td></tr><tr><td>Ph</td><td>4</td><td>(62)</td></tr></table></td><td>94</td></tr>
<tr><td></td><td></td><td></td><td>$PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 80° (X = I) or 120° (X = Br), 24 h</td><td></td><td><table><tr><th>R</th><th>X = I</th><th>X = Br</th></tr><tr><td>CH_2OH</td><td>(53)</td><td>(—)</td></tr><tr><td>$(CH_2)_2OH$</td><td>(59)</td><td>(47)</td></tr><tr><td>CH_2OMe</td><td>(71)</td><td>(12)</td></tr><tr><td>TMS</td><td>(31)</td><td>(58)</td></tr><tr><td>Bu</td><td>(64)</td><td>(43)</td></tr><tr><td>$CH(OEt)_2$</td><td>(63)</td><td>(—)</td></tr><tr><td>$(CH_2)_2CO_2Et$</td><td>(43)</td><td>(49)</td></tr><tr><td>Ph</td><td>(66)</td><td>(20)</td></tr></table></td><td>50</td></tr>
</table>

C_{7-9}

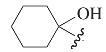
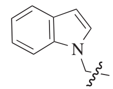
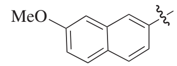
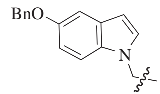
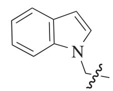




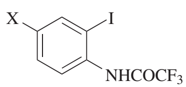
Pd/C, CuI, PPh_3,
2-aminoethanol,
H_2O, 80°

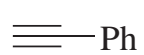


340

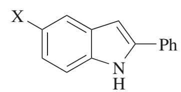
R^1	R^2	Time (h)	
F	$(CH_2)_3Cl$	5	(74)
F		3	(85)
F	$2\text{-}O_2NC_6H_4$	24	(78)
F	$2\text{-}MeC_6H_4$	12	(78)
F		14	(75)
F		12	(78)
F		14	(90)
Cl	$MeCH(OH)CH_2$	10	(79)
Cl	$4\text{-}MeC_6H_4$	4	(86)
Et	$4\text{-}MeC_6H_4$	6	(90)
Et		4	(86)

C_8





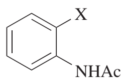
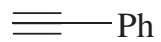
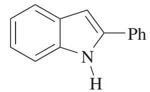
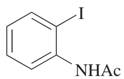
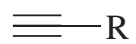
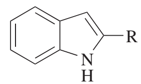
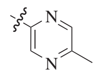
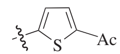
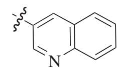
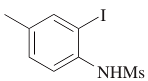
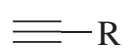
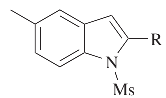
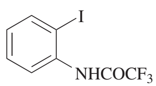
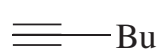
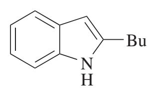
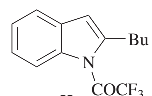
Pd/C, PPh_3, CuI,
2-aminoethanol,
H_2O, 80°



X	Time (h)	
F	12	(78)
Cl	4	(40)

94

TABLE 1B. 2-SUBSTITUTED INDOLES FROM 2-HALOANILIDES AND ALKYNES (*Continued*)

	2-Haloanilide	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8			$PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, rt, 24 h	 X: Br (75); I (69)	79
			Pd(II)/NaY zeolite, LiCl, Cs_2CO_3, DMF, 140°, 6 h	 R: H (40); CH_2OMe (48); CH_2OTHP (69); n-C_5H_{11} (72);  (51); Ph (82); 1-cyclohexenyl (78);  (52);  (50)	96
			Pd/C, PPh_3, Cu, 2-aminoethanol, H_2O, 80°	 R, Time (h): CH_2OH, 8 (70); $(CH_2)_2OH$, 12 (82); CH(OH)Me, 12 (78); $(CH_2)_2Me$, 48 (40); $C(OH)Me_2$, 12 (85); CH(OH)Et, 12 (80); Ph, 3 (70); CH(OH)Ph, 12 (80)	94
			$Pd(OAc)_2$, TPPTS, Et_3N, $MeCN/H_2O$, rt, 72 h	 **I** +  **II** **I** + **II** (70), **I**:**II** = 74:26	92

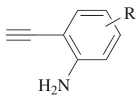
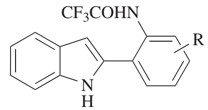
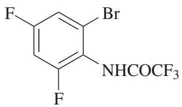
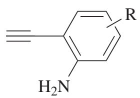
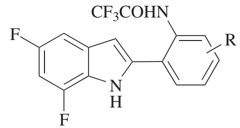
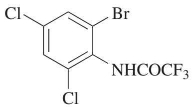
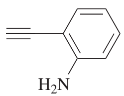
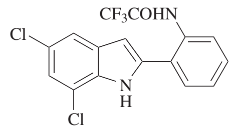
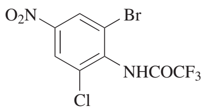
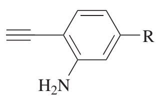
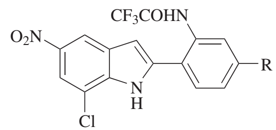
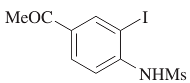
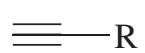
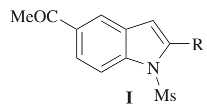
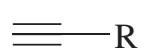
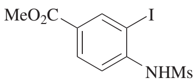
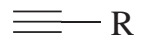
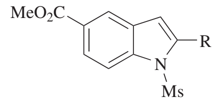
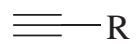
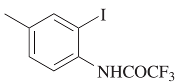
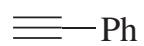
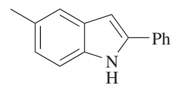
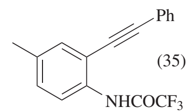
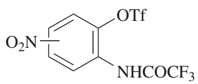
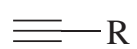
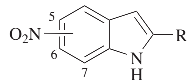
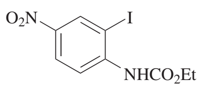
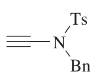
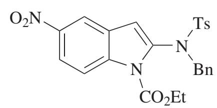
		$PdCl_2(PPh_3)_2$, Et_3N, DMF, 90°	 R / Time (h) H / 4 / (75) 3,5-Cl_2 / 4 / (54) 4-CF_3 / 8 / (56) 3,5-Me_2 / 4.5 / (58)	83
		$PdCl_2(PPh_3)_2$, Et_3N, DMF, 90°, 4 h	 R H (58) 3,5-Cl_2 (54)	83
		$PdCl_2(PPh_3)_2$, Et_3N, DMF, 90°, 4 h	 (55)	83
		$PdCl_2(PPh_3)_2$, Et_3N, DMF, 90°	 R / Time (h) H / 4 / (59) CF_3 / 8 / (45)	83
C_9				
		$Pd(OAc)_2$, Bu_4NOAc, MeCN,)))), 90°, 6 h	 **I** R Ph (52) 4-MeC_6H_4 (65) 4-$MeOC_6H_4$ (66)	84
		$Pd(OAc)_2$, Bu_4NOAc, MeCN, 90°, 12 h	**I** R Ph (45) 4-MeC_6H_4 (71) 4-$MeOC_6H_4$ (67)	84

TABLE 1B. 2-SUBSTITUTED INDOLES FROM 2-HALOANILIDES AND ALKYNES (*Continued*)

2-Haloanilide	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 		$Pd(OAc)_2$, Bu_4NOAc, MeCN,)))), 90°, 6 h	 **I** R CHMeOH (56) Ph (43) 4-MeC_6H_4 (58) 4-$MeOC_6H_4$ (54) 1-Np (60)	84
		$Pd(OAc)_2$, Bu_4NOAc, MeCN, 90°, 12 h	**I** R CHMeOH (56) Ph (43) 4-MeC_6H_4 (58) 4-$MeOC_6H_4$ (54) 1-Np (60)	84
		Pd/C, PPh_3, CuI, 2-aminoethanol, H_2O, 80°, 4 h	 (20) +  (35)	94
		$Pd(PPh_3)_4$, CuI, Bu_4NI, Et_3N, DMF, 80°		80

NO_2 isomer	R	Time (h)		NO_2 isomer	R	Time (h)	
5	$(CH_2)_2OH$	42	(68)	5	$(CH_2)_3Cl$	24	(45)
6	$(CH_2)_2OH$	19	(69)	6	$(CH_2)_3Cl$	20	(66)
7	$(CH_2)_2OH$	12	(48)	5	$(CH_2)_3CN$	25	(75)
5	Pr	24	(90)	6	$(CH_2)_3CN$	8	(73)
6	Pr	21	(84)	5	Ph	41	(85)
7	Pr	7.5	(39)	6	Ph	17	(88)
				7	Ph	3.5	(52)

2-Haloanilide	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$, PPh_3, Bu_4NOAc, DMF, 60°	 (55)	337

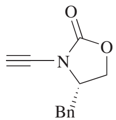
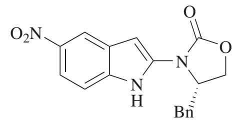
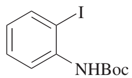
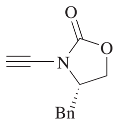
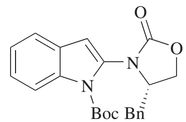
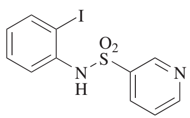
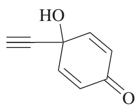
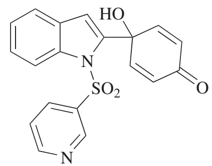
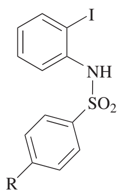
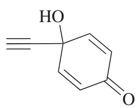
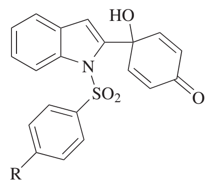
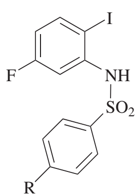
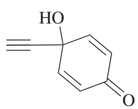
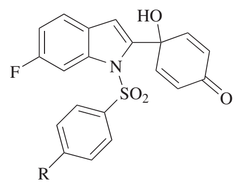
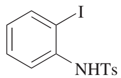
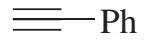
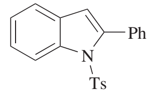
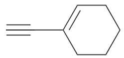
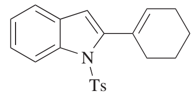
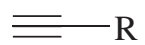
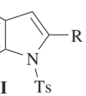
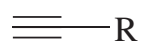
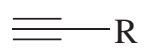
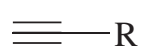
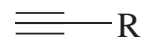
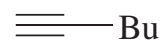
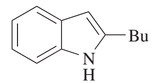
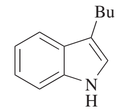
		$Pd(OAc)_2$, PPh_3, Bu_4NOAc, DMF, 60°	 (79)	337
C_{11} 		$Pd(OAc)_2$, PPh_3, Bu_4NOAc, DMF, 60°	 (77)	337
		$Pd(PPh_3)_4$, CuI, $(i\text{-}Pr)_2NH$, DMA, H_2O, 100 W MW, 100°	 (24)	81
$C_{12–16}$ 		$Pd(PPh_3)_4$, CuI, $(i\text{-}Pr)_2NH$, DMA, H_2O, 100 W MW, 100°	 R: H (49); Me (45); CN (10); Ms (23); NHAc (27); $NHCO_2Et$ (38); $(CH_2)_2NHAc$ (28); $(CH_2)_2CO_2Me$ (20)	81
		$Pd(PPh_3)_4$, CuI, $(i\text{-}Pr)_2NH$, DMA, H_2O, 100 W MW, 100°	 R: H (44); $(CH_2)_2CO_2Me$ (48)	81

TABLE 1B. 2-SUBSTITUTED INDOLES FROM 2-HALOANILIDES AND ALKYNES (*Continued*)

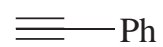
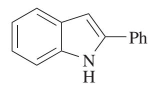
2-Haloanilide	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13} 		Pd(II)/NaY zeolite, LiCl, Cs_2CO_3, DMF, 140°, 6 h	 (68)	95
		Pd(II)/NaY zeolite, LiCl, Cs_2CO_3, DMF, 140°, 6 h	 (52)	95
		$Pd(OAc)_2$, Et_3N, DMF/H_2O, 80°	 I R | Time (d) | $C(Me)_2OH$ | 7 | (35)[a] Bu | 4 | (47) $(CH_2)_3CO_2Me$ | 3 | (76)[a] Ph | 2 | (42)	78
		$[Pd(NH_3)_4]/NaY$, Et_3N, DMF/H_2O, 80°	I R | Time (d) | $C(Me)_2OH$ | 8 | (56) Bu | 1 | (52) $(CH_2)_3CO_2Me$ | 1 | (91)[a] Ph | 6 | (76)	78
		[Pd]/SBA-15, Et_3N, DMF/H_2O, 80°	I R | Time (d) | $C(Me)_2OH$ | 7 | (67) Bu | 1 | (48) $(CH_2)_3CO_2Me$ | 1 | (61) Ph | 6 | (65)	78
		$Pd(OAc)_2$, Bu_4NOAc, MeCN,)))), 90°	I R | Time (h) | $C(Me)_2OH$ | 6 | (44) Ph | 4 | (82) $4\text{-}MeC_6H_4$ | 5 | (71) $4\text{-}MeOC_6H_4$ | 6 | (72) 1-Np | 6 | (63)	84

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, Bu$_4$NOAc, MeCN, 90°	**I**	84

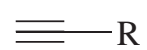
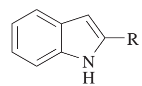
R	Time (h)	
C(Me)$_2$OH	24	(41)
Ph	24	(80)
4-MeC$_6$H$_4$	30	(69)
4-MeOC$_6$H$_4$	3	(76)
1-Np	24	(67)

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd/C, additive, NaOAc, NMP, 120°, 2 h	 **I** +  **II**	341

Additive	**I + II**	**I:II**
LiCl	(92)	89:11
—	(84)	77:23

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd/C, additive, NaOAc, NMP, 120°, 12 h		341

Additive	
LiCl	(69)
—	(70)

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd/C, NaOAc, NMP, 120°		341

R	Time (h)	
c-C$_6$H$_{11}$	24	(77)
4-MeOC$_6$H$_4$	24	(64)
3-MeC$_6$H$_4$	24	(72)
4-MeC$_6$H$_4$	24	(63)
1-Np	24	(52)
6-MeO-2-Np	5	(66)

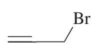
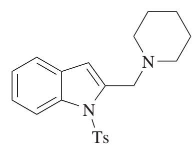
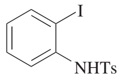
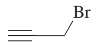
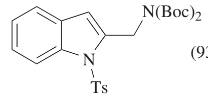
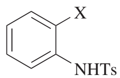
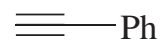
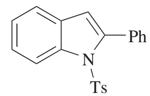
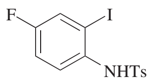
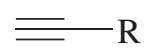
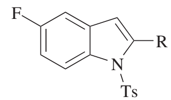
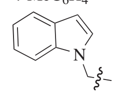
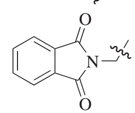
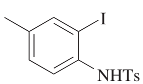
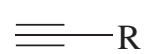
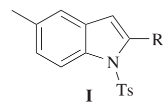
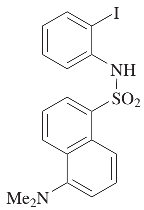
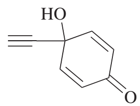
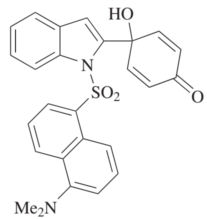
Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	PdCl$_2$(PPh$_3$)$_2$, CuI, piperidine, 50°	 (97)	82

TABLE 1B. 2-SUBSTITUTED INDOLES FROM 2-HALOANILIDES AND ALKYNES (*Continued*)

2-Haloanilide	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13} 		$PdCl_2(PPh_3)_2$, CuI, $KN(Boc)_2$, Et_3N, DMF, rt, 80°	 (93)	82
		$PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, rt, 12 h	 X — Br (68); I (70)	79
		Pd/C, CuI, PPh_3, 2-aminoethanol, H_2O, 80°	 R / Time (h) $HO(CH_2)_3$ 14 (80) $MeCH(OH)CH_2$ 12 (65) $HOCMe_2$ 10 (70) $Me(CH_2)_3$ 12 (74) Ph 8 (68) $4\text{-}MeC_6H_4$ 10 (78)  10 (76)  12 (70)	340
C_{14} 		$Pd(OAc)_2$, Bu_4NOAc, MeCN,)))), 90°	 **I** R / Time (h) Ph 5 (82) $3\text{-}FC_6H_4$ 6 (65) $4\text{-}MeC_6H_4$ 5 (90) $4\text{-}MeOC_6H_4$ 5 (90) 1-Np 6 (42)	84

	$\equiv$—R	$Pd(OAc)_2$, Bu_4NOAc, MeCN, 90°	**I**	R	Time (h)		
				Ph	30	(71)	84
				3-FC_6H_4	36	(56)	
				4-MeC_6H_4	35	(87)	
				4-$MeOC_6H_4$	36	(74)	
				1-Np	6	(46)	
C_{18} 		$Pd(PPh_3)_4$, CuI, $(i\text{-}Pr)_2NH$, DMA, H_2O, 100 W MW, 100°				(70)	81

[a] The reported yield was determined by GC.

TABLE 1C. 2-SUBSTITUTED INDOLES FROM 1,2-DIHALOARENES AND ALKYNES

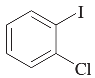
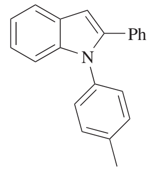
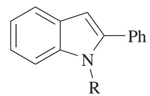
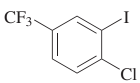
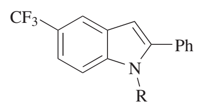
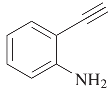
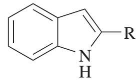
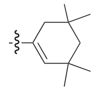
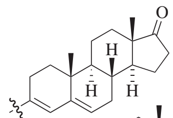
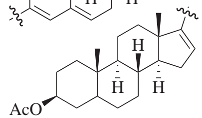
1,2-Dihaloarene	Alkyne	Conditions	Product(s) and Yield(s) (%)		Refs.
C_6					
	≡—Ph	1. $Pd(OAc)_2$, HIPrCl, CuI, Cs_2CO_3, toluene, 105°, 1 h 2. $4\text{-}MeC_6H_4NH_2$, 18 h	 (64)		86
	≡—Ph	1. $Pd(OAc)_2$, HIPrCl, CuI, Cs_2CO_3, toluene, 105°, 1 h 2. RNH_2, *t*-BuOK, 22 h		R	89
				Ph (52)	
				$2\text{-}FC_6H_4$ (61)	
				$4\text{-}FC_6H_4$ (54)	
				$3\text{-}MeC_6H_4$ (66)	
				$4\text{-}MeC_6H_4$ (65)	
				Bn (50)	
				$3,5\text{-}Me_2C_6H_3$ (67)	
				$n\text{-}C_8H_{17}$ (58)	
				$2,4,6\text{-}Me_3C_6H_2$ (58)	
C_7					
	≡—Ph	1. $Pd(OAc)_2$, HIPrCl, CuI, Cs_2CO_3, toluene, 105°, 1 h 2. RNH_2, *t*-BuOK, 22 h		R	87
				$2\text{-}FC_6H_4$ (74)	
				$4\text{-}FC_6H_4$ (79)	
				$4\text{-}MeC_6H_4$ (63)	
				$2\text{-}MeOC_6H_4$ (76)	
				$4\text{-}MeOC_6H_4$ (65)	
				$2,4,6\text{-}Me_3C_6H_2$ (68)	

TABLE 1D. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLANILINES

2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)	R	Time 1 (h)	Time 2 (h)	Yield (%)	Refs.
C_8 	1. ROTf, $Pd(PPh_3)_4$, CuI, Et_2NH, rt, time 1 2. $PdCl_2$, Bu_4NCl, CH_2Cl_2/0.5 N HCl, rt, time 2		1-cyclooctenyl	5.5	14	(62)	71
				5.5	40	(81)	
			4-phenyl-1-cyclohexenyl	5	14	(98)	
				5.5	14	(65)	
				6	48	(96)	

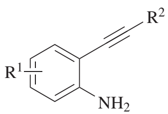
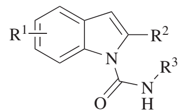
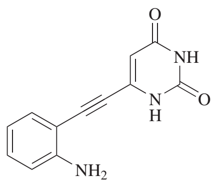
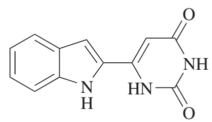
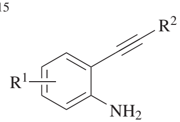
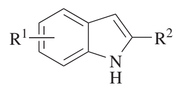
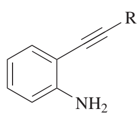
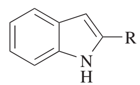
2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)	R^1	R^2	R^3	Yield (%)	Refs.
C_{11-15} 	R^3NCO, $PdCl_2$, THF, 80°		H	c-C_3H_5	Ph	(90)	342
			H	c-C_3H_5	4-FC_6H_4	(72)	
			H	c-C_3H_5	4-$MeOC_6H_4$	(88)	
			H	Ph	Ph	(87)	
			H	Ph	4-FC_6H_4	(75)	
			H	Ph	4-$MeOC_6H_4$	(86)	
			H	4-$MeOC_6H_4$	Ph	(53)	
			H	4-$MeOC_6H_4$	4-FC_6H_4	(65)	
			5-Me	Ph	Ph	(74)	
			5-Me	Ph	4-FC_6H_4	(72)	
			5-CF_3	Ph	Ph	(46)	
			5-CF_3	Ph	4-FC_6H_4	(60)	
			H	4-$MeOC_6H_4$	4-$MeOC_6H_4$	(73)	
			5-Me	Ph	4-$MeOC_6H_4$	(83)	
			5-CF_3	Ph	4-$MeOC_6H_4$	(43)	

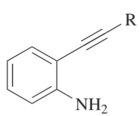
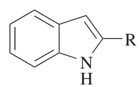
TABLE 1D. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLANILINES (*Continued*)

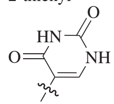
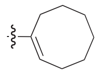
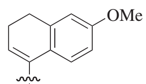
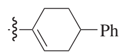
2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12} 	$PdCl_2$, DMF, 120°, 4.5 h	 (28)	74
C_{12-15} 	$PdCl_2$, $FeCl_3$, DCE, 80°		77

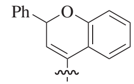
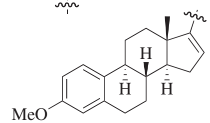
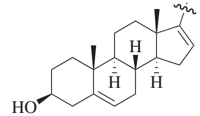
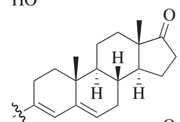
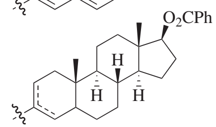
R^1	R^2	Time (h)	
H	2-thienyl	4	(50)
H	Ph	4	(88)
5-Cl	Ph	4	(83)
5-NO_2	Ph	4	(82)
H	4-$O_2NC_6H_4$	20	(40)
4-Me	Ph	4	(80)
H	4-$MeOC_6H_4$	20	(76)

2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-16} 	$PdCl_2$, MeCN, reflux		70

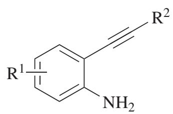
R	Time (h)	
Bu	1	(81)
t-Bu	0.5	(77)
Ph	0.5	(52)
$MeCH(CH_2)_5Me$	0.5	(83)

2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-34} 	$PdCl_2$, MeCN, reflux		74

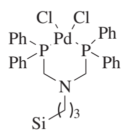
R	Time (h)	
2-thienyl	3	(82)
	4.5	(28)[a]
3-pyridyl	36	(38)
3-FC_6H_4	6	(51)
4-MeC_6H_4	3	(80)
4-$PhCOC_6H_4$	3	(39)
	9	(80)
2-Np	3.5	(76)
	3.5	(64)
	3	(87)

R	Time (h)	
	4	(60)
	4	(75)
	4	(74)
	4.5	(82)
	4.5	(77)

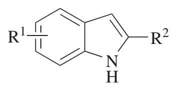
C_{14-16}



C1, DMF, 100°, 1 h



C1



R^1	R^2	
H	Ph	(96)
H	2-thienyl	(90)
6-Cl	3-thienyl	(89)
H	5-indolyl	(65)

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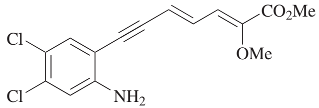
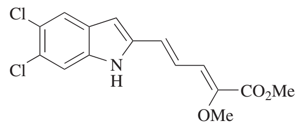
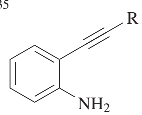
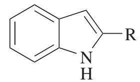
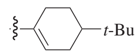
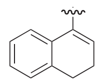
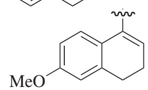
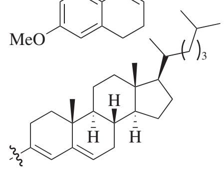
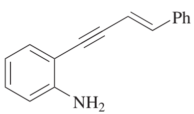
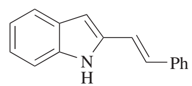
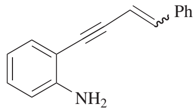
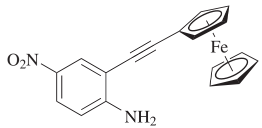
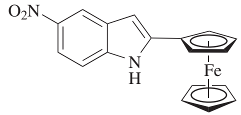
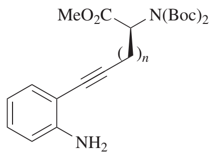
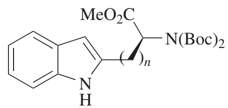
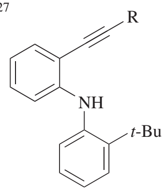
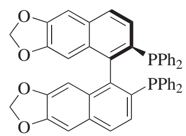
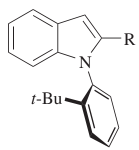
TABLE 1D. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLANILINES (*Continued*)

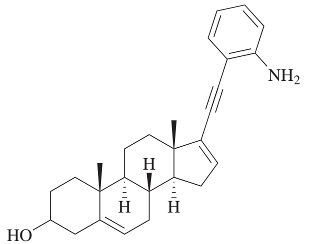
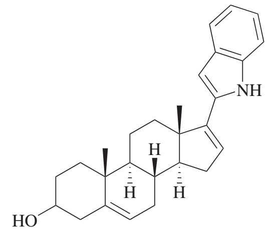
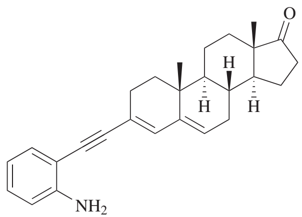
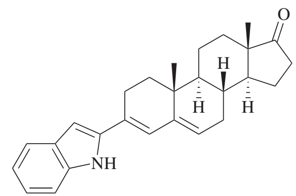
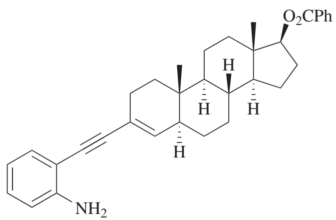
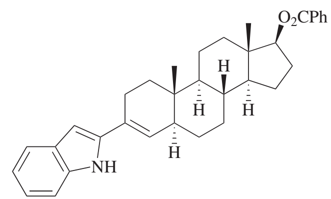
2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)				Refs.
C_{15} 	$PdCl_2(MeCN)_2$, DMF, 70°	 (90)				75
C_{15-35} 	$PdCl_2$, Bu_4NCl, CH_2Cl_2/HCl (*x* N), rt	 R	*x*	Time (h)		71
		4-MeC_6H_4	3	48	(82)	
		4-MeOC_6H_4	3	21	(68)	
		3-FC_6H_4	3	72	(45)	
		CH=CHPh	3	72	(57)	
			0.5	16	(97)	
			—	36	(92)	
			2	72	(70)	
			0.5	10	(89)	
C_{16} 	$PdCl_2(MeCN)_2$, DMF, 70°	 **I** (83)				75

	$PdCl_2$, MeCN, 70°, 2.5 h	**I** (74)[b]	74
C_{18} 	$PdCl_2$, Bu_4NBr, HCl/CH_2Cl_2, rt, 24 h	 (58)	76
C_{18-22} 	$PdCl_2(MeCN)_2$, MeCN, reflux		73, 344
C_{22-27} 	$PdCl_2$, **L1**, EtOH, 80°  **L1**		345

R	*n*	Time (h)	
H	2	0.5	(60)
H	3	0.5	(55)
Boc	1	3	(52)

R	Time (h)		% ee
Bu	24	(84)	35
Ph	4	(93)	60
2-BrC_6H_4	23	(90)	83
2-ClC_6H_4	13	(85)	83
2-$O_2NC_6H_4$	24	(67)	82
2-MeC_6H_4	9	(95)	67
4-MeC_6H_4	7	(89)	49
2-$MOMOCH_2C_6H_4$	7	(71)	77
2-*i*-PrC_6H_4	12	(90)	80

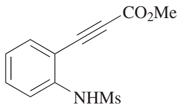
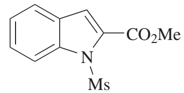
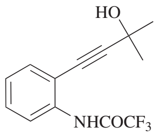
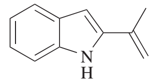
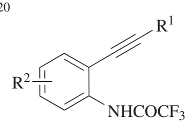
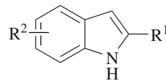
TABLE 1D. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLANILINES (*Continued*)

2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{27}			
	$PdCl_2$, MeCN, 70°, 4 h	 (64)	74
	$PdCl_2$, MeCN, 70°, 4.5 h	 (82)	74
C_{34}			
	$PdCl_2$, MeCN, 70°, 4.5 h	 (77)	74

[a] The reaction was carried out at 120° in DMF.

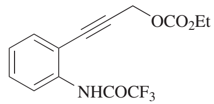
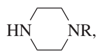
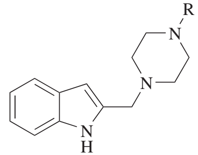
[b] A commercially available (*E*)/(*Z*) mixture was used but the (*E*)-isomer was found to react preferentially.

TABLE 1E. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES

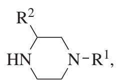
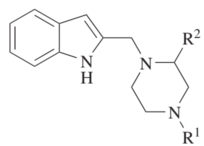
2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11} 	$\equiv$—CO_2Me, $Pd(PPh_3)_4$, $ZnBr_2$, *i*-Pr_2NEt, THF, reflux	 (94)	346
C_{13} 	$Pd(OAc)_2$, LiCl, K_2CO_3, DMF, 100°, 16 h	 (95)	72
C_{13-20} 	$PdCl_2(MeCN)_2$, MeCN, 60°		49

R^1	R^2	Time (h)		R^1	R^2	Time (h)	
Pr	5-Cl	2.75	(76)	Bu	6-OMe	1.5	(66)
i-Pr	5-Cl	1.5	(80)	Ph	6-Cl	4	(48)
Bu	5-Cl	2	(83)	Bu	6-CO_2Me	1.75	(71)
i-Pr	5-OTf	3	(40)	Ph	5-OTf	3.5	(53)
Pr	5-Me	1	(81)	Ph	5-Me	1.25	(80)
Pr	6-OMe	0.5	(75)	Ph	6-OMe	3	(35)
i-Pr	6-OMe	1	(78)	Ph	6-CO_2Me	1.5	(76)
i-Pr	6-CO_2Me	1.5	(82)	$(CH_2)_2OTBS$	5-Me	1.5	(37)
Bu	5-OTf	2.5	(65)	$(CH_2)_2OTBS$	5-Me	2.5	(35)
Bu	5-Me	0.5	(77)	$(CH_2)_4C{\equiv}CTMS$	5-Me	3.5	(53)

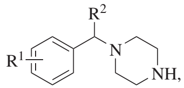
TABLE 1E. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14} 	 $Pd(PPh_3)_4$, THF, 80°		34

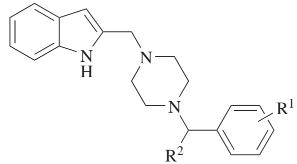
R	Time (h)	
Et	1.5	(91)
CO_2Et	20	(88)
$2\text{-}FC_6H_4$	2.5	(97)
$4\text{-}FC_6H_4$	6	(96)
$3,4\text{-}Cl_2C_6H_3$	2	(96)
$2\text{-}NCC_6H_4$	3	(98
$2\text{-}FC_6H_4CH_2$	6	(98)
$4\text{-}ClC_6H_4CH_2$	3	(92)
$4\text{-}BrC_6H_4CH_2$	3	(94)
$3,4\text{-}Cl_2C_6H_3CH_2$	24	(80)
$2\text{-}Cl\text{-}6\text{-}FC_6H_3CH_2$	12	(78)
$4\text{-}MeC_6H_4CH_2$	4	(85)
$4\text{-}MeOC_6H_4CH_2$	4	(81)
$2,4,6\text{-}Me_3C_6H_2CH_2$	3	(80)
$4\text{-}ClC_6H_4CH(Ph)$	8	(92)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
	 $Pd(PPh_3)_4$, THF, 80°		

R^1	R^2	Time (h)		Refs.
Et	H	1.5	(91)	347
EtO_2C	H	20	(88)	347
$3,4\text{-}Cl_2C_6H_3$	H	2	(96)	347
$4\text{-}FC_6H_4$	H	6	(96)	347
$2\text{-}FC_6H_4$	H	2.5	(97)	347
$2\text{-}NCC_6H_4$	H	3	(98)	347
Me	Ph	6	(58)	347, 34

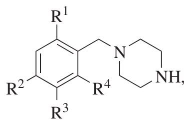


Pd(PPh_3)$_4$, THF, 80°

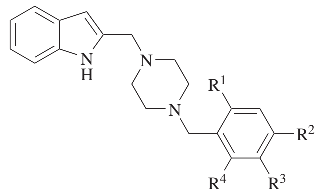


R^1	R^2	Time (h)	
4-MeO	H	4	(81)
2-FC_6H_4	H	6	(98)
4-ClC_6H_4	H	3	(92)
4-BrC_6H_4	H	3	(94)
4-MeC_6H_4	H	4	(85)
4-ClC_6H_4	Ph	8	(92)

347



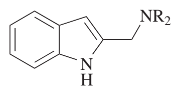
Pd(PPh_3)$_4$, THF, 80°



R^1	R^2	R^3	R^4	Time (h)	
H	Cl	Cl	H	24	(80)
Cl	H	H	F	12	(78)
Me	Me	H	Me	4	(80)

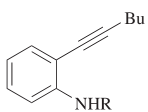
347

R_2NH, Pd(PPh_3)$_4$, THF, 80°

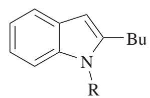


R_2NH	Time (h)	
Et	2	(60)
i-Pr	4	(45)
morpholine	1	(98)
piperidine	1	(94)

34



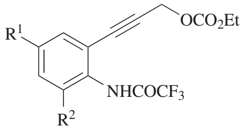
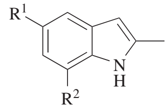
$PdCl_2$, MeCN, reflux



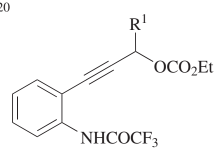
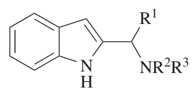
R	Time (h)	
Ac	4	(74)
CO_2Me	2	(78)

70

TABLE 1E. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

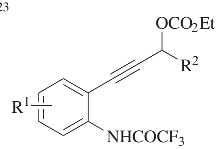
2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14-16} 	HCO_2H, Et_3N, MeCN, 80°		347

R^1	R^2	Time (h)	
H	H	1	(91)
Cl	H	0.5	(60)
Me	H	0.5	(80)
Me	O_2N	2	(78)
Me	Cl	2	(51)
F	Me	1	(65)
Cl	CF_3	1	(86)
Me	Me	1	(99)
MeCO	H	0.66	(73)
MeO_2C	H	1	(70)

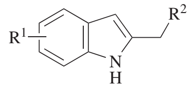
2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14-20} 	HNR^2R^3, $Pd(PPh_3)_4$, THF, 80°		347

R^1	HNR^2R^3	Time (h)	
H	morpholine	1	(98)
H	Et_2NH	2	(60)
H	piperidine	1	(94)
H	$(i\text{-}Pr)_2NH$	4	(45)
Ph	morpholine	1	(98)
Ph	Et_2NH	2	(60)
Ph	$BuNH_2$	5	(80)
Ph	piperidine	1	(94)
Ph	1-ethylpiperazine	1	(92)
Ph	$(i\text{-}Pr)_2NH$	4	(45)
Ph	1-ethylpiperazine	2	(90)
Ph	$BnNH_2$	4	(54)

C_{14-23}



$Pd(PPh_3)_4$, HCO_2H, Et_3N, MeCN, 80°

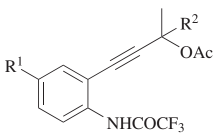


R^1	R^2	Time (h)	
H	H	1	(91)
4-Cl	H	0.5	(60)
H	Me	1	(70)
4-Me	H	0.5	(80)
4-Me-6-Cl	H	2	(51)
4-F-6-Me	H	1	(86)
4-Me-6-O_2N	H	2	(78)
4-Cl-6-CF_3	H	1	(86)
H	Et	2	(70)
4,6-Me_2	H	1	(99)

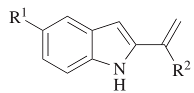
R^1	R^2	Time (h)	
4-MeCO	H	0.66	(73)
4-MeO_2C	H	1	(70)
H	Pr	1	(67)
H	Ph	3	(75)
H	4-FC_6H_4	1	(85)
H	3-$MeOC_6H_4$	1	(75)
4,6-Me_2	Ph	1	(50)
4-Cl-6-CF_3	3-$MeOC_6H_4$	0.5	(95)
4,6-Me_2	3-$MeOC_6H_4$	2	(72)

43

C_{15-20}



$Pd(OAc)_2$, PPh_3, Et_3N, THF, 80°



R^1	R^2	Time (h)	
H	Me	1	(80)
Cl	Me	2	(85)
NC	Me	1	(83)
Me	Me	3	(84)
MeCO	Me	1	(91)
MeO_2C	Me	2	(87)
H	Ph	6	(78)
F	Ph	1	(68)

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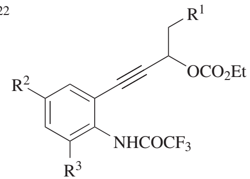
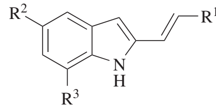
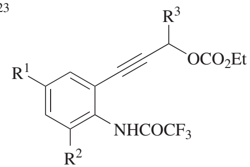
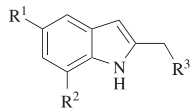
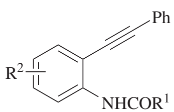
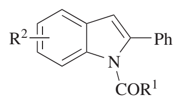
TABLE 1E. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15-22} 	$Pd(OAc)_2$, PPh_3, Et_3N, THF, 80°		347
C_{15-23} 	HCO_2H, Et_3N, MeCN, 80°		347
C_{16-21} 	$PdCl_2$, MeCN, 81°		23

C_{15-22} products (ref. 347):

R^1	R^2	R^3	Time (h)	
H	H	H	0.5	(90)
H	F	F	2	(82)
H	Me	H	2	(63)
Me	H	H	1	(95)
H	Me	Me	1	(87)
Et	H	H	1	(83)
Ph	Me	H	0.5	(85)

C_{15-23} products (ref. 347):

R^1	R^2	R^3	Time (h)	
H	H	Me	1	(70)
H	H	Et	2	(70)
H	H	Pr	1	(67)
H	H	Ph	3	(75)
H	H	4-FC_6H_4	1	(85)
H	H	3-$MeOC_6H_4$	1	(75)
H	H	4-$MeOC_6H_4$	1	(70)
H	H	Bn	1	(50)
Cl	CF_3	3-$MeOC_6H_4$	0.5	(85)
Me	Me	4-$MeOC_6H_4$	2	(72)

C_{16-21} products (ref. 23):

R^1	R^2	
Me	6-Cl	(67)
Me	5-Me	(80)
Me	6-Me	(95)
Me	5,6-Me_2	(90)
Ph	H	(78)

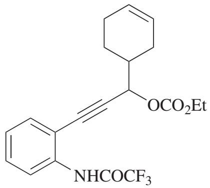
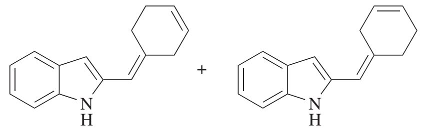
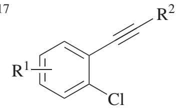
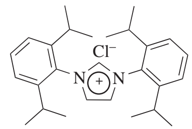
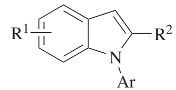
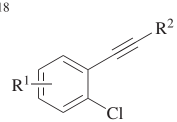
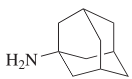
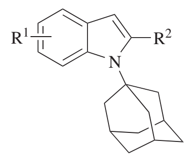
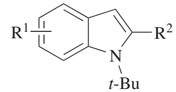
C_{20}		$Pd(OAc)_2$, PPh_3, Et_3N, THF, 80°, 1 h	 **I** + **II**	**I** + **II** (76), **I**:**II** = 1:1	347

TABLE 1F. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLHALOARENES

2-Alkynylhaloarene	Amine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11-17} 	$ArNH_2$	$Pd(OAc)_2$, **L2**, *t*-BuOK, toluene, 14 h  **L2**		348
C_{11-18} 		$Pd(OAc)_2$, **L2**,[a] *t*-BuOK, toluene, 14 h		348

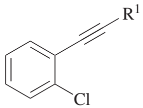
Ar	R^1	R^2	Temp (°)	
2,4,6-$Me_3C_6H_2$	H	*c*-C_3H_5	105	(85)
2,6-(*i*-$Pr)_2C_6H_3$	H	*c*-C_3H_5	105	(82)
2,4,6-$Me_3C_6H_2$	H	Ph	120	(91)
2,6-(*i*-$Pr)_2C_6H_3$	H	Ph	120	(94)
2,4,6-$Me_3C_6H_2$	5-OH	Ph	120	(75)
2,6-(*i*-$Pr)_2C_6H_3$	5-OH	Ph	120	(71)
2,4,6-$Me_3C_6H_2$	H	3-MeC_6H_4	120	(91)
2,4,6-$Me_3C_6H_2$	6-Me	Ph	120	(56)
2,6-(*i*-$Pr)_2C_6H_3$	6-Me	Ph	120	(91)
2,4,6-$Me_3C_6H_2$	H	4-PrC_6H_4	120	(95)
2,6-(*i*-$Pr)_2C_6H_3$	H	4-PrC_6H_4	120	(88)

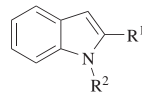
R^1	R^2	Temp (°)	
H	*c*-C_3H_5	105	(80)
H	*n*-C_6H_{13}	105	(59)
H	Ph	120	(83)
H	4-FC_6H_4	120	(94)
H	4-$MeOC_6H_4$	120	(79)
H	4-$CF_3C_6H_4$	120	(83)
6-Me	Ph	120	(94)
H	4-PrC_6H_4	120	(88)
5-MeO	4-PrC_6H_4	120	(55)

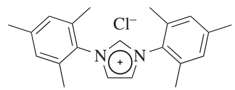
Reactant	Amine	Conditions	Product(s) and Yield(s) (%)	Refs.
	t-$BuNH_2$	$Pd(OAc)_2$, **L2**,[a] t-BuOK, toluene		348

R^1	R^2	Temp (°)	
H	c-C_3H_5	120	(87)
H	Bu	120	(63)
H	Ph	120	(55)
6-Me	Ph	105	(90)
H	4-PrC_6H_4	105	(84)
5-MeO	4-PrC_6H_4	105	(65)

C_{11-19}



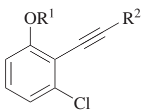
Amine	Conditions	Product	Refs.
R^2NH_2	1. Cp_2TiMe_2, toluene, 110°, 24 h 2. $Pd_2(dba)_3$, **L3**, t-BuOK, 1,4-dioxane, 110°, 12 h		195

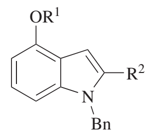


L3

R^1	R^2	
Pr	CHMePh	(65)
c-C_3H_5	4-MeC_6H_4	(77)
Bu	4-$MeOC_6H_4$	(78)
1-cyclohexenyl	t-Bu	(39)
$CH_2(CH_2)_3OBn$	t-Bu	(70)

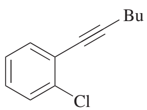
C_{11-21}

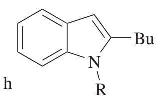


Amine	Conditions	Product	Refs.
$BnNH_2$	$Pd(OAc)_2$, HIPrCl, t-BuOK, toluene, reflux		88

R^1	R^2	
Me	Et	(70)
Me	Pr	(57)
Me	Bu	(79)
Me	Ph	(84)
Bn	Bu	(75)
Bn	Ph	(89)

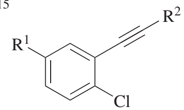
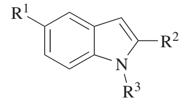
C_{12}



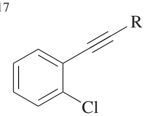
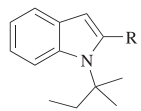
Amine	Conditions	Product	Refs.
RNH_2	$Pd(OAc)_2$, $(t\text{-}Bu)_3P$, t-BuOK, toluene, 110°, 14 h		87

R	
Ph	(23)
Bn	(85)
n-C_8H_{17}	(90)

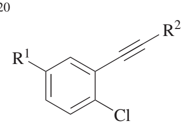
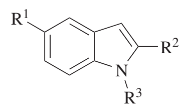
TABLE 1F. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLHALOARENES (*Continued*)

2-Alkynylhaloarene	Amine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-15} 	R^3NH_2	$Pd(OAc)_2$, HIPrCl, base, toluene, 105°, 2 h		86

R^1	R^2	R^3	Base	
H	*t*-Bu	2-MeC_6H_4	*t*-BuOK	(83)
H	*t*-Bu	Bn	*t*-BuOK	(74)
H	Ph	*n*-C_6H_{13}	*t*-BuOK	(93)
H	Ph	*n*-C_8H_{17}	*t*-BuOK	(93)
H	Ph	2-MeC_6H_4	*t*-BuOK	(99)
H	Ph	$PhCH_2$	*t*-BuOK	(92)
H	Ph	4-$MeOC_6H_4CH_2$	*t*-BuOK	(78)
H	Ph	2,4,6-$Me_3C_6H_2$	*t*-BuOK	(99)
CF_3	*n*-C_6H_{13}	$PhCH_2$	*t*-BuOK	(66)
CF_3	*n*-C_6H_{13}	4-$EtO_2CC_6H_4$	K_2CO_3/CuI[b]	(67)
CF_3	Ph	4-MeC_6H_4	K_2CO_3/CuI[b]	(95)
CF_3	Ph	4-$EtO_2CC_6H_4$	K_2CO_3/CuI[b]	(92)

2-Alkynylhaloarene	Amine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-17} 		$Pd(OAc)_2$, **L2**,[a] *t*-BuOK, toluene, 120°		348

R	
Bu	(43)
4-$CF_3C_6H_4$	(80)
3-MeC_6H_4	(85)
4-PrC_6H_4	(92)

2-Alkynylhaloarene	Amine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-20} 	R^3NH_2	1. Cp_2TiMe_2, toluene, 110°, 24 h 2. $Pd_2(dba)_3$, **L3**,[c] *t*-BuOK, 1,4-dioxane, 110°, 12 h		195

R^1	R^2	R^3	
OMe	Pr	*t*-Bu	(65)
CF_3	*c*-C_3H_5	4-MeC_6H_4	(77)
OMe	$CH_2(CH_2)_3OBn$	4-$MeOC_6H_4$	(78)

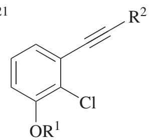
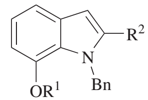
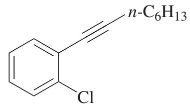
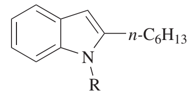
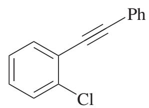
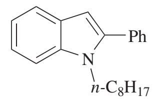
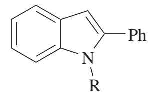
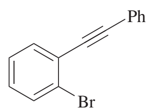
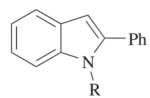
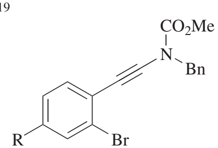
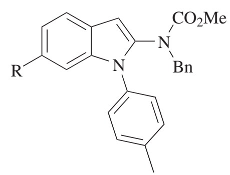
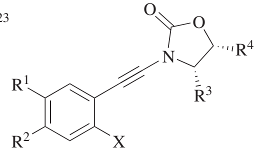
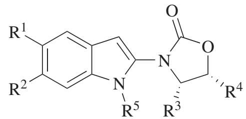
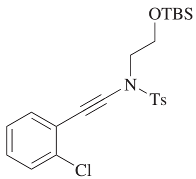
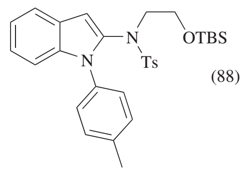
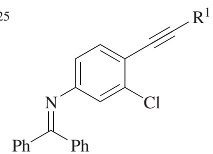
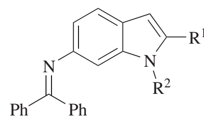
C_{13-21} 	$BnNH_2$	$Pd(OAc)_2$, HIPrCl, *t*-BuOK, toluene, reflux		R^1 R^2 Me Bu (74) Me Ph (63) Bn Bu (64) Bn Ph (70)	88
C_{14} 	RNH_2	$Pd(OAc)_2$, $(t\text{-Bu})_3P$, *t*-BuOK, toluene, 110–112°, 14 h		R Bn (85) n-C_8H_{17} (74)	87
	n-$C_8H_{17}NH_2$	$Pd(OAc)_2$, $(t\text{-Bu})_3P$, *t*-BuOK, toluene, 110°, 14 h		(99)	87
	RNH_2	$Pd(OAc)_2$, $(t\text{-Bu})_3P$, K_3PO_4, DMA, 130°, 14 h		R Ph (99) Bn (95) 4-$MeOC_6H_4$ (95)	87
	RNH_2	$Pd(OAc)_2$, $(t\text{-Bu})_3P$, *t*-BuOK, toluene, 110°, 14 h		R Ph (95) Bn (95)	87
C_{17-19} 	4-$MeC_6H_4NH_2$	$Pd_2(dba)_3$, XPhos, Cs_2CO_3, 1,4-dioxane, 110°, 8–24 h		R H (82) MeO_2C (75)	349

TABLE 1F. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLHALOARENES (*Continued*)

2-Alkynylhaloarene	Amine	Conditions	Product(s) and Yield(s) (%)	Refs.
$C_{17–23}$ 	R^5NH_2	$Pd_2(dba)_3$, XPhos, Cs_2CO_3, 110°, 8–24 h		349

X	R^1	R^2	R^3	R^4	R^5	Solvent	
Br	H	H	Ph	H	4-MeC_6H_4	1,4-dioxane	(91)
Br	H	H	Ph	H	2-MeC_6H_4	1,4-dioxane	(82)
Cl	O_2N	H	Ph	H	4-MeC_6H_4	toluene	(64)
Cl	H	H	Bn	H	4-$MeOC_6H_4$	1,4-dioxane	(91)
Br	Me	H	Ph	H	4-MeC_6H_4	toluene	(65)
Br	H	MeO_2C	Ph	H	*c*-C_6H_{11}	1,4-dioxane	(80)
Br	MeO	MeO	Ph	H	4-MeC_6H_4	toluene	(60)
Cl	MeO_2C	H	Ph	H	Bn	1,4-dioxane	(72)
Br	H	H	Ph	Ph	Bn	toluene	(71)

2-Alkynylhaloarene	Amine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{23} 	4-$MeC_6H_4NH_2$	$Pd_2(dba)_3$, XPhos, Cs_2CO_3, 1,4-dioxane, 110°, 8–24 h	 (88)	349
$C_{24–25}$ 	R^2NH_2	1. Cp_2TiMe_2, toluene, 110°, 24 h 2. $Pd_2(dba)_3$, **L3**,[c] *t*-BuOK, 1,4-dioxane, 110°, 12 h		195

R^1	R^2	
c-C_3H_5	4-MeC_6H_4	(75)
Bu	4-$MeOC_6H_4$	(64)

[a] The structure of ligand **2** is shown in the first entry of the first page of Table 1F.

[b] The reaction time was 5–18 hours.

[c] The structure of ligand **3** is shown in the second entry of the second page of Table 1F.

TABLE 1G. 2-SUBSTITUTED INDOLES FROM 2-HALO-*N*-ALKYNYLANILIDES

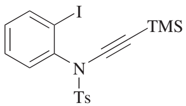
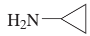
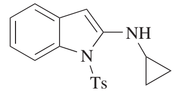
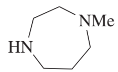
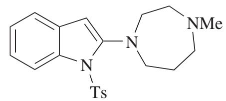
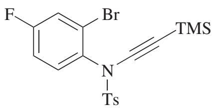
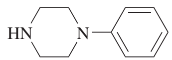
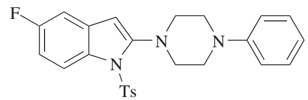
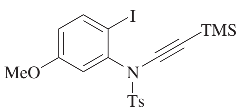
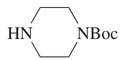
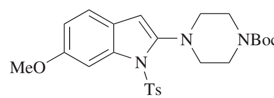
2-Halo-*N*-alkynylanilide	Amine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18}				
		1. $PdCl_2(PPh_3)_2$, K_2CO_3, THF, 80° 2. Bu_4NF, THF	 (66)	29
		1. $PdCl_2(PPh_3)_2$, K_2CO_3, THF, 80° 2. Bu_4NF, THF	 (75)	29
		1. $PdCl_2(PPh_3)_2$, K_2CO_3, THF, 80° 2. Bu_4NF, THF	 (99)	29
C_{19}				
		1. $PdCl_2(PPh_3)_2$, K_2CO_3, THF, 80° 2. Bu_4NF, THF	 (89)	29

TABLE 1H. 2-SUBSTITUTED INDOLES FROM 2-ALKYNYLISOCYANATOBENZENES

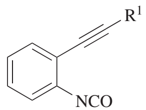
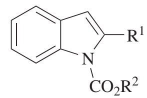
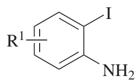
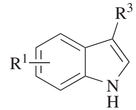
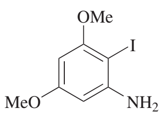
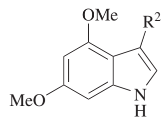
2-Alkynylisocyanatobenzene	Conditions	Product(s) and Yield(s) (%)					Refs.
C_{12-16}							
	Na_2PdCl_4, DCE, 100°, R^2OH		R^1	R^2	Time (h)		28
			Pr	Me	1.5	(69)	
			Pr	Pr	1.5	(74)	
			Pr	*i*-Pr	2	(67)	
			Pr	Bu	3	(64)	
			Pr	Bu	24	(56)	
			Pr	$CH_2{=}CHCH_2$	4	(85)	
			t-Bu	Pr	2	(89)	
			c-C_5H_9	Pr	1.5	(83)	
			Ph	Pr	1.5	(59)	
			4-$MeOC_6H_4$	Pr	1.5	(58)	
			4-$CF_3C_6H_4$	Pr	1.5	(55)	

TABLE 2A. 3-SUBSTITUTED INDOLES FROM 2-HALOANILINES AND ALKYNES

2-Haloaniline	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 	TES—≡—R^2	1. Catalyst, base, DMF, 120° 2. HCl (2 M) or Bu_4NF (1 M in THF)		350

R^1	R^2	R^3	Catalyst	Base	Time (h)	
H	$(CH_2)_2OTES$	$(CH_2)_2OH$	$Pd_{(ALD)}$[a]	K_2CO_3	14	(48)
H	$(CH_2)_2OTES$	$(CH_2)_2OH$	$Pd_{(ALD)}$[a]	Na_2CO_3	14	(62)
H	$(CH_2)_2OTES$	$(CH_2)_2OH$	Pd/NaY	Na_2CO_3	14	(98)
5-O_2N	$(CH_2)_2OTES$	$(CH_2)_2OH$	$Pd_{(ALD)}$[a]	Na_2CO_3	216	(60)
5-O_2N	$(CH_2)_2OTES$	$(CH_2)_2OH$	Pd/NaY	Na_2CO_3	144	(70)
H	Ph	Ph	$Pd_{(ALD)}$[a]	Na_2CO_3	24	(80)
H	Ph	Ph	Pd/NaY	Na_2CO_3	24	(70)
5-O_2N	Ph	Ph	$Pd_{(ALD)}$[a]	Na_2CO_3	288	(42)
5-O_2N	Ph	Ph	Pd/NaY	Na_2CO_3	84	(80)

2-Haloaniline	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8 	TES—≡—R^1	1. Catalyst, K_2CO_3, DMF, 120°, 14 h 2. HCl (2 M) or Bu_4NF (1 M in THF)		350

R^1	R^2	Catalyst	
Ph	Ph	$Pd_{(ALD)}$[a]	(83)
Ph	Ph	Pd/NaY	(88)
$(CH_2)_2OTES$	$(CH_2)_2OH$	$Pd_{(ALD)}$[a]	(70)
$(CH_2)_2OTES$	$(CH_2)_2OH$	Pd/NaY	(81)

[a] $Pd_{(ALD)}$ is palladium supported on activated carbon purchased from Aldrich.

TABLE 2B. 3-SUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES

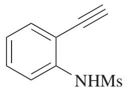
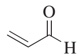
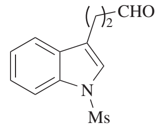
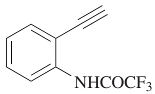
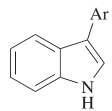
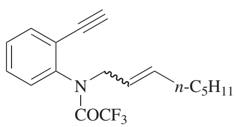
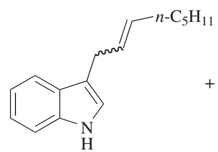
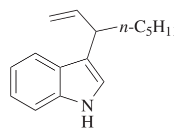
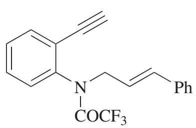
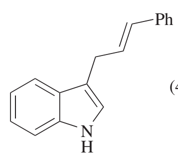
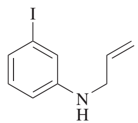
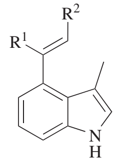
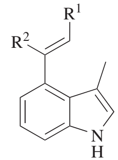
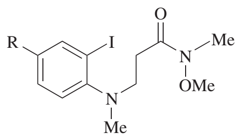
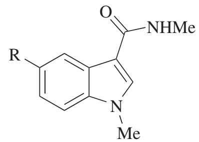
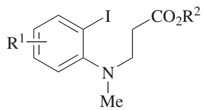
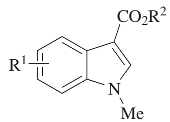
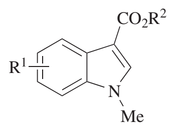
2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)			Refs.
C_9 	 , $Pd(OAc)_2$, LiBr, THF, rt, 3 d		(27)		103
C_{10} 	ArI, $Pd_2(dba)_3$, K_2CO_3, DMSO, 40°		**Ar**	**Time (h)**	100
			Ph	1.5 (67)	
			$3\text{-}FC_6H_4$	1.5 (57)	
			$4\text{-}ClC_6H_4$	1.25 (71)	
			$3\text{-}O_2NC_6H_4$	2 (86)	
			$4\text{-}MeC_6H_4$	2 (63)	
			$3\text{-}CF_3C_6H_4$	2 (82)	
			$4\text{-}MeOC_6H_4$	1.75 (56)	
			$3\text{-}O_2N\text{-}4\text{-}Me\text{-}C_6H_3$	1 (69)	
			$4\text{-}MeCONHC_6H_4$	4 (62)	
			$4\text{-}EtO_2CC_6H_4$	8 (69)	
			$3\text{-}EtO_2CC_6H_4$	1.15 (78)	
C_{18}  (*E*):(*Z*) = 90:10	$Pd(PPh_3)_4$, K_2CO_3, MeCN, 90°, 24 h	 **I** (*E*):(*Z*) = 89:11 +  **II**	**I** + **II** (38), **I**:**II** = 92:8		102
C_{19} 	$Pd(PPh_3)_4$, K_2CO_3, MeCN, 90°, 24 h		(49)		102

TABLE 2C. 3-SUBSTITUTED INDOLES FROM 3-IODO-*N*-ALLYLANILINE AND INTERNAL ALKYNES

3-Iodo-*N*-allylaniline	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 	$R^1C\equiv CR^2$	$Pd(OAc)_2$, dppm, CsO_2CCMe_3, DMF, 100°, 3 h	 **I** +  **II**	

R^1	R^2	**I + II**	**I:II**	Refs.
Me	Ph	(26)	15:1	104
Et	Ph	(45)	10:1	
Ph	Ph	(31)	—	

TABLE 2D. 3-SUBSTITUTED INDOLES FROM 2-HALO-*N*-ALKYLANILINES

2-Halo-*N*-alkylaniline	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-13}			
	$Pd(PPh_3)_4$, phenol, *t*-BuOK, THF, reflux		351, 352
C_{12-19}			
	$Pd(PPh_3)_4$, *t*-BuOK, THF, reflux		351, 352
	$Pd(PPh_3)_4$, K_3PO_4, DMF, 90°		351, 352

Product yields for $Pd(PPh_3)_4$, phenol, *t*-BuOK, THF, reflux:

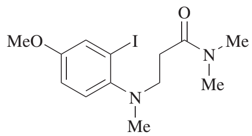
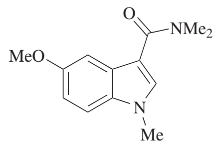
R	Time (h)	
H	8	(58)
Cl	18	(78)
Me	8	(59)

Product yields for $Pd(PPh_3)_4$, *t*-BuOK, THF, reflux:

R^1	R^2	Time (h)	[a]
H	Me	8	(20)
5-Cl	Me	24	(6)
5-F	Me	20	(70)
6-F	Me	24	(20)
6-Cl	Me	24	(20)
6-Me	Me	8	(23)
5-MeO	Me	8	(46)
5-MeO_2C	Me	16	(24)
5-Me	Bn	8	(7)

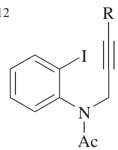
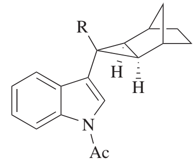
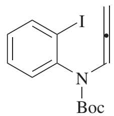
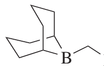
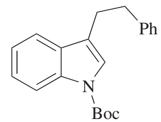
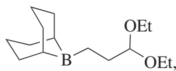
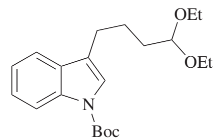
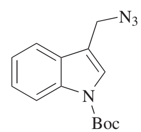
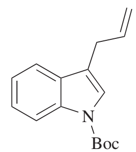
Product yields for $Pd(PPh_3)_4$, K_3PO_4, DMF, 90°:

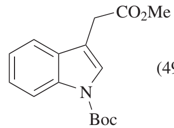
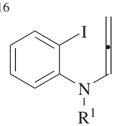
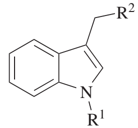
R^1	R^2	Time (h)	[a]
H	Me	24	(51)
5-Cl	Me	24	(32)
5-F	Me	24	(60)
6-F	Me	24	(7)
6-Cl	Me	24	(30)
6-Me	Me	24	(42)
5-MeO	Me	48	(67)
5-MeO_2C	Me	36	(29)
5-Me	Bn	48	(36)

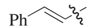
C_{13}				
	$Pd(PPh_3)_4$, phenol, *t*-BuOK, THF, reflux, 18 h	 (58)		351, 352

[a] The corresponding indolines were isolated in variable amounts.

TABLE 2E. 3-SUBSTITUTED INDOLES FROM 2-IODO-*N*-PROPARGYLANILIDES AND *N*-2-(HALOPHENYL)ALLENAMIDES

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11-12} 	Norbornene, $Pd(OAc)_2$, PPh_3, K_2CO_3, Et_4NCl, MeCN, rt, 18 h	 R: H (40); Me (45)	32
C_{14} 	 Ph, $Pd_2(dba)_3$, aq Cs_2CO_3 (3 M), EtOH, 80°	 (64)	353
	 $PdCl_2(dppf)$, aq Cs_2CO_3 (3 M), DMF, 50°	 (66)	353
	NaN_3, $Pd(PPh_3)$, DMF, rt	 (97)	353
	 $SnBu_3$, $Pd_2(dba)_3$, DMF, 80°	 (96)	353

	CO (1 atm), $PdCl_2$(dppf), Et_3N, MeOH/DMF, 60°	 (49)	353
C_{14-16} 	$(HO)_2BR^2$, $Pd_2(dba)_3$, aq Cs_2CO_3 (3 M), EtOH, 80°		353

R^1	R^2	
Boc	4-$MeOC_6H_4$	(90)
Boc	2-thienyl	(58)
Ts	Ph	(88)
Ts	4-ClC_6H_4	(71)
Ts		(73)

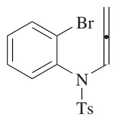
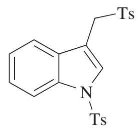
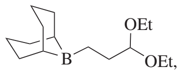
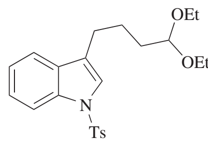
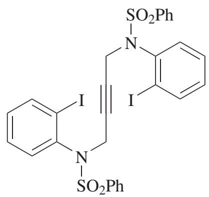
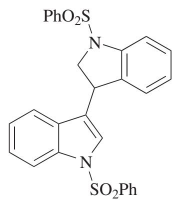
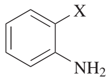
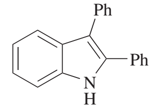
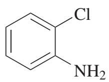
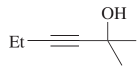
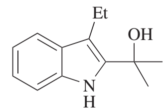
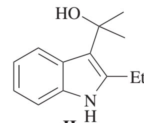
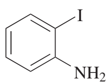
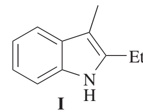
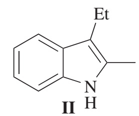
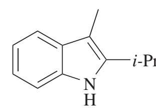
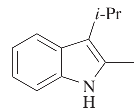
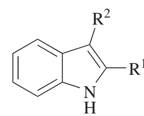
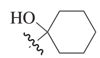
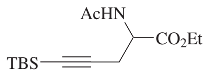
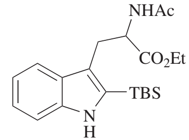
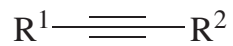
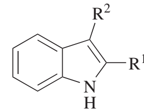
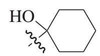
C_{16} 	NaTs, $Pd(PPh_3)_4$, DMF, 70°	 (83)	353
	 $PdCl_2$(dppf), aq Cs_2CO_3 (3 M), DMF	 (82)	353
C_{28} 	$Pd(OAc)_2$, PPh_3, $(Me_3Sn)_2$, anisole, 100°, 16 h	 (48)	101

TABLE 3A. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILINES, 2-IODOBENZOIC ACIDS, OR ANILINES AND ALKYNES

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 	Ph—≡—Ph	$Pd(OAc)_2$, PCy_3, K_2CO_3, NMP	 X: Br (99); Cl (97)	122
		$Pd(OAc)_2$, dtbpf, K_2CO_3, NMP	 I +  II **I** + **II** (60), **I**:**II** = >99:1	122
	Et—≡—	$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, DMF, 100°, 24 h	 I +  II **I** + **II** (62), **I**:**II** = 60:40	30, 31
	i-Pr—≡—	$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, DMF, 100°, 24 h	 (62) +  (25)	30, 31
	R^1—≡—R^2	$Pd(OAc)_2$, LiCl, base, DMF, 100°	 R^1 / R^2 / Base / Time (h) Pr / Pr / K_2CO_3 / 20 / (80)  / Et / KOAc / 24 / (85)	30, 31

	$Pd(OAc)_2$, Bu_4NCl, KOAc, DMF, 90–100°, 22 h	 (38)	115
	$Pd(OAc)_2$, phosphine, Bu_4NCl, base, DMF, 100°		30, 31

R^1	R^2	Phosphine	Base	Time (h)	
CMe_2OH	Me	PPh_3	Na_2CO_3	12	(52)
TMS	Me	PPh_3	Na_2CO_3	24	(98)
TMS	CH_2OH	PPh_3	Na_2CO_3	24	(60)
t-Bu	Me	PPh_3	Na_2CO_3	24	(82)
CMe_2OH	CMe_2OH	PPh_3	Na_2CO_3	72	(54)
TMS	TMS	—	NaOAc	20	(54)
TMS	Bu	—	NaOAc	12	(81)
c-C_6H_{11}	Me	—	KOAc	20	(54)
TMS	Ph	—	NaOAc	16	(68)
	$MeC{=}CH_2$	—	KOAc	24	(70)

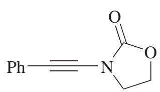
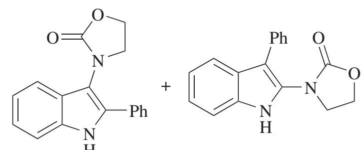
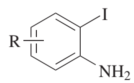
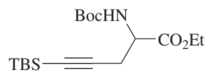
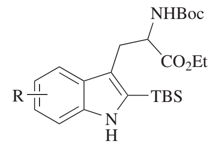
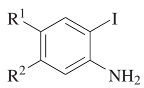
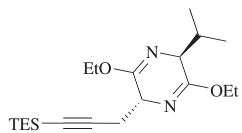
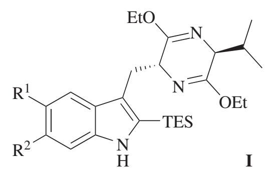
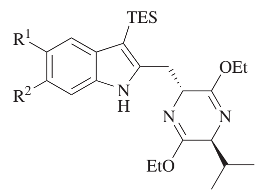
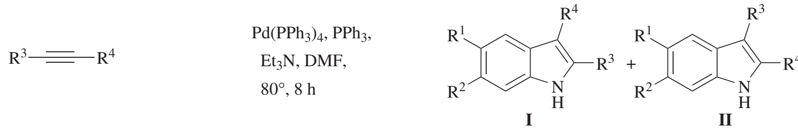
	$Pd(OAc)_2$, *t*-Bu_3P•HBF_4, K_2CO_3, DMF, 100°, 21 h	 **I** **II** **I** + **II** (65), **I**:**II** = 4:1	354

TABLE 3A. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILINES, 2-IODOBENZOIC ACIDS, OR ANILINES AND ALKYNES (*Continued*)

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6				
		$Pd(OAc)_2$, Bu_4NCl, Et_3N, DMF, 90–100°		115
C_{6-7}				
		$Pd(OAc)_2$, LiCl, Na_2CO_3, DMF, 100°	 **I** +  **II**	112, 117

R	Time (h)	
H	23	(62)
5-NO_2	24	(53)
5-Cl	20	(48)
5-F	22	(47)
6-NO_2	24	(46)

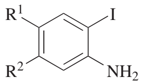
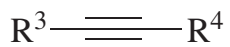
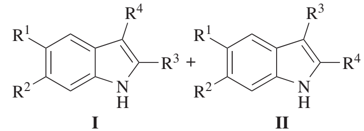
R^1	R^2	**I**	**II**
NO_2	H	(83)	(4)
F	H	(62)	(—)
Cl	Cl	(80)	(—)
OMe	H	(65)	(<5)
H	OMe	(77)	(<5)



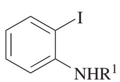
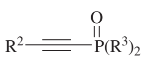
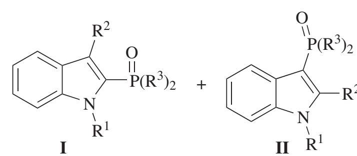
355, 356

R^1	R^2	R^3	R^4	**I + II**	**I:II**[a]
H	H	CF_3	$4\text{-}ClC_6H_4$	(79)	78:22
H	H	CF_3	$2\text{-}ClC_6H_4$	(59)	76:24
H	H	CF_3	$3\text{-}ClC_6H_4$	(80)	72:28
H	H	CHF_2	$4\text{-}ClC_6H_4$	(70)	100:0
Cl	H	CF_3	$4\text{-}ClC_6H_4$	(79)	84:16
O_2N	H	CF_3	$4\text{-}ClC_6H_4$	(57)	84:16
Cl	Cl	CF_3	$4\text{-}ClC_6H_4$	(74)	84:16
H	H	CF_3	$4\text{-}MeC_6H_4$	(81)	88:12
H	H	CF_3	$4\text{-}MeOC_6H_4$	(73)	91:9
H	H	CF_3	$4\text{-}EtO_2CC_6H_4$	(92)	68:32
H	H	CF_3	$4\text{-}O_2NC_6H_4$	(65)	53:47
H	H	CF_3	$Ph(CH_2)_2$	(47)	81:19
H	H	CF_3	$PhCH(Me)CH_2$	(55)	72:28
Me	H	CF_3	$4\text{-}ClC_6H_4$	(82)	81:19
H	MeO	CF_3	$4\text{-}ClC_6H_4$	(65)	88:12

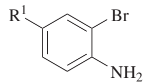
TABLE 3A. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILINES, 2-IODOBENZOIC ACIDS, OR ANILINES AND ALKYNES (*Continued*)

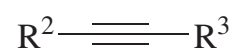
Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{6-7} 		$Pd_2(dba)_3$•$CHCl_3$, $P(o\text{-tol})_3$, Et_3N, DMF, 80°, 8 h		356

R^1	R^2	R^3	R^4	I + II	I:II[a]
H	H	CF_3	4-ClC_6H_4	(85)	34:66
H	H	CF_3	2-ClC_6H_4	(56)	16:84
H	H	CF_3	3-ClC_6H_4	(74)	27:73
H	H	CHF_2	4-ClC_6H_4	(—)	—
Cl	H	CF_3	4-ClC_6H_4	(89)	22:78
O_2N	H	CF_3	4-ClC_6H_4	(81)	36:64
Cl	Cl	CF_3	4-ClC_6H_4	(86)	11:89
H	H	CF_3	4-MeC_6H_4	(79)	9:91
H	H	CF_3	4-$MeOC_6H_4$	(52)	8:92
H	H	CF_3	4-$EtO_2CC_6H_4$	(85)	34:66
H	H	CF_3	4-$O_2NC_6H_4$	(51)	48:52
H	H	CF_3	$Ph(CH_2)_2$	(60)	22:78
H	H	CF_3	$PhCH(Me)CH_2$	(27)	17:83
Me	H	CF_3	4-ClC_6H_4	(62)	27:73
H	MeO	CF_3	4-ClC_6H_4	(66)	17:83

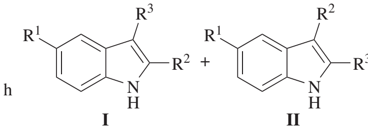
Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(acac)_2$, K_2CO_3, DMSO		357

R^1	R^2	R^3	Time (h)	Temp (°)	**I**	**II**
H	Ph	Ph	11	120	(80)	(—)
Me	Ph	*t*-Bu	22	120	(50)	(—)
Me	Ph	Ph	11	90	(80)	(20)
Me	$Ph_2P(O)$	Ph	11	90	(57)	(—)



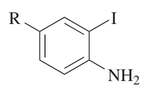


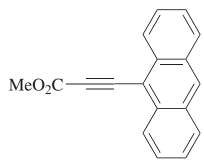
$Pd(OAc)_2$, phenylurea, K_2CO_3, DMF, 130°, 30 h



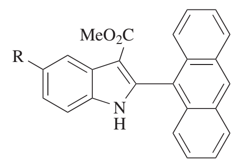
358

R^1	R^2	R^3	**I + II**	**I:II**
H	Ph	Ph	(84)	—
H	Ph	Me	(62)	96:4
H	Ph	Pr	(67)	82:18
H	Pr	Pr	(80)	—
H	Ph	CO_2H	(—)	—
H	Ph	CO_2Ph	(—)	—
H	2-$MeOC_6H_4$	Ph	(71)	70:30
Me	Ph	Ph	(86)	—
Me	Ph	Me	(65)	88:12
Me	Ph	Pr	(55)	80:20





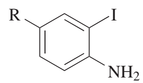
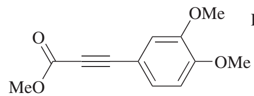
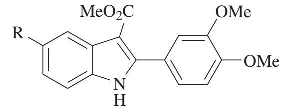
$PdCl_2(PPh_3)_2$, Bu_4NBr, NaOAc, DMF, 100°, 10 h



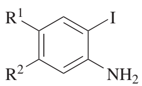
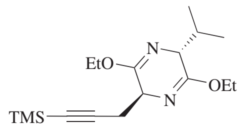
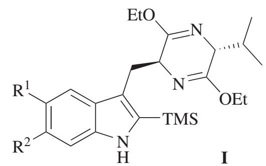
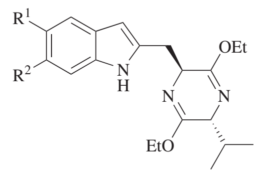
R	
H	(34)
Me	(30)

359

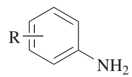
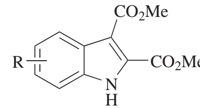
TABLE 3A. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILINES, 2-IODOBENZOIC ACIDS, OR ANILINES AND ALKYNES (*Continued*)

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{6-8} 		$PdCl_2(PPh_3)_2$, Bu_4NBr, NaOAc, DMF, 100°, 0.5 h		359

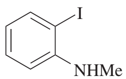
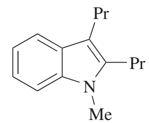
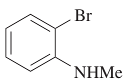
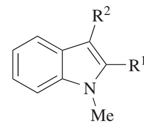
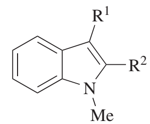
R		R	
H	(65)	Me	(40)
F	(40)	NC	(38)
Cl	(47)	MeO_2C	(33)
O_2N	(30)		

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$, LiCl, Na_2CO_3, DMF, 100°	 **I** +  **II**	112

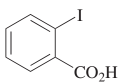
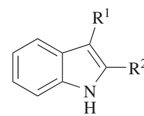
R^1	R^2	**I**	**II**
H	H	(81)	(—)
F	H	(50)	(15)
NO_2	H	(65)	(22)
Me	H	(63)	(—)
Me	Me	(70)	(—)

Reactant	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{6-12} 	MeO_2C—≡—CO_2Me	$Pd(OAc)_2$, O_2 (1 atm), DMA/pivOH (4:1), 120°, 12 h		360

R		R	
5-Cl	(45)	5-MeO	(99)
5-F	(88)	7-MeO	(81)
5-OH	(38)	5-CF_3O	(46)
5-Me	(93)	5-EtO_2C	(97)
6-Me	(95)	6-*i*-Pr	(99)
7-Me	(72)	6-*c*-C_6H_{11}	(81)

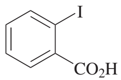
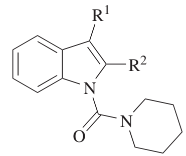
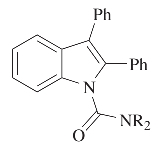
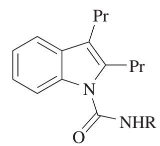
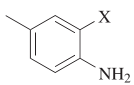
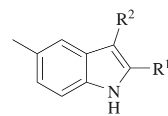
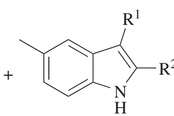
Reactant	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7 	Pr—≡—Pr	$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, DMF, 100°, 24 h	 (71)	30, 31
	R^1—≡—R^2	$Pd(OAc)_2$, phenylurea, K_2CO_3, DMF, 130°, 30 h	 I +  II	358

R^1	R^2	**I + II**	**I:II**
Ph	Me	(51)	78:22
Ph	Ph	(67)	—

Reactant	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
	R^1—≡—R^2	1. NaN_3, CbzCl, *t*-BuONa, DMF, 75°, 5 h 2. $Pd(OAc)_2$, alkyne, Na_2CO_3, 120°, 16 h		361

R^1	R^2	
t-Bu	Me	(56)
Ph	TMS	(82)
Ph	Ph	(77)

TABLE 3A. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILINES, 2-IODOBENZOIC ACIDS, OR ANILINES AND ALKYNES (*Continued*)

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
	R^1—≡—R^2	1. NaN_3, PhOCOCl, *t*-BuONa, NMP, 75°, 5 h 2. Piperidine, NMP, 75°, 3 h 3. $Pd(OAc)_2$, alkyne, Na_2CO_3, 120°, 16 h	 R^1 / R^2 Pr / Pr (54) Ph / Ph (68)	361
	Ph—≡—Ph	1. NaN_3, PhOCOCl, *t*-BuONa, NMP, 75°, 5 h 2. HNR_2, NMP, 75°, 3 h 3. $Pd(OAc)_2$, alkyne, Na_2CO_3, 120°, 16 h	 Amine morpholine (64) pyrrolidine (62)	361
	Pr—≡—Pr	1. NaN_3, PhOCOCl, *t*-BuONa, NMP, 75°, 5 h 2. RNH_2, NMP, 75°, 3 h 3. $Pd(OAc)_2$, alkyne, Na_2CO_3, 120°, 16 h	 R Ph(Me)CH (59) $Ph(CH_2)_2$ (39)	361
	R^1—≡—R^2	$Pd(OAc)_2$, dtbpf, K_2CO_3, NMP, 110 or 130°	 **I** +  **II**	122

X	R^1	R^2	**I**	**I**:**II**
Br	Ph	Pr	(86)	78:22
Cl	$MeCH{=}CH_2$	Et	(60)	>99:1
Cl	Pr	Pr	(82)	—
Cl	Ph	Pr	(76)	91:9

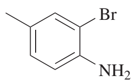
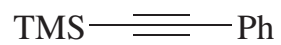
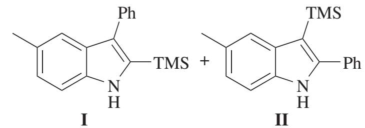
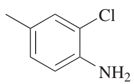
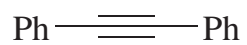
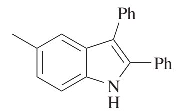
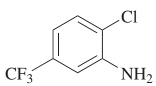
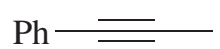
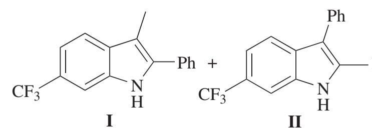
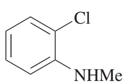
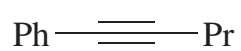
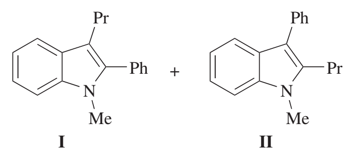
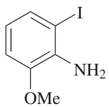
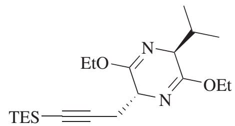
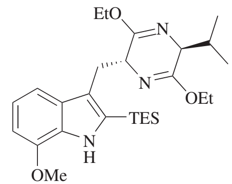
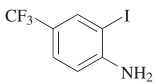
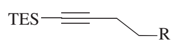
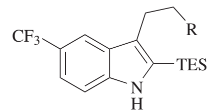
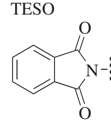
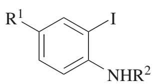
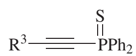
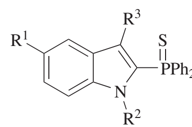
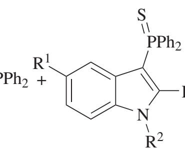
		$Pd(OAc)_2$, dtbpf, $KHCO_3$, NMP	 **I** (63), **I**:**II** = >99:1	122
		$Pd(OAc)_2$, PCy_3, K_2CO_3, NMP	 (86)	122
		$Pd(OAc)_2$, dtbpf, K_2CO_3, NMP	 **I** (63), **I**:**II** = >89:11	122
		$Pd(OAc)_2$, dtbpf, K_2CO_3, NMP	 **I** (68), **I**:**II** = 91:9	122

TABLE 3A. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILINES, 2-IODOBENZOIC ACIDS, OR ANILINES AND ALKYNES (*Continued*)

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		$Pd(OAc)_2$, LiCl, Na_2CO_3, DMF, 100°, 36 h	 (75)	118, 120
		$PdCl_2(PPh_3)_2$, LiCl, Na_2CO_3, DMF, 100°		362

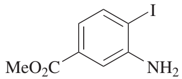
R	Time (h)	
TESO	12	(40)
	18	(83)

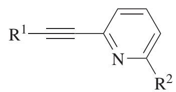
Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{7-13}				
		$Pd(acac)_2$, K_2CO_3, DMSO, 90°, 11 h	 **I** +  **II**	357

R^1	R^2	R^3	I	II
H	Me	2-thienyl	(57)	(10)
H	Me	*t*-Bu	(35)	(—)
H	Me	*c*-C_6H_{11}	(91)	(—)
H	Me	*n*-C_6H_{13}	(67)	(—)
H	Me	Ph	(74)	(6)

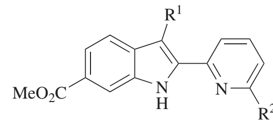
H	Me	4-$MeOC_6H_4$	(75)	(8)
H	Me	2-$MeOC_6H_4$	(54)	(17)
H	Me	4-$MeO_2CC_6H_4$	(58)	(6)
H	Me	4-$MeCOC_6H_4$	(59)	(6)
Br	Me	Ph	(57)	(11)
Cl	Me	Ph	(56)	(18)
Me	Me	Ph	(71)	(13)
H	Et	Ph	(78)	(6)
H	*i*-Pr	Ph	(73)	(—)
H	Bn	Ph	(59)	(5)

C_8



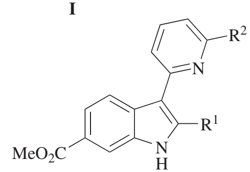


$Pd(OAc)_2$, dppf, KOAc, NMP, 140°, 1 h



I

+



II

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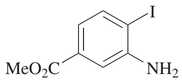
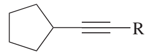
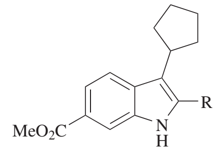
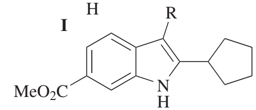
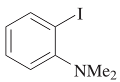
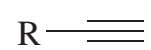
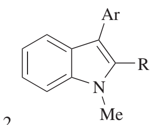
R^1	R^2	**I + II**	**I:II**[b]
Bu	H	(91)	97:3
t-Bu	H	(78)	31:69
c-C_5H_9	H	(94)	94:6
c-C_5H_9	Me	(88)	87:13
c-C_5H_9	MeO	(84)	80:20
Ph	H	(63)	57:43
4-$MeOC_6H_4$	H	(63)	41:59

TABLE 3A. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILINES, 2-IODOBENZOIC ACIDS, OR ANILINES AND ALKYNES (*Continued*)

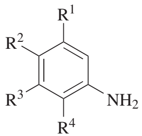
Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8				
		$Pd(OAc)_2$, dppf, AcOK, NMP, 140°, 1 h	 + **I**  **II**	363

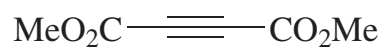
R	I + II	I:II[b]
3-pyridyl	(93)	68:32
4-pyridyl	(76)	72:28
Ph	(86)	67:33

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
		1. $PdCl_2(PPh_3)_2$, CuI, Et_3N, 300 W MW, 60°, time 1 2. ArI, MeCN, 300 W MW, 90°, time 2		364

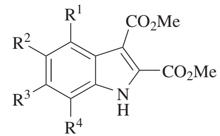
R	Ar	Time 1 (h)	Time 2 (h)	
$NC(CH_2)_3$	$4\text{-}O_2NC_6H_4$	0.3	0.5	(72)
$NC(CH_2)_3$	$4\text{-}MeO_2CC_6H_4$	0.3	0.5	(63)
3-thienyl	$3\text{-}EtO_2CC_6H_4$	0.3	0.5	(78)
Ph	$4\text{-}EtO_2CC_6H_4$	6	4	(82)
Ph	$4\text{-}EtO_2CC_6H_4$	0.3	0.5	(86)
1-cyclohexenyl	$4\text{-}O_2NC_6H_4$	0.3	0.5	(91)
$2\text{-}MeOC_6H_4$	$4\text{-}ClC_6H_4$	0.3	0.83	(87)
$3\text{-}MeOC_6H_4$	Ph	0.3	0.5	(91)
$4\text{-}MeOC_6H_4$	$4\text{-}EtO_2CC_6H_4$	0.3	0.3	(86)
$4\text{-}NCC_6H_4$	$4\text{-}EtO_2CC_6H_4$	0.5	0.83	(77)

C_{8-10}





Pd(OAc)$_2$, O_2 (1 atm),
DMA/pivOH (4:1),
120°, 12 h



R^1	R^2	R^3	R^4	
H	MeO	H	MeO	(99)
MeO	H	H	MeO	(63)
H	MeO	MeO	H	(93)

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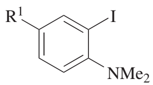
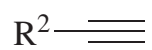
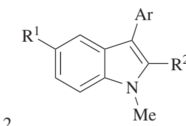




1. $PdCl_2(PPh_3)_2$, CuI, Et_3N, 300 W MW, 60°, time 1
2. ArI, MeCN, 300 W MW, 90°, time 2



R^1	R^2	Ar	Time 1 (h)	Time 2 (h)	
Br	3-thienyl	2-thienyl	0.3	0.5	(85)
Br	Ph	2-thienyl	0.3	0.5	(79)
Br	3,5-$(MeO)_2C_6H_3$	2-thienyl	5	4	(82)
Br	3,5-$(MeO)_2C_6H_3$	2-thienyl	0.3	0.5	(74)
Br	3,5-$(MeO)_2C_6H_3$	3-thienyl	0.3	0.5	(76)
Me	$HOCH_2CH_2$	3,4-$(MeO)_2C_6H_3$	0.5	0.5	(33)
Me	4-$MeOC_6H_4$	4-ClC_6H_4	0.5	0.5	(94)
Me	Ph	3-$EtO_2CC_6H_4$	0.5	0.5	(68)
MeO_2C	3-$MeOC_6H_4$	3-thienyl	0.5	0.5	(70)

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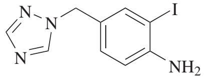
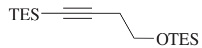
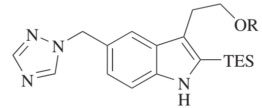
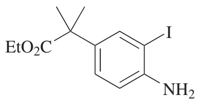
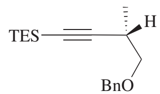
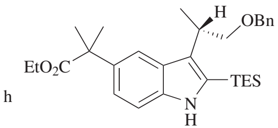
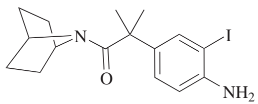
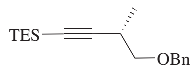
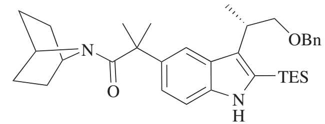
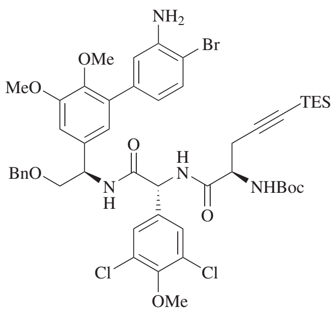
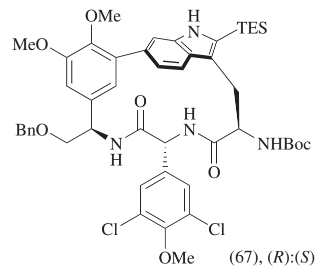
TABLE 3A. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILINES, 2-IODOBENZOIC ACIDS, OR ANILINES AND ALKYNES (*Continued*)

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 		$Pd(OAc)_2$, Na_2CO_3, DMF, 100°	 R: **I** TES; **II** H **I** + **II** (88), **I**:**II** = 75:25	121
C_{12} 		$Pd(OAc)_2$, PPh_3, LiCl, K_2CO_3, DMF, 100°, 16 h	 (89)	114
C_{16} 		$Pd(OAc)_2$, PPh_3, LiCl, K_2CO_3, DMF, 100°, 16 h	 (72)	114
C_{48} 		$Pd(OAc)_2$, dtbpf, Et_3N, toluene/MeCN, 110°, 1 h	 (67), (*R*):(*S*) = 1:1	365

[a] The ratios were determined by ^{19}F NMR spectroscopy.

[b] The ratios were determined by ^{1}H NMR spectroscopy.

TABLE 3B. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILIDES OR *N*-ACYL BENZOTRIAZOLES AND ALKYNES

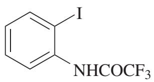
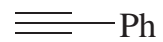
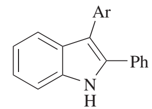
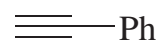
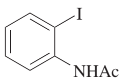
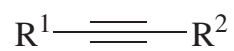
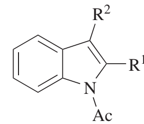
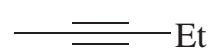
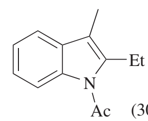
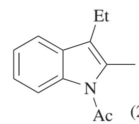
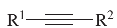
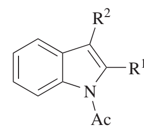
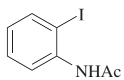
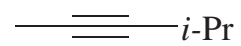
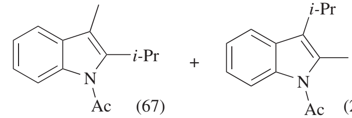
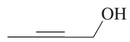
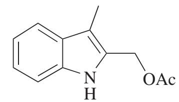
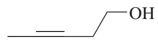
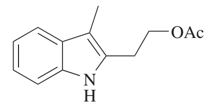
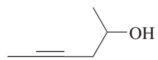
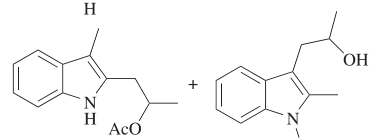
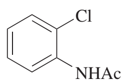
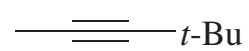
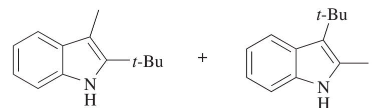
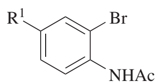
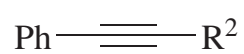
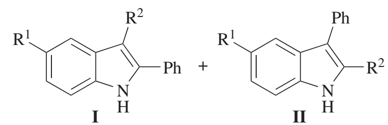
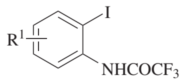
Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8 		ArBr, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 60°	 **I** Ar / Time (h) Ph / 0.5 / (91) 4-$MeOC_6H_4$ / 1 / (60)	139
		1. $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 60° 2. ArBr	**I** Ar / Time (h) Ph / 4.5 / (86) 4-$O_2NC_6H_4$ / 8 / (98) 4-$MeO_2CC_6H_4$ / 2.5 / (85)	139
		$Pd(OAc)_2$, LiCl, KOAc, DMF, 100°	 R^1 / R^2 / Time (h) TMS / Me / 12 / (70) Ph / Me / 24 / (75)	30, 31
		$Pd(OAc)_2$, LiCl, K_2CO_3, DMF, 100°, 24 h	 (30) +  (28)	31
		$Pd(OAc)_2$, Bu_4NCl, base, DMF, 100°, 24 h	 R^1 / R^2 / Base CH_2OH / $MeCH{=}CH_2$ / NaOAc / (27) Pr / Pr / KOAc / (91)	30, 31

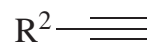
TABLE 3B. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILIDES OR *N*-ACYL BENZOTRIAZOLES AND ALKYNES (*Continued*)

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8 		$Pd(OAc)_2$, Bu_4NCl, Na_2CO_3, DMF, 100°, 24 h	 (67) + (26)	30, 31
		$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, DMF, 100°, 24 h	 (60)	31
		$Pd(OAc)_2$, Bu_4NCl, KOAc, DMF, 100°, 24 h	 (43)	31
		$Pd(OAc)_2$, PPh_3, Bu_4NCl, Na_2CO_3, DMF, 100°, 12 h	 (60) + (16)	31
		$Pd(OAc)_2$, dtbpf, K_2CO_3, NMP	 **I** + **II**; **I** (73), **I**:**II** = >99:1	122
C_{8-9} 		$Pd(OAc)_2$, phenylurea, K_2CO_3, DMF, 130°, 30 h	 **I** + **II**	358

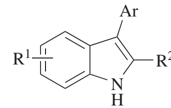
R^1	R^2	**I + II**	**I:II**
H	Ph	(74)	—
H	Me	(59)	93:7
Me	Ph	(70)	—

C_{8-10}





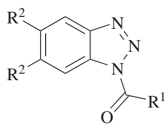
1. $PdCl_2(PPh_3)_2$, CuI, Et_3N, 300 W MW, 60°, 0.5 h
2. ArI, MeCN, 300 W MW, 90°, 0.5 h

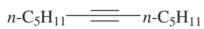


R^1	R^2	Ar	
H	3-$MeOC_6H_4$	4-$MeOC_6H_4$	(82)
H	Ph	3-$EtO_2CC_6H_4$	(93)
5-Me	4-NCC_6H_4	Ph	(66)
5-Me	4-$MeOC_6H_4$	3-$O_2NC_6H_4$	(88)
5-Me	3-thienyl	4-ClC_6H_4	(67)
5-MeO_2C	Ph	3-$MeOC_6H_4$	(76)
5-MeO_2C	4-$MeOC_6H_4$	4-$EtO_2CC_6H_4$	(60)

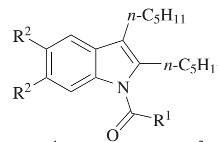
364

C_{8-16}





$Pd(PPh_3)_4$, neat, 130°, 30 h



R^1	R^2	Time (h)	
Me	H	72	(—)
EtO	H	9	traces
Ph	H	18	(42)
3-FC_6H_4	H	8	(54)
3,5-$F_2C_6H_3$	H	24	(66)
4-$CF_3C_6H_4$	H	8	(69)
4-$MeOC_6H_4$	H	72	(47)
3,5-$(CF_3)_2C_6H_3$	H	12	(39)
4-$MeCOC_6H_4$	H	18	(64)
4-$CF_3C_6H_4$	Me	8	(74)
4-$CF_3C_6H_4$	MeO	11	(41)
4-$CF_3C_6H_4$	NC	41	(—)

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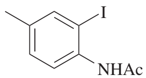
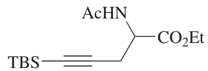
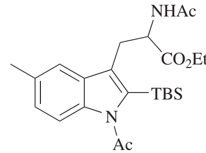
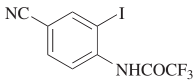
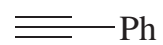
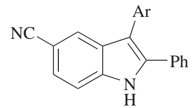
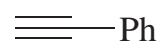
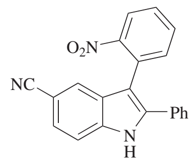
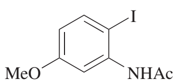
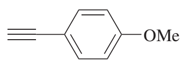
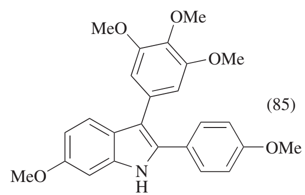
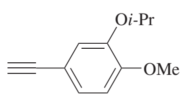
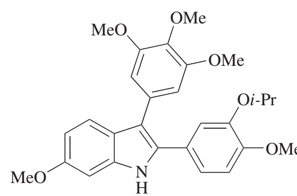
TABLE 3B. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILIDES OR *N*-ACYL BENZOTRIAZOLES AND ALKYNES (*Continued*)

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9				
		$Pd(OAc)_2$, Bu_4NCl, KOAc, DMF, 90–100°, 22 h	 (27)	115
		ArBr, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 60°	 Ar / Time (h): Ph 12.5 (91); 4-$MeOC_6H_4$ 1.5 (78)	139
		1. $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 60° 2. 2-$O_2NC_6H_4Br$, 12.5 h	 (80)	139
		1. MeMgCl, THF, 0° 2. $PdCl_2(PPh_3)_2$, 65°, 1–2 h 3. 18° 4. 3,4,5-$(MeO)_3C_6H_2I$, DMSO, 80°, 16–18 h	 (85)	137, 138
		1. $PdCl_2(PPh_3)_2$, CuI, Et_3N, MeCN, 18°, 1 h 2. 3,4,5-$(MeO)_3C_6H_2I$, 18°, 18 h	 (77)	138

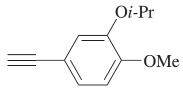
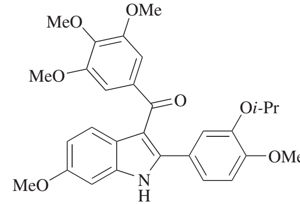
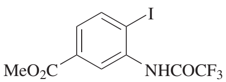
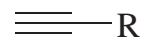
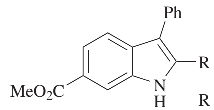
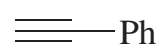
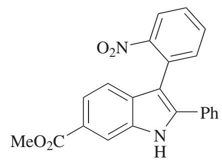
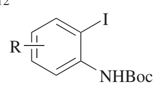
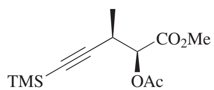
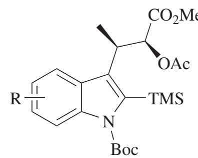
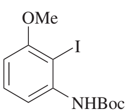
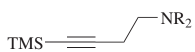
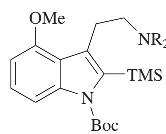
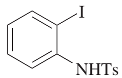
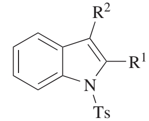
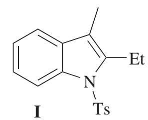
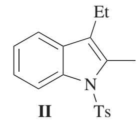
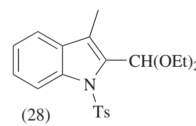
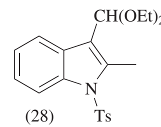
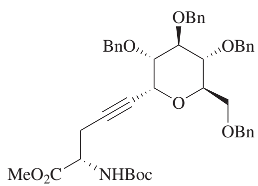
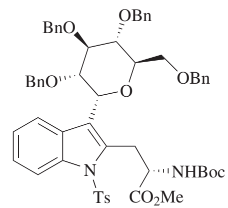
Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
		1. $PdCl_2(PPh_3)_2$, CuI, CO (balloon), Et_3N, MeCN, 18°, 1 h 2. 3,4,5-$(MeO)_3C_6H_2I$, 18°, 18 h	 (73)	138
C_{10} 		PhBr, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 60°	 R / Time (h) Ph / 5 / (86) 4-MeC_6H_4 / 3.5 / (82)	139
		1. $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 60° 2. 2-$O_2NC_6H_4Br$, 60°, 3.8 h	 (94)	139
C_{11-12} 		$Pd(OAc)_2$, PPh_3, Et_4NCl, i-Pr_2NEt, DMF, 100°, 1.5 h	 R H (85) MeO (88)	367
C_{12} 		$Pd(OAc)_2$, PPh_3, Bu_4NCl, i-Pr_2EtN, DMF, 80°, 48 h	 R H (83) Me (69) Bn (77)	368

TABLE 3B. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILIDES OR *N*-ACYL BENZOTRIAZOLES AND ALKYNES (*Continued*)

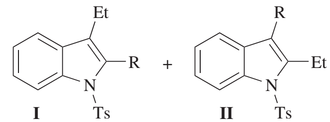
Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13} 	R^1—≡—R^2	$Pd(OAc)_2$, additive, base, DMF, 100°		31, 30

R^1	R^2	Additive	Base	Time (h)	
t-Bu	Me	Bu_4NCl	KOAc	24	(86)
Pr	Pr	Bu_4NCl	KOAc	24	(86)
CMe_2OH	$MeCH{=}CH_2$	Bu_4NCl	KOAc	24	(45)
Ph	Ph	LiCl	K_2CO_3	48	(60)

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
	—≡—Et	$Pd(OAc)_2$, LiCl, K_2CO_3, DMF, 100°, 36 h	 **I** +  **II** **I** + **II** (60), **I**:**II** = 1:1	31, 30
	—≡—$CH(OEt)_2$	$Pd(OAc)_2$, Bu_4NCl, NaOAc, DMF, 100°, 24 h	 (28) +  (28)	31, 30
		$Pd(OAc)_2$, PPh_3, Bu_4NCl, Na_2CO_3, DMF, 100°, 24 h	 (89)	113

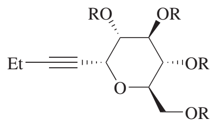
R—≡—Et

Pd(OAc)$_2$, PPh$_3$, Bu_4NCl, Na_2CO_3, 100°

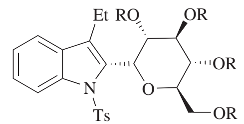


R	Time (h)	**I + II**	**I:II**
$MeO_2C(CH_2)_2$	2	(75)	60:40
$BocNH(CH_2)_2$	24	(90)	56:44
$MeO_2CCH(NHBoc)CH_2$	40	(50)	56:44

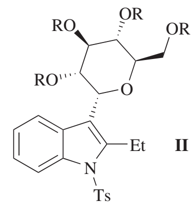
369



Pd(OAc)$_2$, PPh$_3$, Bu_4NCl, Na_2CO_3, 100°



I +



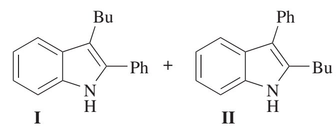
II

R	Time (h)	**I + II**	**I:II**
H	1	(60)	65:35
Bn	48	(16)	69:31

369

Bu—≡—Ph

Pd/C, additive, NaOAc, NMP, 120°, 24 h



Additive	**I + II**	**I:II**
LiCl	(90)	72:28
—	(84)	77:23

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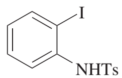
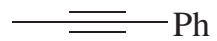
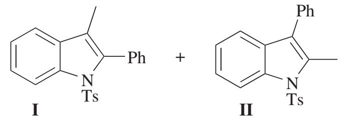
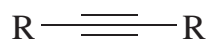
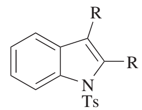
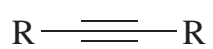
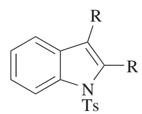
TABLE 3B. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILIDES OR *N*-ACYL BENZOTRIAZOLES AND ALKYNES (*Continued*)

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13} 		Pd/C, additive, NaOAc, NMP, 120°, 24 h	 **I** + **II**	341

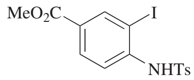
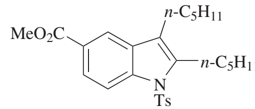
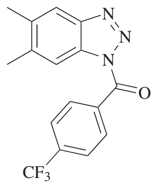
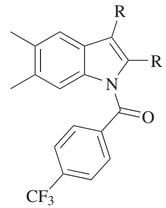
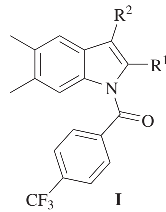
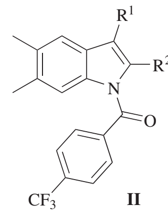
Additive	Time (h)	**I** + **II**	**I**:**II**
LiCl	10	(84)	64:36
—	2	(90)	68:32

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
		Pd/C, additive, NaOAc, NMP, 120°		341

R	Additive	Time (h)	
Et	LiCl	24	(97)
Pr	LiCl	7	(96)
Pr	—	6	(90)
n-C_5H_{11}	LiCl	24	(100)
n-C_5H_{11}	—	3	(100)
Ph	LiCl	8	(69)
Ph	—	8	(94)

Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
		Pd/C, NaOAc, NMP		341

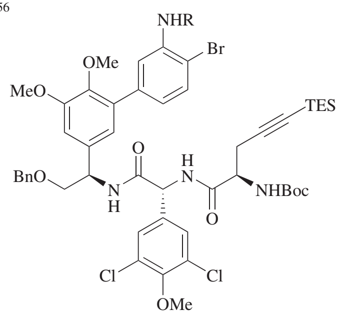
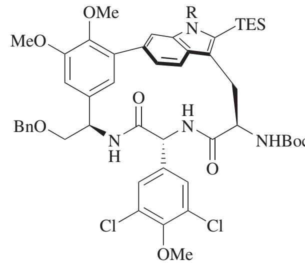
R	Temp (°)	Time (h)	
Pr	120	24	(86)
Bu	120	6	(86)
n-C_5H_{11}	110	12	(88)
n-C_5H_{11}	120	3	(99)
Ph	130	24	(87)

C_{15} 	n-C_5H_{11}—≡—n-C_5H_{11}	Pd/C, NaOAc, NMP, 120°, 24 h	 (70)	341
C_{16} 	R—≡—R	$Pd(PPh_3)_4$, neat, 130°, 8–9 h		366
	R^1—≡—R^2	$Pd(PPh_3)_4$, neat, 130°, 8–9 h	 I +  II	366

R	
Pr	(71)
$MeCO(CH_2)_2$	(64)
$MOMO(CH_2)_3$	(67)
$TBSO(CH_2)_3$	(51)
Ph	(41)

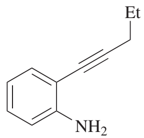
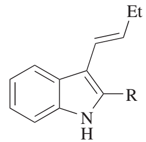
R^1	R^2	**I + II**	**I:II**
t-Bu	Me	(22)	78:22
c-C_6H_{11}	Me	(65)	55:45
Ph	Bu	(72)	74:26
4-$MeOC_6H_4$	Bu	(66)	52:48
4-$CF_3C_6H_4$	Bu	(59)	82:18

TABLE 3B. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOANILIDES OR *N*-ACYL BENZOTRIAZOLES AND ALKYNES (*Continued*)

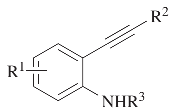
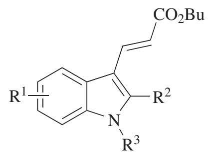
Substrate	Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{50-56} 		$Pd(OAc)_2$, dtbpf, Et_3N, toluene/MeCN, 110°, 1 h		365

R		(*R*):(*S*)
CO_2Me	(78)	12.2:1
COMe	(89)	4:1
COPh	(70)	>20:1
CO_2Bn	(74)	6.5:1

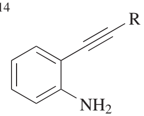
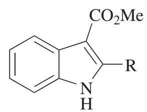
TABLE 3C. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILINES

2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11} 	RCHO, $Pd(OAc)_2$, Bu_3P, THF, 100°		33

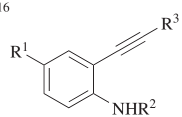
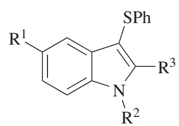
R	
i-Pr	(57)[a]
c-C_6H_{11}	(52)
Ph	(74)[a]
Bn	(30)
PhMeCH	(67)[a]

2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11-17} 	 CO_2Bu, $PdCl_2$, KI, DMF, 100°, 20 h		370

R^1	R^2	R^3	
H	TMS	H	(72)
H	$HO(CH_2)_4$	H	(32)
H	*n*-C_6H_{13}	H	(76)
H	4-MeC_6H_4	H	(85)
H	4-MeC_6H_4	Me	(74)
Me	4-MeC_6H_4	H	(57)
5-MeO_2C	4-MeC_6H_4	H	(76)

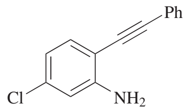
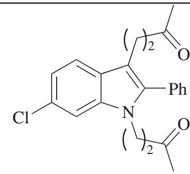
2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-14} 	CO, $PdCl_2$, $CuCl_2$, AcONa, K_2CO_3, MeOH, rt, 3 h		128

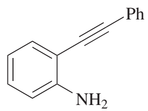
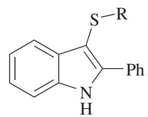
R	
Bu	(30)
Ph	(51)

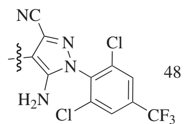
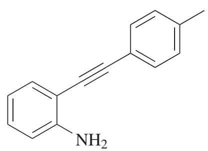
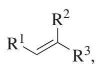
2-Alkynylaniline	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-16} 	PhS—SPh, $PdCl_2$, DMSO, 80°		371

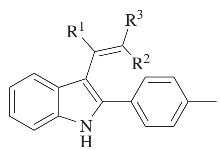
R^1	R^2	R^3	Time (h)	
H	H	*t*-Bu	24	(83)
H	H	2-thienyl	24	(82)
H	H	4-pyridyl	96	trace
H	H	*n*-C_6H_{13}	24	(56)
Cl	H	Ph	24	(95)
H	H	2-BrC_6H_4	30	(59)
H	H	2-$MeOC_6H_4$	24	(35)
Me	H	Ph	24	(61)
H	Me	Ph	24	(65)
H	H	4-$MeCOC_6H_4$	24	(19)

TABLE 3C. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILINES (*Continued*)

<table>
<tr><th></th><th>2-Alkynylaniline</th><th>Conditions</th><th>Product(s) and Yield(s) (%)</th><th>Refs.</th></tr>
<tr><td>C_{14}</td><td>
</td><td>Methyl vinyl ketone, $PdCl_2$, $FeCl_3$, DCE</td><td>

(80)</td><td>77</td></tr>
<tr><td></td><td>
</td><td>RS—SR, $PdCl_2$, DMSO, 80°</td><td>

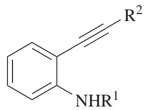
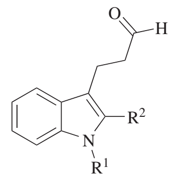
<table>
<tr><th>R</th><th>Time (h)</th><th></th></tr>
<tr><td>Me</td><td>24</td><td>(78)</td></tr>
<tr><td>2-pyridyl</td><td>24</td><td>(74)</td></tr>
<tr><td>2-$NH_2C_6H_4$</td><td>48</td><td>(27)</td></tr>
<tr><td>4-ClC_6H_4</td><td>24</td><td>(92)</td></tr>
<tr><td>4-FC_6H_4</td><td>24</td><td>(89)</td></tr>
<tr><td>4-$O_2NC_6H_4$</td><td>24</td><td>(96)</td></tr>
<tr><td>Bn</td><td>24</td><td>trace</td></tr>
<tr><td>4-$MeOC_6H_4$</td><td>24</td><td>(70)</td></tr>
<tr><td>4-MeC_6H_4</td><td>25</td><td>(58)</td></tr>
<tr><td>
</td><td>48</td><td>(27)</td></tr>
</table></td><td>371</td></tr>
<tr><td>C_{15}</td><td>
</td><td>

$PdCl_2$, KI, DMF, 100°, 20 h</td><td>

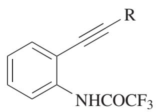
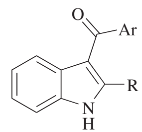
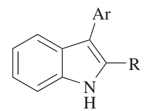
<table>
<tr><th>R^1</th><th>R^2</th><th>R^3</th><th></th></tr>
<tr><td>H</td><td>H</td><td>CN</td><td>(77)</td></tr>
<tr><td>H</td><td>H</td><td>$CONH_2$</td><td>(95)</td></tr>
<tr><td>H</td><td>H</td><td>SO_2Me</td><td>(87)</td></tr>
<tr><td>H</td><td>H</td><td>COMe</td><td>(79)</td></tr>
<tr><td>Me</td><td>H</td><td>CO_2Me</td><td>(51)</td></tr>
<tr><td>H</td><td>Me</td><td>CO_2Me</td><td>(67)</td></tr>
</table></td><td>370</td></tr>
</table>

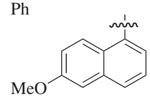
[a] The yield was determined by NMR spectroscopy.

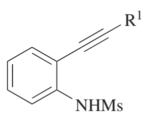
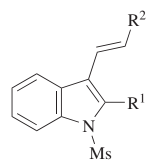
TABLE 3D. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11-21}			
	Acrolein, $Pd(OAc)_2$, LiBr, THF, rt		103

R^1	R^2	Time (d)	
Ms	CH_2OMe	1	(89)
Ms	TMS	4	(72)
Ms	Bu	0.5	(75)
Ms	Ph	1	(85)
Ts	CH_2OMe	0.5	(94)
Ts	Bu	0.5	(88)
Ts	Ph	0.5	(83)

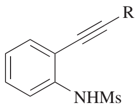
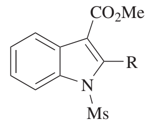
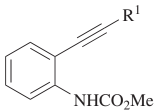
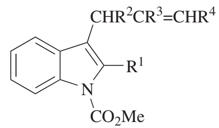
2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
	ArI, CO (balloon), $Pd(PPh_3)_4$, K_2CO_3, MeCN, 45°, overnight	 **I** +  **II**	106, 124

R	Ar	**I**	**II**
Me	$4\text{-}MeOC_6H_4$	(73)	(15)
Bu	$4\text{-}MeOC_6H_4$	(83)	(—)
Bu	$4\text{-}MeCONHC_6H_4$	$(72)^a$	(—)
2-thienyl	$4\text{-}MeC_6H_4$	(73)	(—)
Ph	$3\text{-}MeC_6H_4$	(57)	(—)
Ph	$4\text{-}MeOC_6H_4$	(60)	(—)
	$3\text{-}FC_6H_4$	$(64)^b$	(8)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-15}			
	$CH_2{=}CHR^2$, $PdCl_2$, $CuCl_2$, NaOAc, K_2CO_3, MeCN, 50°		130

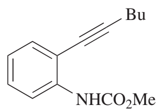
R^1	R^2	Time (h)	
TMS	CO_2Et	1	(32)
$(CH_2)_5Me$	CO_2Et	1	(46)
Ph	CHO	1.5	(48)
Ph	CO_2Et	1	(74)
Ph	Ac	1.5	(55)

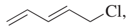
TABLE 3D. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13-15}			
	CO, $PdCl_2$, $CuCl_2$, AcONa, K_2CO_3, MeOH, rt, 3 h	 R: Bu (67); Ph (76)	128
C_{13-18}			
	$R^2CH{=}CR^3CHR^4Cl$, $PdCl_2(MeCN)_2$, methyloxirane, THF		70

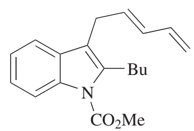
R^1	R^2	R^3	R^4	Temp	Time (h)	
$CH_2{=}CMe$	H	H	H	rt	20	(81)
Bu	H	H	H	rt	20	(73)
Bu	H	H	Me	rt	5.5	(80)[c]
Bu	H	Me	H	rt	2.5	(74)
Bu	Me	H	H	rt	48	(69)
Bu	H	H	Et	rt	72	(31)
Bu	H	H	CH_2Cl	rt	1	(71)[d]
Bu	H	Cl	H	rt	20	(52)
Bu	CH_2Cl	H	H	rt	5	(51)
Bu	H	CH_2Cl	H	rt	1	(72)
t-Bu	H	H	H	reflux	5	(33)
Ph	H	H	H	rt	48	(82)
Ph	H	H	H	reflux	0.5	(82)
$MeCH(CH_2)_5Me$	H	H	H	rt	20	(81)

C_{14}



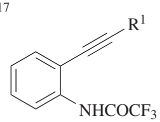


$PdCl_2(MeCN)_2$,
methyloxirane,
THF, reflux, 1 h

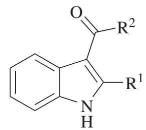


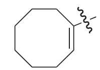
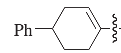
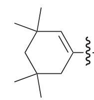
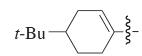
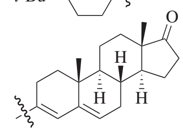
(30) 70

C_{14-17}

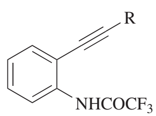


R^2OTf, CO (balloon),
$Pd(PPh_3)_4$, K_2CO_3,
MeCN, 45°, overnight

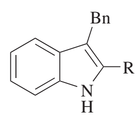


R^1	R^2		
Bu		(60)	106, 124
Bu		(52)	
Ph		(45)	
Ph		(45)	
$3\text{-}MeC_6H_4$		(64)	

C_{14-18}

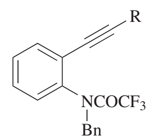


BrBn, $Pd_2(dba)_3$, ttmpp,
K_2CO_3, THF, 80°



I

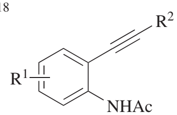
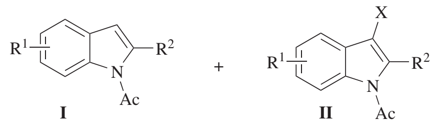
+



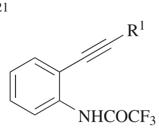
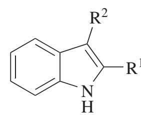
II

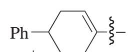
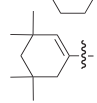
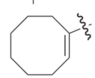
R	Time (h)	**I**	**II**	
2-thienyl	5.5	(50)	(22)	125
Ph	4	(70)	(22)	
$4\text{-}MeCOC_6H_4$	6	(65)	(22)	
$4\text{-}MeO_2CC_6H_4$	7	(62)	(16)	

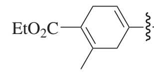
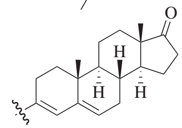
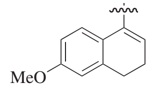
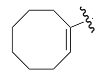
TABLE 3D. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

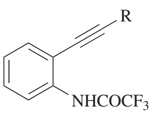
2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14-18} 	PdX_2, CuX_2, DCE, 40°	 **I** + **II**	372

R^1	R^2	X	Time (h)	**I**	**II**
H	*t*-Bu	Br	15	(5)	(5)
H	*t*-Bu	Cl	15	(5)	(88)
H	$MeC(O)CH_2$	Br	5	(5)	(57)
H	Ph	Br	12	(18)	(64)
H	Ph	Cl	12	(20)	(59)
H	*n*-C_8H_{17}	Cl	5	(25)	(56)
5-O_2N	*n*-C_8H_{17}	Br	5	(18)	(58)
5-O_2N	*n*-C_8H_{17}	Cl	5	(13)	(65)
5,6-F_2	*n*-C_8H_{17}	Br	11	(30)	(62)
5,6-F_2	*n*-C_8H_{17}	Cl	11	(40)	(45)
5,7-Cl_2	*n*-C_8H_{17}	Br	5	(50)	(41)
5,7-Cl_2	*n*-C_8H_{17}	Cl	5	(41)	(54)

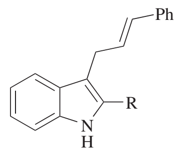
2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14-21} 	R^2OTf, $Pd(PPh_3)_4$, K_2CO_3, MeCN, rt		123

R^1	R^2	Time (h)	
Bu		35	(81)
Bu		1.5	(74)
Ph		4	(74)

Ph		22	(90)
Ph		48	(89)
		4	(70)



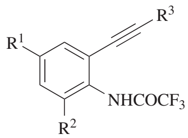
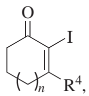
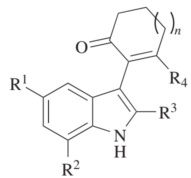
1. EtO_2CO–CH₂CH=CH–Ph, $Pd(PPh_3)_4$, THF, 60°, time 1
2. K_2CO_3, 80°, time 2



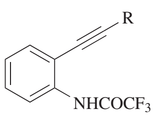
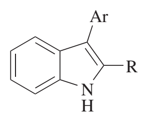
R	Time 1 (h)	Time 2 (h)	
$CH_2NHCOEt$	48	1	(45)
n-C_5H_{11}	5.5	24	(75)
Ph	3	1.5	(91)
CH_2OTHP	1.5	1.5	(77)
4-$MeOC_6H_4$	1	2	(74)
4-$MeCOC_6H_4$	0.5	8	(91)
2-$THPOC_6H_4$	3	24	(64)

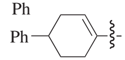
102, 106

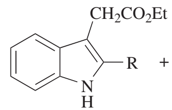
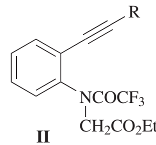
TABLE 3D. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

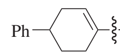
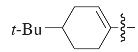
2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14-22} 	 $Pd_2(dba)_3$, $AsPh_3$, Cs_2CO_3, MeCN, 80°		373

R^1	R^2	R^3	R^4	*n*	Time (h)	
H	H	Bu	H	1	2	(77)
H	H	2-thienyl	H	1	2	(95)
O_2N	NC	Bu	H	1	3.5	(60)
H	H	Ph	H	0	2.5	(76)
H	H	Ph	H	1	2	(95)
H	H	2-BrC_6H_4	H	1	2	(87)
H	H	Ph	H	2	3	(67)
H	H	Ph	Me	1	2	(58)
H	H	3-$MeO_2CC_6H_4$	H	1	3.5	(95)
H	H	4-$MeCOC_6H_4$	H	1	2	(67)
F	F	4-$MeCOC_6H_4$	H	1	3	(72)
H	H	4-phenyl-1-cyclohexenyl	H	1	2	(40)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
	ArI, $Pd(PPh_3)_4$, K_2CO_3, MeCN, 80°		123

R	Ar	Time (h)	
Bu	4-ClC_6H_4	2	(82)
Ph	4-$MeOC_6H_4$	7	(80)
	4-$MeO_2CC_6H_4$	2	(68)

	ICH_2CO_2Et, $Pd_2(dba)_3$, ttmpp, K_2CO_3, THF, 80°	 I +  II	106, 125

R	Time (h)	I	II
Bu	4.5	(44)	(14)
2-thienyl	4	(41)	(14)
Ph	2	(73)	(trace)
3-MeC_6H_4	4	(70)	(20)
4-$MeCOC_6H_4$	3	(64)	(17)
4-$MeO_2CC_6H_4$	3	(61)	(14)
	5	(60)	(15)
	5	(78)	(trace)

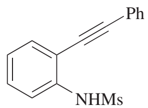
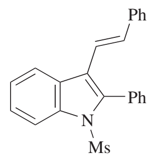
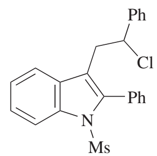
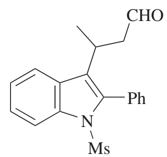
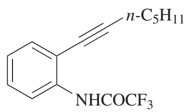
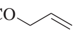
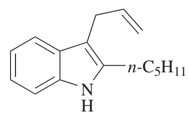
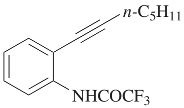
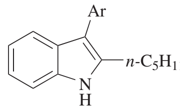
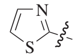
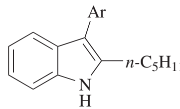
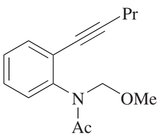
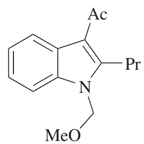
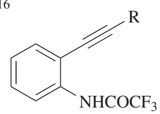
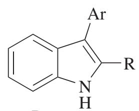
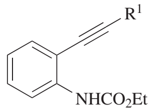
C_{15} 	CH_2=CHPh, $PdCl_2$, $CuCl_2$, NaOAc, K_2CO_3, MeCN, 50°	 (16) +  (64)	130
	Crotonaldehyde, $Pd(OAc)_2$, LiBr, THF, rt, 4 d	 (81)	103
	1. EtO_2CO, $Pd(PPh_3)_4$, THF, 60°, 3.5 h 2. K_2CO_3, 80°, 5 h	 (74)	102

TABLE 3D. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

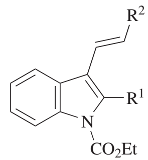
2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15} 	ArBr, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 100°, 3 h	 Ar:  (75); 3-NCC_6H_4 (88)	105, 106
	ArCl, $Pd_2(dba)_3$, XPhos, Cs_2CO_3, MeCN, 120°, 1.5 h	 Ar: Ph (40); 3-$MeOC_6H_4$ (54)	107
	$PdBr_2$, toluene, 80°	 (52)	140
C_{15-16} 	ArN_2BF_4, $Pd(PPh_3)_4$, K_2CO_3, Bu_4NI, MeCN (anhyd), 60°, 1–5.5 h		374

R	Ar		R	Ar	
n-C_5H_{11}	Ph	(63)	Ph	2-$MeOC_6H_4$	(69)
n-C_5H_{11}	4-ClC_6H_4	(89)	Ph	4-MeC_6H_4	(84)
n-C_5H_{11}	4-MeC_6H_4	(81)	2-BrC_6H_4	4-MeC_6H_4	(66)
Ph	Ph	(76)	Ph	4-$MeCOC_6H_4$	(96)
Ph	4-ClC_6H_4	(89)	Ph	2-Me-4-$MeOC_6H_3$	(49)
Ph	4-$O_2NC_6H_4$	(93)	4-$MeOC_6H_4$	Ph	(82)
2-BrC_6H_4	4-$O_2NC_6H_4$	(91)	4-$MeOC_6H_4$	4-MeC_6H_4	(86)
Ph	3-$CF_3C_6H_4$	(85)	4-$MeOC_6H_4$	4-NCC_6H_4	(86)
Ph	4-$MeOC_6H_4$	(69)	4-$MeCOC_6H_4$	4-$MeOC_6H_4$	(65)
Ph	3-$MeOC_6H_4$	(68)			

C_{15-17}



CH_2=CHR^2, $PdCl_2$,
$CuCl_2$, H_2O,
Bu_4NF, THF, reflux



R^1	R^2	Time (h)	
Bu	CO_2Me	6	(42)
t-Bu	Ac	2.5	(22)
Ph	CO_2Me	4	(64)
Ph	Bu	3	(68)
Ph	Ac	16	(51)

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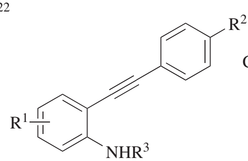
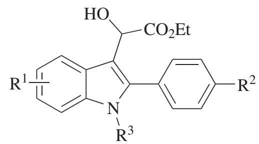
C_{15-22}



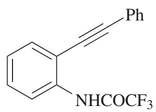
$CHOCO_2Et$,
$Pd(bpy)(H_2O)_2(OTf)_2$,
1,4-dioxane, 60°,
overnight

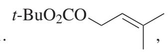


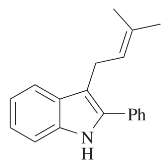
R^1	R^2	R^3	
H	H	Ms	(51)
H	H	$COCF_3$	(—)[e]
H	H	Ts	(89)
5-F	H	Ts	(81)
5-Cl	H	Ts	(73)
6-Cl	H	Ts	(67)
H	Br	Ts	(81)
H	Me	Ts	(83)
5-Me	H	Ts	(80)

375

C_{16}



1.  ,
Pd(PPh_3)$_4$, THF, 60°, 48 h
2. K_2CO_3, 80°, 2 h



(52)

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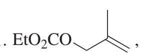
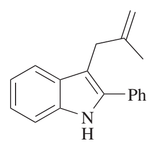
1.  ,
Pd(PPh_3)$_4$, THF, 60°, 24 h
2. K_2CO_3, 80°, 10 h



(74)

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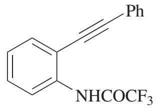
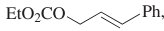
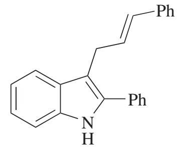
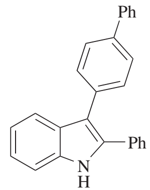
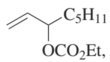
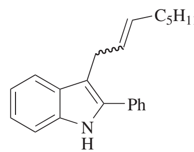
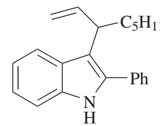
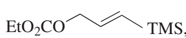
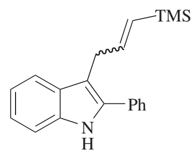
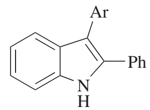
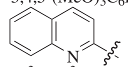
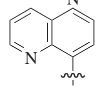
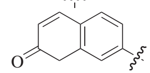
TABLE 3D. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16} 	 EtO_2CO ~ Ph, $Pd_2(dba)_3$, ttmpp, THF, 60°, 3 h	 (94)	102
	4-PhC_6H_4ONf, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 100°, 1 h	 (89)	105
	 C_5H_{11}, OCO_2Et, $Pd_2(dba)_3$, ttmpp, THF, 60°, 3 h	 **I** +  **II** **I + II** (80), **I**:**II** = 97:3, **I** (*E*):(*Z*) = 88:12	102
	 EtO_2CO ~ TMS, $Pd_2(dba)_3$, ttmpp, THF, 60°, 3 h	 (46), (*E*):(*Z*) = 95:5	102

ArOTf, Pd(PPh$_3$)$_4$, Cs_2CO_3, MeCN, 100°



I

Ar	Time (h)	
Ph	0.5	(97)
4-$O_2NC_6H_4$	1	(94)
4-$MeOC_6H_4$	1	(98)
3,4,5-(MeO)$_3C_6H_4$	1	(98)
	2	(35)
	1	(91)
	1	(80)
4-$PhCOC_6H_4$	1	(99)

105, 106

ArCl, Pd_2(dba)$_3$, XPhos, Cs_2CO_3, MeCN, 120°

I

Ar	Time (h)	
2-pyridyl	3	(83)
3-pyridyl	2	(80)
Ph	3.5	(90)
4-MeC_6H_4	5.5	(48)
2-MeC_6H_4	5.5	(40)
3-$CF_3C_6H_4$	1.5	(85)
4-$MeOC_6H_4$	12	(65)
3-$MeOC_6H_4$	3	(88)
3-$MeCOC_6H_4$	2	(94)
3-$MeO_2CC_6H_4$	3	(84)

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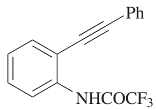
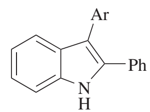
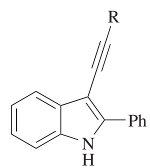
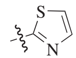
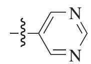
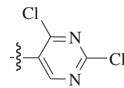
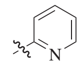
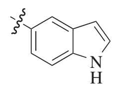
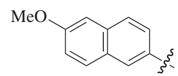
TABLE 3D. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16} 	ArBr, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 100°		105, 106
	Br—≡—R, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 60°	 **I**	108

Ar	Time (h)	
	2	(70)
	5	(85)
	5	(70)
	2	(94)
	5	(56)

Ar	Time (h)	
Ph	0.5	(98)
$3\text{-}FC_6H_4$	0.5	(97)
$4\text{-}O_2NC_6H_4$	1	(98)
$4\text{-}MeC_6H_4$	1	(98)
$3\text{-}MeC_6H_4$	1	(96)
$2\text{-}MeC_6H_4$	1	(98)
$3\text{-}CF_3C_6H_4$	0.5	(88)
$4\text{-}MeOC_6H_4$	0.25	(86)
$3\text{-}MeOC_6H_4$	0.5	(99)
$3\text{-}NCC_6H_4$	0.5	(90)
$4\text{-}NCC_6H_4$	0.5	(84)
$3\text{-}OHCC_6H_4$	0.5	(94)
$4\text{-}OHCC_6H_4$	1	(98)
$3,5\text{-}Me_2C_6H_3$	0.5	(98)
$4\text{-}MeCOC_6H_4$	0.5	(91)
$4\text{-}t\text{-}BuC_6H_4$	0.5	(98)
$4\text{-}PhC_6H_4$	1	(98)

R	Time (h)	
CMe_2OH	8	(50)
Ph	6	(76)
$4\text{-}O_2NC_6H_4$	8	(58)
$4\text{-}MeOC_6H_4$	55	(57)
$4\text{-}MeCOC_6H_4$	7	(65)
2-quinolinyl	48	(52)
	22	(63)

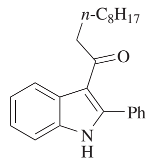
$Br-\equiv-R$,
$Pd(PPh_3)_4$, K_2CO_3,
MeCN, 60°

I

R	Time (h)	
CMe_2OH	30	(62)
Ph	16	(78)
4-$O_2NC_6H_4$	6	(66)
4-$CHOC_6H_4$	16	(86)
3-O_2N-4-MeC_6H_3	4	(81)
4-$MeCOC_6H_4$	9	(50)
n-C_8H_{17}	30	(40)
2-quinolyl	16	(45)

108

1. $Br-\equiv-n$-C_8H_{17},
$Pd_2(dba)_3$, $HP(t\text{-}Bu)_3BF_4$,
Cs_2CO_3, MeCN, 60°, 6 h
2. TsOH, MeOH/Me_2CO, rt, 2 h



(57)

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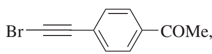
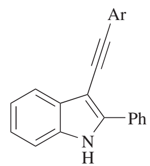


$Pd(PPh_3)_4$, K_2CO_3,
MeCN, 60°, 5 h



Ar = 4-$MeCOC_6H_4$
(56)

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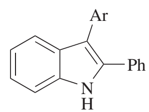
ArI, supported Pd nanoparticles,
K_2CO_3, MeCN, 110°



Ar	Time (h)		[f]
Ph	9	(82)	—
4-ClC_6H_4	5	(96)	(92, 83)
4-$O_2NC_6H_4$	4	(90)	—
4-NCC_6H_4	4	(84)	(92, 90, 86)
3-MeC_6H_4	40	(77)	—
4-$MeOC_6H_4$	48	(70)	—
3-$CF_3C_6H_4$	2	(91)	(90, 86, 87)
4-$MeCOC_6H_4$	2	(89)	(91, 87)

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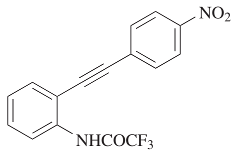
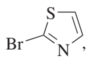
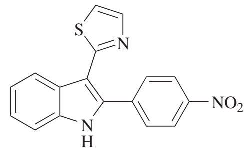
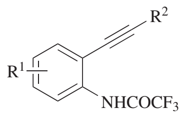
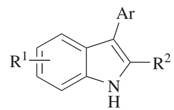
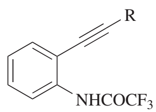
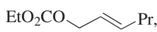
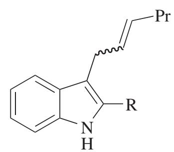
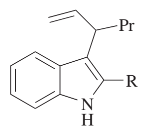
TABLE 3D. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16} 	, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 100°, 2 h	 (40)	105
$C_{16–18}$ 	ArN_2BF_4, $Pd(PPh_3)_4$, K_2CO_3, Bu_4NI, MeCN (anhyd), 60°, 1–5.5 h		374

R^1	R^2	Ar	
5-F	Ph	$4\text{-}NCC_6H_4$	(71)
5-F	Ph	$4\text{-}MeC_6H_4$	(71)
5-Cl	Ph	$4\text{-}MeCOC_6H_4$	(74)
5-Cl	$4\text{-}MeC_6H_4$	$2\text{-}Me\text{-}4\text{-}MeOC_6H_3$	(66)
5-MeCO	Ph	Ph	(68)
5-Cl	$4\text{-}MeCOC_6H_4$	$4\text{-}O_2NC_6H_4$	(75)
5,7-Me_2	Ph	$4\text{-}FC_6H_4$	(70)
5,7-Me_2	Ph	$4\text{-}MeOC_6H_4$	(50)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
$C_{16–21}$ 	 EtO_2CO, Pr, $Pd_2(dba)_3$, ttmpp, THF, 60°	 **I** +  **II**	102

R	Time (h)	**I + II**	**I**:**II**	**I** (*E*):(*Z*)
Ph	3	(76)	97:3	87:13
$2\text{-}BrC_6H_4$	10	(34)	100	91:9
$4\text{-}MeOC_6H$	4	(72)	97:3	87:13
$4\text{-}MeCOC_6H_4$	8	(67)	>99:1	82:18
$4\text{-}THPOC_6H_4$	2	(96)	100	82:18

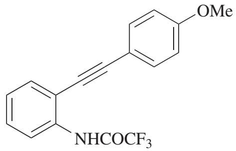
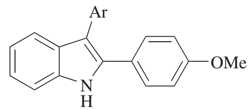
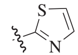
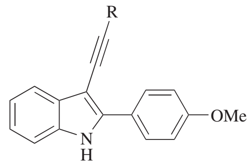
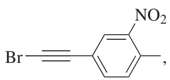
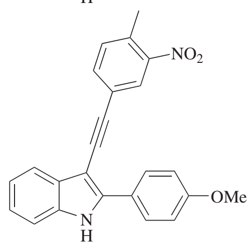
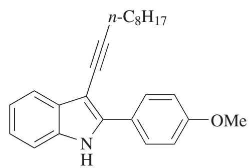
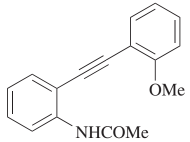
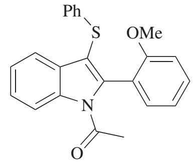
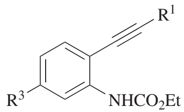
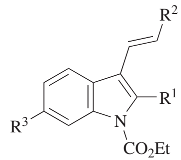
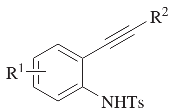
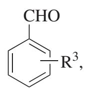
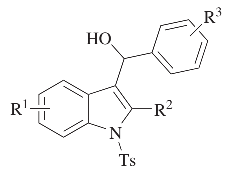
C_{17} 	ArBr, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 100°	 **I**	Ar / Time (h)  / 1 / (87) 4-t-BuC_6H_4 / 2 / (80)	105, 106
	ArCl, $Pd_2(dba)_3$, XPhos, Cs_2CO_3, MeCN, 120°	**I**	Ar / Time (h) Ph / 3 / (60) 4-$MeOC_6H_4$ / 5 / (40) 4-$MeCOC_6H_4$ / 5 / (73)	107
	Br—C≡C—R, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 60°		R / Time (h) Ph / 8 / (75) 4-$MeCOC_6H_4$ / 6 / (73)	108
	, $Pd(PPh_3)_4$, K_2CO_3, MeCN, 60°, 3 h		(85)	108
	Br—C≡C—n-C_8H_{17}, $Pd_2(dba)_3$, $HP(t\text{-}Bu)_3BF_4$, Cs_2CO_3, MeCN, 60°, 2 h		(43)	108

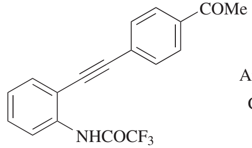
TABLE 3D. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{17} 	PhS—SPh, $PdCl_2$, DMSO, 80°, 24 h	 (35)	371
C_{17-18} 	CH_2=CHR^2, $PdCl_2$, $CuCl_2$•H_2O, Bu_4NF, THF, reflux		131
C_{17-22} 	 Pd(bpy)$(H_2O)_2(OTf)_2$, 1,4-dioxane, 60°, overnight		375

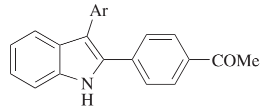
R^1	R^2	R^3	Time (h)	
Ph	CN	Cl	4.5	(31)
Ph	CO_2Me	Cl	3	(66)
Ph	Bu	OMe	8	(42)
Ph	CO_2Me	CN	22	(66)

R^1	R^2	R^3	
H	$MeOCH_2$	$4\text{-}O_2N$	traces
H	Ph	$4\text{-}O_2N$	(75)
H	Ph	$3\text{-}O_2N$	(63)
H	Ph	$5\text{-Cl-}4\text{-}O_2N$	(93)
H	Ph	H	(—)[a]
5-F	Ph	$4\text{-}O_2N$	(64)
5-Cl	Ph	$4\text{-}O_2N$	(62)
6-Cl	Ph	$4\text{-}O_2N$	(49)
H	4-BrC_6H_4	$4\text{-}O_2N$	(62)
H	$n\text{-}C_6H_{13}$	$4\text{-}O_2N$	traces
H	Ph	4-NC	traces
H	Ph	4-MeCO	traces
5-Me	Ph	$4\text{-}O_2N$	(65)
H	4-MeC_6H_4	$4\text{-}O_2N$	(78)

C_{18}



ArCl, $Pd_2(dba)_3$, XPhos, Cs_2CO_3, MeCN, 120°



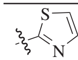
I

Ar	Time (h)	
Ph	5.5	(50)
3-$MeOC_6H_4$	2.5	(56)
4-$MeCOC_6H_4$	1	(87)

107

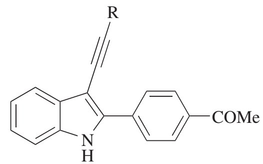
ArBr, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 100°

I

Ar	Time (h)	
	2	(74)
4-*t*-BuC_6H_4	1	(98)

105, 106

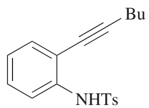
Br—≡—R, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 60°



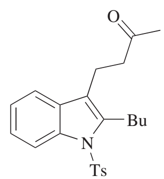
R	Time (h)	
Ph	16	(52)
4-$MeCOC_6H_4$	8	(59)

108

C_{19}



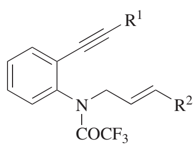
methyl vinyl ketone, $Pd(OAc)_2$, LiBr, THF, rt, 2 d



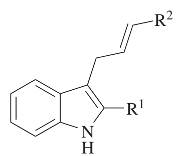
(76)

103

$C_{19–27}$



$Pd(PPh_3)_4$, K_2CO_3, MeCN, 90°



R^1	R^2	Time (h)	
Ph	H	1	(91)
$CH_2NHCOEt$	Ph	1	(76)
Ph	Ph	1.5	(91)
Ph	4-$MeOC_6H_4$	1.5	(84)
Ph	4-$MeCOC_6H_4$	2	(77)

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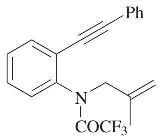
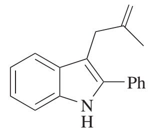
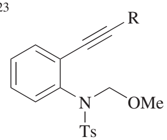
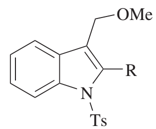
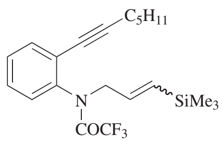
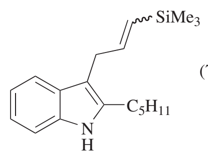
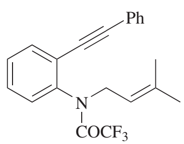
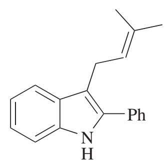
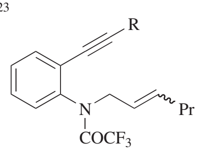
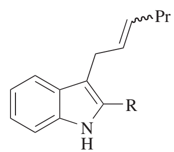
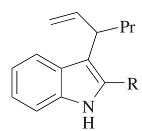
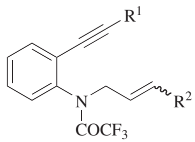
TABLE 3D. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLANILIDES (*Continued*)

2-Alkynylanilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20} 	$Pd(PPh_3)_4$, K_2CO_3, MeCN, 90°, 3 h	 (95)	102
$C_{20–23}$ 	$PdBr_2$, toluene, 80°	 R: Pr (33); Ph (33)	140
C_{21}  (*E*):(*Z*) = 89:11	$Pd_2(dba)_3$, ttmpp, DME, 100°, 4 h	 (75), (*E*):(*Z*) = 88:12	102
	$Pd(PPh_3)_4$, K_2CO_3, MeCN, 90°, 24 h	 (44)	102
$C_{21–23}$ 	$Pd(PPh_3)_4$, K_2CO_3, MeCN, 90°	 **I** +  **II**	102

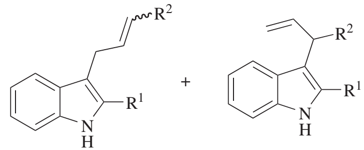
(*E*):(*Z*) = 97:3
(*E*):(*Z*) = 92:8
(*E*):(*Z*) = 92:8
(*E*):(*Z*) = 92:8

R	Time (h)	**I + II**	**I:II**	**I** (*E*):(*Z*)
n-C_5H_{11}	8	(66)	81:18	81:19
CH_2OTHP	5	(71)	88:12	88:12
4-$MeOC_6H_4$	2	(81)	65:35	88:12
4-$MeOC_6H_4$	4	(83)	75:25	78:22

$C_{21–24}$



$Pd(PPh_3)_4$, K_2CO_3, DME, 100°



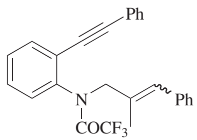
I **II**

102

(*E*):(*Z*) = 97:3
(*E*):(*Z*) = 93:7
(*E*):(*Z*) = 92:8

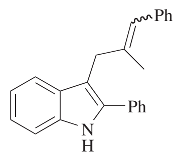
R^1	R^2	Time (h)	**I + II**	**I:II**	**I** (*E*):(*Z*)
n-C_5H_{11}	Pr	24	(69)	97:3	85:15
CH_2OTHP	Pr	12	(76)	96:4	82:18
CH_2OTHP	C_5H_{11}	12	(69)	97:3	83:17

C_{26}



(*E*):(*Z*) = 98:2

$Pd(PPh_3)_4$, K_2CO_3, MeCN, 90°, 5.5 h



(78), (*E*):(*Z*) = 67:33

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[a] The reaction time was 40 hours.

[b] The reaction was carried out in a stainless steel bomb, under 7 atm of CO, in anhydrous MeCN.

[c] The product was a mixture of isomers, (*E*):(*Z*) = 77:23.

[d] The product was a mixture of isomers.

[e] The starting material was recovered.

[f] Yields are of successive runs carried out with the recovered catalyst.

TABLE 3E. 2,3-DISUBSTITUTED INDOLES FROM 2-HALO-*N*-ALKYNYLANILIDES AND 2-HALO-*N*-ALKYLANILINES

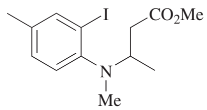
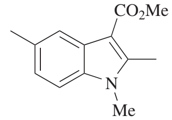
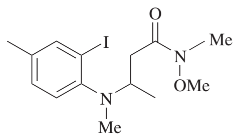
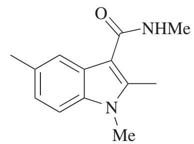
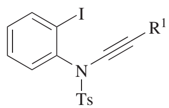
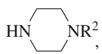
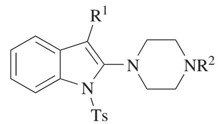
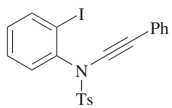
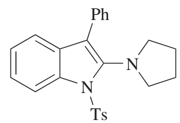
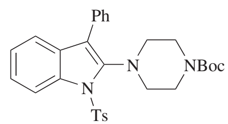
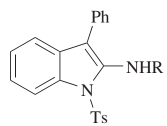
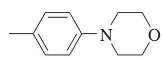
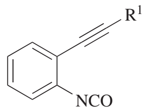
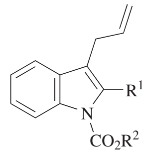
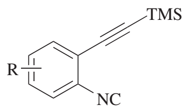
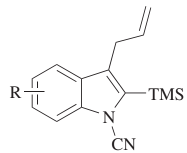
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13} 	$Pd(PPh_3)_4$, K_3PO_4, DMF, 90°, 70 h	 (42)	351, 352
C_{14} 	$Pd(PPh_3)_4$, phenol, *t*-BuOK, THF, reflux, 12 h	 (58)	351, 352
$C_{18–20}$ 	, $PdCl_2(PPh_3)_2$, K_2CO_3, THF, 80°, 5–24 h	 R^1 / R^2: TMS / Boc (83); TMS / Me (95); *n*-C_5H_{11} / Ph (97)	29
C_{21} 	, $PdCl_2(PPh_3)_2$, K_2CO_3, THF, 80°	 (94)	29
	, $PdCl_2(PPh_3)_2$, K_2CO_3, THF, 80°, 2–24 h	 (95)	29
	RNH_2, $PdCl_2(PPh_3)_2$, K_2CO_3, THF, 80°, 2–24 h	 R: $CH_2CH{=}CH_2$ (98); *c*-C_3H_5 (94);  (77)	29

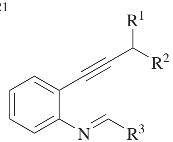
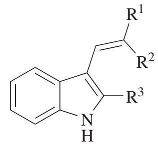
TABLE 3F. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLISOCYANOBENZENES, -ISOCYANATOBENZENES, AND -*N*-ALKYLIDENEANILINES

Alkyne	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-16} 	CH_2=$CHCH_2OCO_2R^2$, $Pd(PPh_3)_4$, CuCl, THF, 100°		28
C_{12-18} 	CH_2=$CHCH_2OCO_2Me$, $Pd_2(dba)_3$•$CHCl_3$, (2-furyl)$_3$P, TMSN$_3$, rt, 10 min; 100°, 1 h		26

R^1	R^2	Time (h)	
Pr	Me	1	(81)
Pr	*i*-Pr	1	(69)
Pr	*t*-Bu	1	(72)
Pr	Ph	1	(86)
Pr	Bn	1	(83)
c-C_5H_9	Me	3	(71)
Ph	Me	2	(62)
4-$MeOC_6H_4$	Me	6	(62)
4-$CF_3C_6H_4$	Me	7	(65)

R	Solvent		R	Solvent	
H	octane	(59)	7-MeO	octane	(63)
5-F	THF	(56)	5-MeS	octane	(67)
5-Cl	THF	(54)	5-CF_3	octane	(65)
6-Cl	octane	(47)	5-CN	THF	(30)
5-Br	octane	(47)	5-CO_2Me	THF	(53)
5-NO_2	THF	(34)	5-COMe	THF	(37)
6-NO_2	THF	(59)	6-COMe	THF	(45)
5-Me	octane	(68)	5-*i*-Pr	octane	(77)
6-Me	octane	(65)	5-C≡C-*t*-Bu	octane	(58)
4-MeO	octane	(62)	6-C≡C-*t*-Bu	THF	(61)
5-MeO	octane	(69)	5-Ph-N=N	octane	(45)
6-MeO	octane	(57)			

TABLE 3F. 2,3-DISUBSTITUTED INDOLES FROM 2-ALKYNYLISOCYANOBENZENES, -ISOCYANATOBENZENES, AND -*N*-ALKYLIDENEANILINES (*Continued*)

Alkyne	Conditions	Product(s) and Yield(s) (%)					Refs.
			R^1	R^2	R^3		
C_{16-21} 	$Pd(OAc)_2$, Bu_3P, 1,4-dioxane, 100°		Et	H	2-thienyl	(70)	33
			Et	H	5-methyl-2-furyl	(63)	
			Et	H	4-pyridyl	(64)	
			Et	H	Ph	(58)	
			Et	H	$4\text{-}O_2NC_6H_4$	(70)	
			CH_2OMOM	H	$4\text{-}O_2NC_6H_4$	(55)	
			—$(CH_2)_5$—		$4\text{-}O_2NC_6H_4$	(71)[a]	
			OTHP	H	$4\text{-}O_2NC_6H_4$	(56)	
			$(CH_2)_2CO_2Et$	H	$4\text{-}O_2NC_6H_4$	(59)	

[a] The reaction was run at 80°.

TABLE 3G. 2,3-DISUBSTITUTED INDOLES FROM *N*-(2-HALOPHENYL)ALLENAMIDES

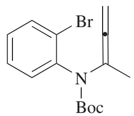
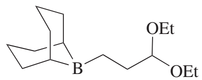
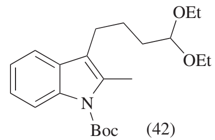
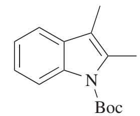
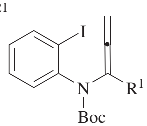
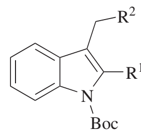
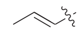
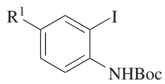
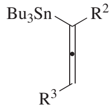
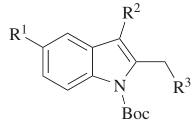
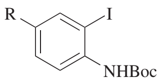
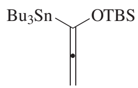
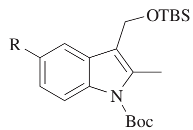
N-(2-Halophenyl)allenamide	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15} 		$PdCl_2$(dppf), aq Cs_2CO_3 (3 M), DMF, 70°	 (42) +  (56)	353
C_{15-21} 	$(HO)_2BR^2$	$Pd_2(dba)_3$, aq Cs_2CO_3 (3 M), EtOH, 80°	 R^1 / R^2 Me / Ph (81) $Me_2(HO)Si$ / Ph (61) TMS / Ph (71) Bn / Ph (98) Bn /  (84)	353

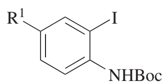
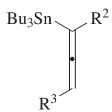
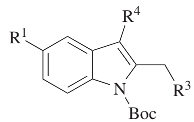
TABLE 3H. 2,3-DISUBSTITUTED INDOLES FROM 2-ALLENYLANILIDES PREPARED IN SITU

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11} 		$Pd_2(dba)_3$, P(2-furyl)$_3$, Bu_4NCl, CuI, DMF		377

R^1	R^2	R^3	Temp	Time (h)	
H	CH_2OPMB	H	rt	5.5	(65)
H	$(CH_2)_2OTBS$	H	rt	4	(57)
H	n-C_6H_{13}	H	rt	0.5	(46)
O_2N	$(CH_2)_2OTBS$	Me	50°	6	(71)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11-12} 		$Pd_2(dba)_3$, P(2-furyl)$_3$, Bu_4NCl, CuI, DMF		377

R	Temp	Time (h)	[a]
O_2N	50°	3	(72)
MeO	rt	4	(65)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
		1. $Pd_2(dba)_3$, P(2-furyl)$_3$, Bu_4NCl, CuI, DMF, temp 2. Bu_4NF, 0°		377

R^1	R^2	R^3	R^4	Temp	
H	CH_2OTBS	Me	CH_2OH	rt	(70)
H	CH_2OTBS	Pr	CH_2OH	rt	(69)
H	n-C_7H_{15}	Me	n-C_7H_{15}	rt	(56)
H	H	n-C_5H_{11}	H	rt	(54)
MeO	CH_2OPMB	Me	CH_2OH	50°	(62)

[a] The coupling products were isolated in variable amount.

TABLE 4A. 2,3-UNSUBSTITUTED INDOLES FROM 2-VINYLANILINES AND -ANILIDES

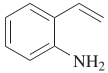
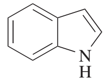
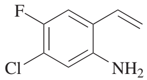
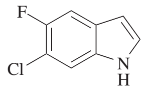
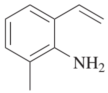
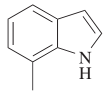
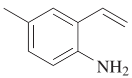
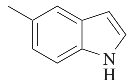
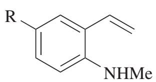
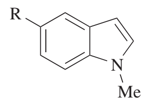
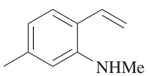
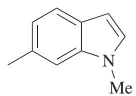
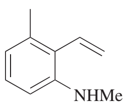
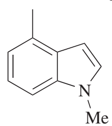
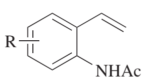
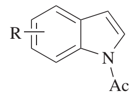
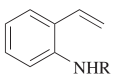
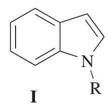
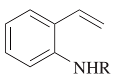
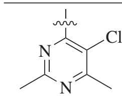
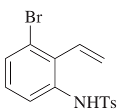
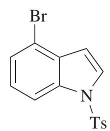
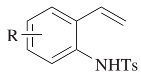
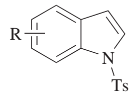
	2-Vinylaniline or -anilide	Conditions	Product(s) and Yield(s) (%)		Refs.
C_8		$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, reflux, 18 h		(74)	142
		$PdCl_2$, LiCl, benzoquinone, THF, reflux, 16 h		(50)	146
C_9		$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, reflux, 10 h		(82)	148
		$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, reflux, 10 h		(83)	148
C_{9-13}		$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, reflux, 18 h		R: H (94); Cl (83); MeO (85); *i*-Pr (93); *t*-Bu (87)	148
C_{10}		$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, reflux, 18 h		(81)	148
		$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, reflux, 18 h		(79)	148

TABLE 4A. 2,3-UNSUBSTITUTED INDOLES FROM 2-VINYLANILINES AND -ANILIDES (*Continued*)

2-Vinylaniline or -anilide	Conditions	Product(s) and Yield(s) (%)	Refs.
$C_{10–12}$ 	$PdCl_2$, CuCl, O_2, 1,3-propanediol, DME, 50–60°, 24 h	 R: H (61); 6-Cl (64); 4-Me (49); 5-Me (55); 6-Me (70); 5-OMe (54); 6-OMe (35); 4-CO_2Me (67); 5-CO_2Me (65); 6-CO_2Me (57); 7-CO_2Me (62)	147
$C_{12–15}$ 	$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, 18 h, reflux	 **I** R: Bu (53); Bn (80)	148
$C_{14–15}$ 	$Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, DMF, 100°, 12 h	**I** R:  (91); 2-ClC_6H_4 (98); 2-Cl-4-MeC_6H_3 (87)	378
C_{15} 	$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, 18 h, reflux	 (77–80)	143, 144

C_{15-20}			
	$PdCl_2(MeCN)_2$, LiCl, benzoquinone, DMF, 100°		145

R	
H	(48)
5-Cl	(78)
4-Me	(87)
4-OMe	(68)
4-OTf	(88)
6-CH_2=CH	(47)
4-Ac	(58)
4-CO_2Me	(49)
4-CH$(OAc)_2$	(60)

TABLE 4B. 2,3-UNSUBSTITUTED INDOLES FROM 2-NITROSTYRENES

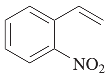
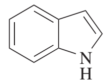
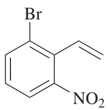
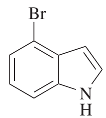
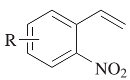
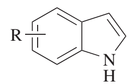
	2-Nitrostyrene	Conditions	Product(s) and Yield(s) (%)				Refs.
C_8		CO (20 atm), $PdCl_2(PPh_3)_2$, $SnCl_2$, 1,4-dioxane, 100°, 16 h		(50)			154, 155
		CO (4 atm), $Pd(OAc)_2$, PPh_3, Et_3N, DMF, MeOH, 60°		(63)			156
C_{8-10}		CO (4 atm), $Pd(OAc)_2$, PPh_3, MeCN, 70°		R	Time (h)		156
				H	15	(87)	
				4-OH	12	(96)	
				4-NO_2	26	(89)	
				5-Me	24	(51)	
				4-OMe	20	(89)	
				5-OMe	19	(63)	
				6-OMe	21	(40)	
				4-OTf	48	(40)	
				4-CO_2Me	23	(100)	
				5-CO_2Me	120	(47)	
				6-CO_2Me	21	(78)	
				7-CO_2Me	27	(71)	

TABLE 5A. 2-SUBSTITUTED INDOLES FROM 2-ALLYLANILINES AND -ANILIDES

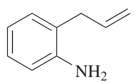
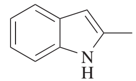
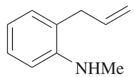
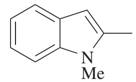
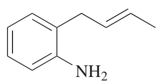
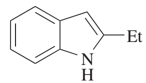
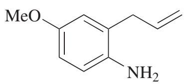
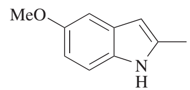
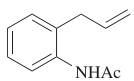
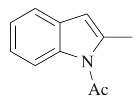
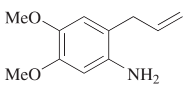
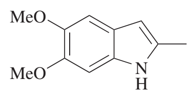
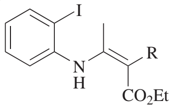
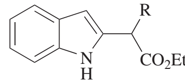
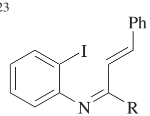
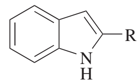
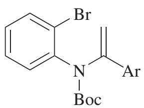
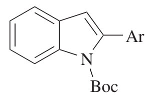
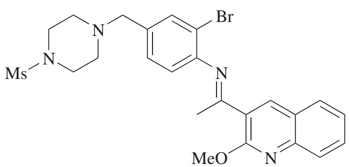
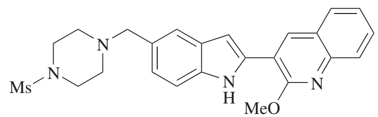
2-Allylaniline or -anilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9			
	$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, reflux, 5 h	 (86)	142
C_{10}			
	$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, reflux, 18 h	 (89)	142
	$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, reflux, 18 h	 (79)	142
	$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, rt, 18 h	 (32)	142
C_{11}			
	$PdCl_2(MeCN)_2$, $Cu(OAc)_2$, Na_2CO_3, THF, reflux, 60 h	 (71)	142
	$PdCl_2(MeCN)_2$, LiCl, benzoquinone, THF, rt, 18 h	 (48)	142

TABLE 5B. 2-SUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES

2-Haloarylenamine or -imine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15-19}			
	$Pd(PPh_3)_4$, Ag_3PO_4, DMSO, 100°	 R / Time (h): Pr 3.0 (67); Bn 2.5 (82)	379
C_{15-23}			
	$Pd(OAc)_2$, PPh_3, *t*-BuOK, DMSO, 120°, 12–16 h	 R: H (71); 2-thienyl (71); Ph (63); 4-BrC_6H_4 (65); 4-ClC_6H_4 (75); 4-FC_6H_4 (63); 4-$O_2NC_6H_4$ (51); 4-MeC_6H_4 (67); 4-$CF_3C_6H_4$ (52); 4-$MeOCC_6H_4$ (70)	380
C_{17-20}			
	$Pd(PPh_3)_4$, Et_3N, DMF, 100°, 20 h	 Ar: 2-furyl (54) (44)[a]; 2-thienyl (63) (31)[a]; 4-ClC_6H_4 (59); 2-MeC_6H_4 (91); 4-$MeOC_6H_4$ (71)	162
C_{24}			
	$Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, DMF, reflux	 (55)	160

[a] These yields refer to the corresponding *N*-deprotected indole.

TABLE 5C. 2-SUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES PREPARED IN SITU

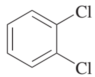
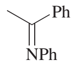
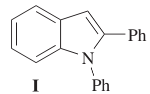
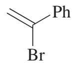
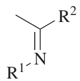
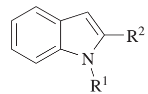
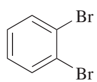
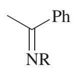
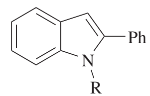
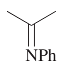
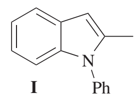
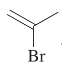
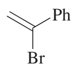
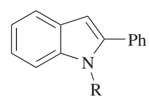
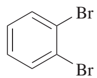
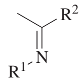
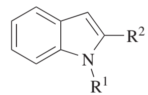
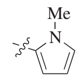
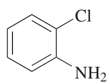
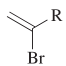
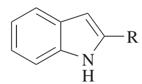
Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 **I** (80)	196
	 , $PhNH_2$	$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 72 h	**I** (77)	196
		$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 R^1 / R^2 *t*-Bu / *i*-Pr (55) Ph / Ph (80) Ph / (*E*)-CH=CHPh (75)	197
		$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 R *t*-Bu (72) Ph (86) 2-ClC_6H_4 (77) 4-$MeOC_6H_4$ (80) Bn (56)	196
		$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 **I** (71)	196
	 , $PhNH_2$	$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 50°, 3 h; 90°, 14 h	**I** (68)	196
	 , RNH_2	$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 R Ph (76) Bn (65)	196

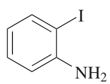
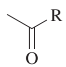
TABLE 5C. 2-SUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES PREPARED IN SITU (*Continued*)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h		197

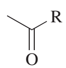
R^1	R^2		R^1	R^2	
Ph	Me	(77)	*c*-C_6H_{11}	Ph	(80)
t-Bu	CH=CMe_2	(78)	Ph	Ph	(86)
Bu	Ph	(52)	2-ClC_6H_4	Ph	(77)
t-Bu	Ph	(72)	2-$MeOC_6H_4$	Ph	(80)
t-Bu	1-cyclohexenyl	(63)	Bn	Ph	(56)
			Ph	(*E*)-CH=CHPh	(83)
Ph		(82)			

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd_2(dba)_3$, XPhos, *t*-BuONa, toluene, 110°, 20 h	 **I**	165

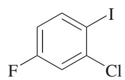
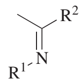
R	
Ph	(65)
4-MeC_6H_{14}	(58)
n-C_8H_{17}	(60)
CH_2OBn	(55)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$, additive, DABCO, DMF, 105°, 3–12 h	**I**	162

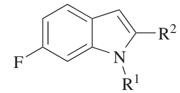
R	Additive	
CO_2H	—	(82)
TMS	$MgSO_4$	(64)[a]

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(dba)_2$, dipf, *t*-BuONa, 1,4-dioxane, reflux, 20 h	**I**	381

R		R	
MeCH(Me)	(30)	2-MeC_6H_4	(66)
MeCH(Me)CH_2	(31)	3-MeC_6H_4	(68)
2-thienyl	(51)	4-MeC_6H_4	(69)
Me$(CH_2)_4$	(36)	4-$MeOC_6H_4$	(60)
Ph	(71)	3-$CF_3C_6H_4$	(75)
4-FC_6H_4	(68)	2-Np	(74)

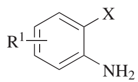
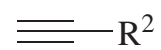
 

$Pd_2(dba)_3$, XPhos, t-BuONa, 1,4-dioxane, 110°, 14 h

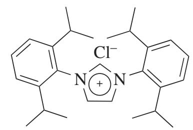


R¹	R²		Refs.
t-Bu	n-C_5H_{11}	(60)	197
t-Bu	Ph	(83)	
c-C_6H_{11}	Ph	(72)	
Ph	Ph	(83)	

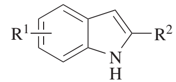
C_{6-7}

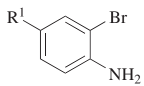
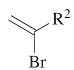
1. $Ru_3(CO)_{12}$, PF_6NH_4, toluene, 105°, 18 h
2. $Pd(OAc)_2$, **L2**, t-BuOK, 105°, 24 h



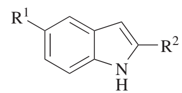
L2



R¹	X	R²		Refs.
H	Cl	Ph	(60)	382
H	Cl	1-cyclohexenyl	(49)	
H	Br	Ph	(78)	
5-Cl	Br	Ph	(87)	
6-CF_3	Cl	1-cyclohexenyl	(35)	
5-Me	Br	Ph	(75)	

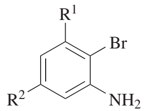
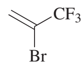
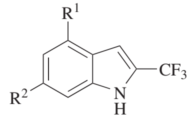
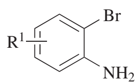
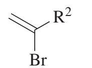
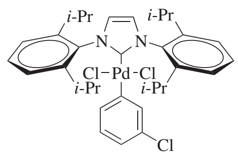
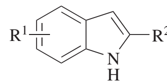
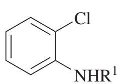
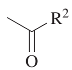
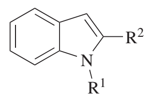
 

$Pd_2(dba)_3$, DavePhos, t-BuONa, toluene, 100°, 20 h



R¹	R²		Refs.
H	Ph	(64)	165
H	4-MeC_6H_4	(62)	
H	n-C_8H_{17}	(63)	
H	CH_2OBn	(61)	
Cl	Ph	(55)	
Cl	n-C_8H_{17}	(53)	
Me	Ph	(62)	
Me	4-MeC_6H_4	(61)	
Me	n-C_8H_{17}	(60)	
Me	CH_2OBn	(59)	

TABLE 5C. 2-SUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES PREPARED IN SITU (*Continued*)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{6-8} 		$Pd(OAc)_2$, XPhos, Cs_2CO_3, toluene, 125°, 15 h		383
C_{6-9} 		Pd-PEPPSI-IP, Pd-coated 1200 mm capillary, *t*-BuONa, toluene, 75 atm back pressure, 15 µL min^{-1} flow rate, 215°  Pd-PEPPSI-IP		206
C_{6-13} 		$Pd[P(t\text{-}Bu)_3]_2$, K_3PO_4, $MgSO_4$, DMA		164

Products for C_{6-8} (ref. 383):

R^1	R^2	[b]
H	F	(84)
F	F	(66)
H	Cl	(44)
H	Me	(64)
H	CF_3	(81)
H	CF_3O	(66)
Me	Me	(17)

Products for C_{6-9} (ref. 206):

R^1	R^2		R^1	R^2	
H	Me	(72)	5,7-F_2	Ph	(72)
H	Et	(81)	5-Me	Me	(82)
H	Ph	(68)	5-Me	Et	(72)
5-F	Me	(73)	5-Me	Ph	(70)
5-F	Et	(76)	5,7-Me_2	Me	(85)
5-F	Ph	(62)	5,7-Me_2	Et	(72)
5-Cl	Me	(62)	5,7-Me_2	Ph	(82)
5-Cl	Et	(70)	5-*i*-Pr	Me	(79)
5-Cl	Ph	(82)	5-*i*-Pr	Et	(83)
5,7-F_2	Me	(65)	5-*i*-Pr	Ph	(80)
5,7-F_2	Et	(64)			

Products for C_{6-13} (ref. 164):

R^1	R^2	Time (h)	Temp (°)	
H	4-$MeOC_6H_4$	21	140	(80)
H	TMS	14	125	(80)
Me	CO_2H	14	140	(98)
4-$MeOC_6H_4$	Ph	14	140	(78)

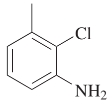
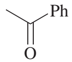
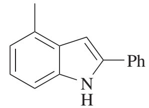
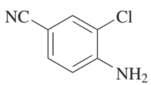
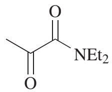
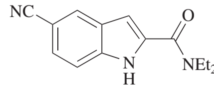
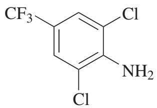
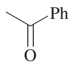
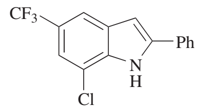
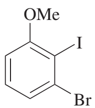
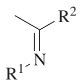
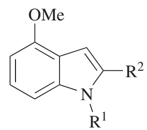
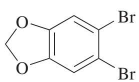
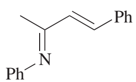
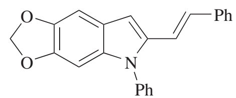
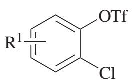
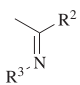
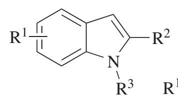
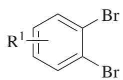
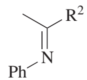
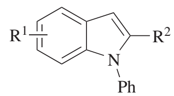
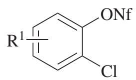
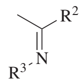
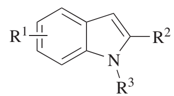
C_7			$Pd[P(t\text{-}Bu)_3]_2$, K_3PO_4, $MgSO_4$, DMA, 90°, 2 h	 (81)	164
			$Pd[P(t\text{-}Bu)_3]_2$, K_3PO_4, $MgSO_4$, DMA, 140°, 14 h	 (65)	164
			$Pd[P(t\text{-}Bu)_3]_2$, K_3PO_4, $MgSO_4$, DMA, 140°, 14 h	 (65)	164
			$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 R^1 / R^2 Ph / Me (45) *t*-Bu / Ph (76) Ph / Ph (64)	197
			$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 (71)	197
$C_{7–8}$			Pd_2dba_3, XPhos, *t*-BuOLi, 1,4-dioxane, 110°, 14–24 h	 R^1 / R^2 / R^3 / Addn Rate (mL/h)[c] 6-F / Ph / Ph / 0.1 (65) 5-Me / Me / Ph / 0.1 (45) 5-Me / Ph / *t*-Bu / 0.1 (70) 5-Me / Ph / Ph / 0.16 (78) 6-MeO / Ph / Ph / 0.12 (36)	197

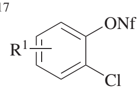
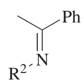
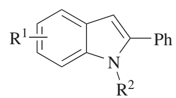
TABLE 5C. 2-SUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES PREPARED IN SITU (*Continued*)

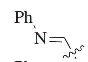
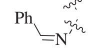
Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{7-13} 		$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h		197

R^1	R^2	
5-MeO	(*E*)-CH=CHPh	(74)
6-BnO	Ph	(57)
6-BnO	(*E*)-CH=CHPh	(60)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10-16} 		$Pd_2(dba)_3$, XPhos, *t*-BuOLi, 1,4-dioxane, addition rate 0.1 mL/h,[c] 110°, 10–20 h		197

R^1	R^2	R^3	
6-F	2-*N*-Me-pyrrolyl	Ph	(78)
6-F	4-pyridyl	Ph	(83)
5-Me	$(CH_2)_4Me$	*t*-Bu	(65)
6-CF_3	4-pyridyl	Ph	(66)
5-Me	4-pyridyl	Ph	(88)
5-Me	2-*N*-Me-pyrrolyl	Ph	(88)
6-Ph	$CH=CMe_2$	*t*-Bu	(61)
6-Ph	4-pyridyl	Ph	(87)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10-17} 		$Pd_2(dba)_3$, XPhos, *t*-BuOLi, 1,4-dioxane, addition rate 0.1 mL/h,[c] 110°, 10–20 h		197

R^1	R^2		R^1	R^2	
H	Ph	(92)	5-Me	4-$MeOC_6H_4$	(89)
6-F	Ph	(81)	6-MeO	4-$MeOC_6H_4$	(63)
6-F	4-$MeOC_6H_4$	(64)	4,6-Me_2	Ph	(64)
5-Me	*t*-Bu	(93)	6-*t*-BuO_2C	Ph	(62)
6-Me	*t*-Bu	(79)	6-Ph	*c*-C_6H_{11}	(75)
5-Me	Ph	(86)			
6-MeO	Ph	(80)		Ph	(80)
6-NC	Ph	(78)		Ph	(72)

[a] The number is the combined yield of the 2-silyl derivative and indole.

[b] The yield was determined by NMR spectroscopy.

[c] Refers to the addition rate of the halogenated arene.

TABLE 5D. 2-SUBSTITUTED INDOLES FROM 2-NITROSTYRENES

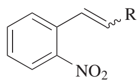
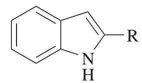
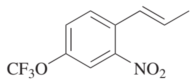
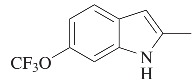
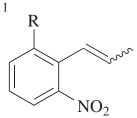
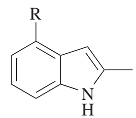
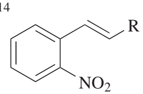
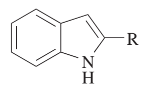
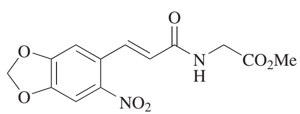
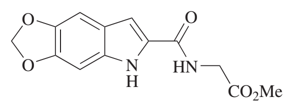
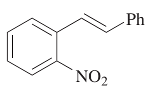
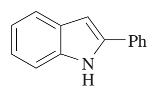
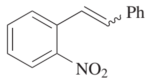
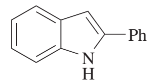
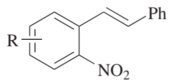
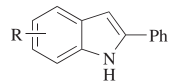
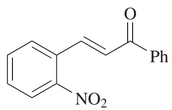
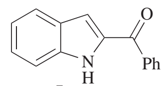
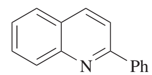
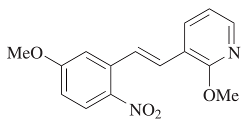
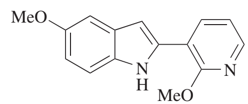
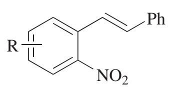
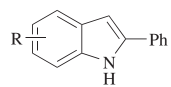
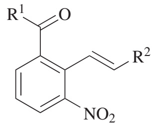
2-Nitrostyrene	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{9-14}  *trans*:*cis* = 50:50	$Pd(OAc)_2$, PPh_3, MeCN, CO (4 atm), 70°	 R / Time (h) Me / 24 / (96) Ph / 21 / (91)	156
C_{10} 	$Pd(OAc)_2$, phen, DMF, CO (1 atm), 80°, 16 h	 (84)[a]	161
C_{10-11} 	$Pd(OAc)_2$, MeCN, CO (4 atm), 70°	 R / Time (h) Me / 17 / (66) CH_2OMe / 46 / (76) CO_2Me / 24 / (90)	158
C_{10-14} 	$PdCl_2(PPh_3)_2$, $SnCl_2$, 1,4-dioxane, CO (20 atm), 100°, 16 h	 R CO_2Me (60) Ph (74)	154, 155
C_{13} 	$Pd(TFA)_2$, tmphen, DMF, CO (1 atm), 80°, 16 h	 (72)	161
C_{14} 	$Pd(OAc)_2$, PPh_3, MeCN, CO (4 atm), 70°, 18.5 h	 (100)	156

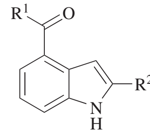
TABLE 5D. 2-SUBSTITUTED INDOLES FROM 2-NITROSTYRENES (*Continued*)

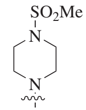
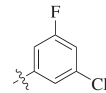
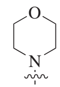
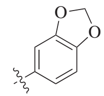
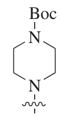
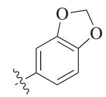
2-Nitrostyrene	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}  *trans*:*cis* = 50:50	$Pd(OAc)_2$, phen, DMF, 80°, 16 h	 (86)	161
C_{14-15} 	$Pd(OAc)_2$, phen, DMF, CO (1 atm), 80°, 16 h	 R: H (87); 5-Cl (96); 5-Me (89)	161
C_{15} 	$Pd(OAc)_2$, phen, DMF, CO (1 atm), 80°, 16 h	 **I** (84)	161
	$PdCl_2(PPh_3)_2$, $SnCl_2$, 1,4-dioxane, CO (20 atm), 100°, 16 h	**I** (52) +  (34)	154, 155
	$Pd(OAc)_2$, phen, DMF, CO (2 atm), 70°, 16 h	 (72)	161
C_{15-16} 	$Pd(TFA)_2$, tmphen, DMF, CO (1 atm), 80°, 16 h	 R: 7-OMe (18); 5-CO_2Me (98); 6-NMe_2 (61)	161

C$_{15-25}$



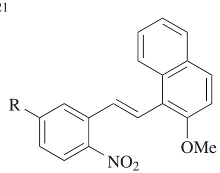
Pd(OAc)$_2$, phen, DMF, CO (2 atm), 80°, 16 h



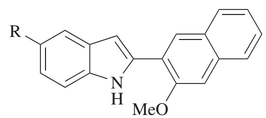
R^1	R^2	
NMe$_2$	2-furyl	(98)
N-pyrrolidino	4-FC$_6$H$_4$	(97)
		(98)
		(98)
		(99)

384

C$_{19-21}$



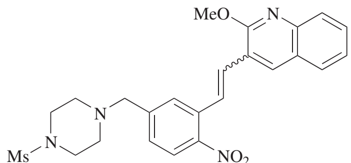
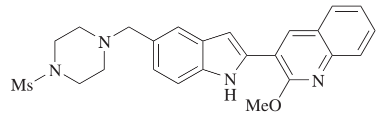
Cat, ligand, DMF, CO (1 atm), 80°, 16 h



R	Cat	Ligand	
Cl	Pd(OAc)$_2$	phen	(91)
CO$_2$Me	Pd(TFA)$_2$	tmphen	(78)

161

TABLE 5D. 2-SUBSTITUTED INDOLES FROM 2-NITROSTYRENES (*Continued*)

2-Nitrostyrene	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{24}  **I**	See table		160

I config.	Catalyst	Ligand	Solvent	CO pressure (atm)	Temp (°)	Time (h)	
(*E*)	$Pd(OAc)_2$	PPh_3	MeCN	4	70	15	(95)
(*E*)	$Pd(OAc)_2$	phen	DMF	1	70	14	(94)
(*E*)	$Pd(OCOCF_3)_2$	tmphen	DMF	1	80	—	(95)
(*E*)	$phen_2Pd(BF_4)_2$	—	DMF	1	70	—	(99)
(*E*)	$Pd(OCOCF_3)_2$	tmphen	DMF	1	70	—	(100)
(*E*)	$Pd(OAc)_2$	tmphen	DMF	1	70	—	(92)
(*Z*)	$Pd(OAc)_2$	PPh_3	MeCN	4	70	15	(92)

[a] The yield was calculated by HPLC analysis.

TABLE 6A. 3-SUBSTITUTED INDOLES FROM 2-HALO- AND 2-PSEUDOHALO-*N*-ALLYLANILINES AND -ANILIDES

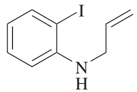
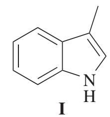
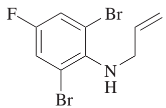
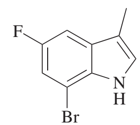
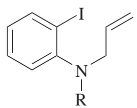
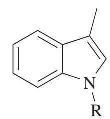
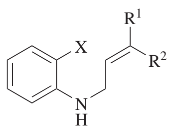
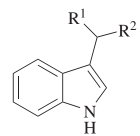
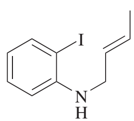
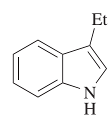
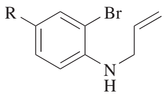
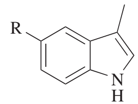
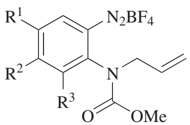
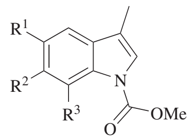
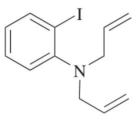
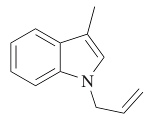
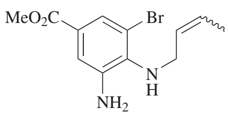
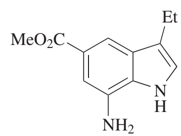
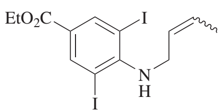
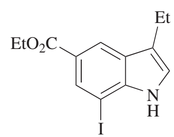
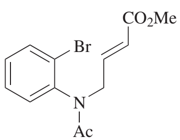
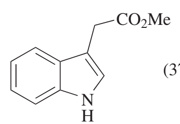
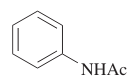
<table>
<tr><th>2-Halo-N-allylaniline or -anilide</th><th>Conditions</th><th>Product(s) and Yield(s) (%)</th><th>Refs.</th></tr>
<tr><td>C_9
</td><td>$Pd(OAc)_2$, TPTTS, Et_3N, $MeCN/H_2O$ (15:1), rt, 1.5 h</td><td> (97)
I</td><td>169</td></tr>
<tr><td></td><td>$Pd(OAc)_2$, $(C_6F_{13}CH_2CH_2)_2PPh$, Et_3N, $scCO_2$, 100°, 64 h</td><td>I (37)</td><td>170</td></tr>
<tr><td></td><td>$Pd(OAc)_2$, P(o-tol)$_3$, Et_3N, MeCN, reflux, 5 h</td><td> (65)</td><td>178</td></tr>
<tr><td>C_{9-11}
</td><td>$Pd(OAc)_2$, base, Bu_4NCl, DMF</td><td>
<table>
<tr><th>R</th><th>Base</th><th>Temp</th><th>Time (d)</th><th></th></tr>
<tr><td>H</td><td>Na_2CO_3</td><td>rt</td><td>1</td><td>(97)</td></tr>
<tr><td>Me</td><td>Et_3N</td><td>rt</td><td>2</td><td>(81)</td></tr>
<tr><td>Ac</td><td>NaOAc</td><td>80°</td><td>1</td><td>(90)</td></tr>
</table></td><td>168</td></tr>
<tr><td></td><td>$Pd(OAc)_2$, Et_3N, MeCN, 110°, 72 h</td><td>
<table>
<tr><th>X</th><th>R^1</th><th>R^2</th><th></th></tr>
<tr><td>I</td><td>H</td><td>H</td><td>(87)</td></tr>
<tr><td>Br</td><td>H</td><td>H</td><td>(60)</td></tr>
<tr><td>I</td><td>H</td><td>Me</td><td>(51)</td></tr>
<tr><td>I</td><td>Me</td><td>Me</td><td>(73)</td></tr>
</table></td><td>167</td></tr>
<tr><td>C_{10}
</td><td>$Pd(OAc)_2$, Et_3N, Bu_4NCl, DMF, 80°, 1 d</td><td> (73)</td><td>168</td></tr>
</table>

TABLE 6A. 3-SUBSTITUTED INDOLES FROM 2-HALO- AND 2-PSEUDOHALO-*N*-ALLYLANILINES AND -ANILIDES (*Continued*)

2-Halo-*N*-allylaniline or -anilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10-12}			
	$Pd(OAc)_2$, ligand, Et_3N, MeCN, 110°, 72 h	 R / Ligand: Me / — (77); CO_2Et / P(*o*-tol)$_3$ (50)	167
C_{11-13}			
	$Pd(OAc)_2$, NaOAc, MeOH, 50°, 0.5 h	 R^1 / R^2 / R^3: H / H / H (85); Me / H / H (57); MeO / H / H (45); H / Me / Me (41); Me / Me / H (32)	385
C_{12}			
	$Pd(OAc)_2$, Et_3N, MeCN, 110°, 72 h	 (87)	167
	$Pd(OAc)_2$, Bu_4NCl, Na_2CO_3, DMF, 100°	 (61)	179
C_{13}			
	$Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, DMF, 80°	 (58)	179
	$Pd(OAc)_2$, PPh_3, $NaHCO_3$, DMF, 130°, 3 h	 (37) +  (6)	166

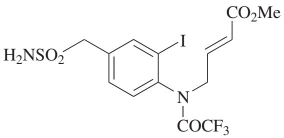
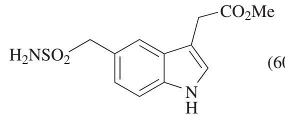
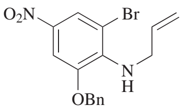
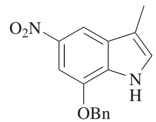
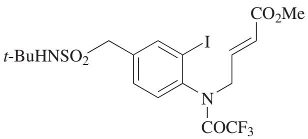
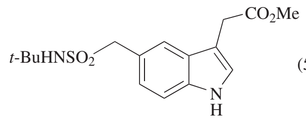
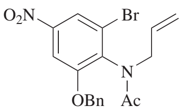
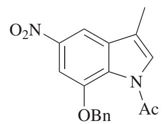
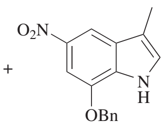
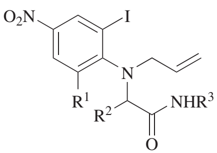
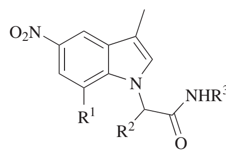
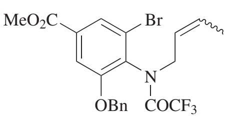
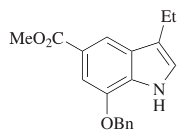
<table>
<tr><td>C_{14}
</td><td>$Pd(OAc)_2$, Bu_4NBr, Et_3N, DMF, 80°, 3 h</td><td> (60)</td><td>174</td></tr>
<tr><td>C_{16}
</td><td>$Pd(OAc)_2$, Bu_4NBr, Et_3N, DMF, 24 h</td><td> (96)</td><td>171</td></tr>
<tr><td>C_{18}
</td><td>$Pd(OAc)_2$, Bu_4NBr, Et_3N, DMF, 80°, 3 h</td><td> (57)</td><td>174</td></tr>
<tr><td></td><td>$Pd(OAc)_2$, $P(o\text{-tol}_3)_2$, Bu_3N, toluene, 120°</td><td> (74) +  (18)</td><td>176</td></tr>
<tr><td>$C_{20–22}$
</td><td>$Pd(OAc)_2$, PPh_3, Et_3N, toluene, 100°</td><td><table><tr><th>R^1</th><th>R^2</th><th>R^3</th><th></th></tr><tr><td>H</td><td>Et</td><td>Bn</td><td>(64)</td></tr><tr><td>H</td><td>t-Bu</td><td>Bn</td><td>(70)</td></tr><tr><td>H</td><td>t-Bu</td><td>$4\text{-}ClC_6H_4CH_2$</td><td>(70)</td></tr><tr><td>Cl</td><td>t-Bu</td><td>$4\text{-}ClC_6H_4CH_2$</td><td>(74)</td></tr></table></td><td>386</td></tr>
<tr><td>C_{21}
</td><td>$Pd(OAc)_2$, Bu_4NCl, Na_2CO_3, DMF, 100°, 2 h</td><td> (86)</td><td>179</td></tr>
</table>

TABLE 6A. 3-SUBSTITUTED INDOLES FROM 2-HALO- AND 2-PSEUDOHALO-*N*-ALLYLANILINES AND -ANILIDES (*Continued*)

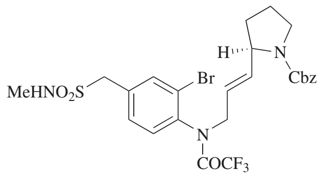
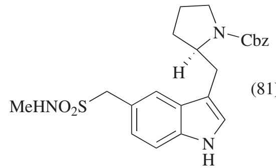
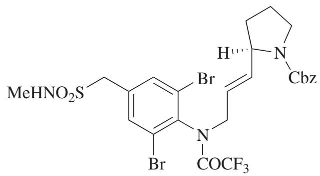
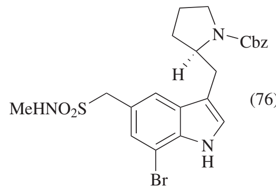
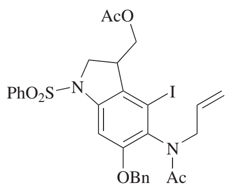
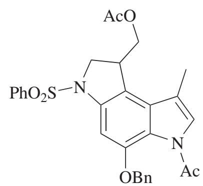
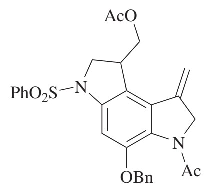
2-Halo-*N*-allylaniline or -anilide	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{25}			
	$Pd(OAc)_2$, Bu_4NCl, Et_3N, DMF/DME, 80°, 1 h	 (81)	175
	$Pd(OAc)_2$, Bu_4NCl, Et_3N, DMF/DME, 80°, 1 h	 (76)	175
C_{29}			
	$Pd(OAc)_2$, Et_3N, MeCN, 110°, 72 h	 (70) +  (10)	177

TABLE 6B. 3-SUBSTITUTED INDOLES FROM 2-HALO-*N*-ALLYLANILINES AND -ANILIDES PREPARED IN SITU

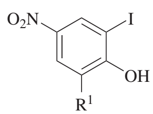
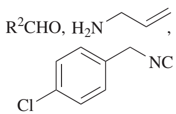
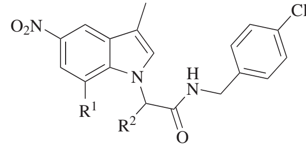
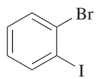
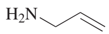
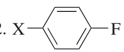
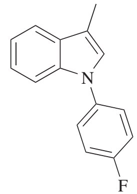
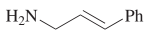
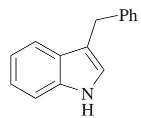
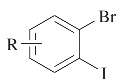
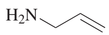
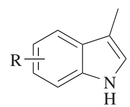
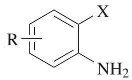
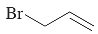
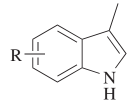
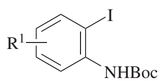
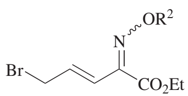
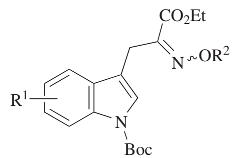
Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6				
		1. NH_4Cl, toluene/H_2O, rt 2. CF_3CO_2H 3. $Pd(OAc)_2$, PPh_3, Et_3N, toluene, 100°	 R^1 / R^2 H, Et (51) Cl, *i*-Bu (74)	386
		1. $Pd_2(dba)_3$, dppf, *t*-BuONa, toluene, rt to 140° 2. 	 X I (21) Br (30)	387
		$Pd_2(dba)_3$, dppf, *t*-BuONa, toluene, rt to 140°	 (59)	387
C_{6-7}				
		$Pd_2(dba)_3$, dppf, *t*-BuONa, toluene, rt to 140°	 R: H (85), 4-F (72), 5-F (65), 6-F (75), 7-F (63), 5-Cl (60) R: 6-Cl (56), 5-Me (73), 6-CF_3 (64), 4-MeO (71), 6-MeO (67), 5-CF_3O (71)	387

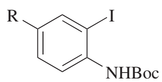
TABLE 6B. 3-SUBSTITUTED INDOLES FROM 2-HALO-*N*-ALLYLANILINES AND -ANILIDES PREPARED IN SITU (*Continued*)

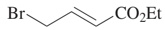
Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{6-10} 		$Pd(OAc)_2$, XPhos, K_2CO_3, DME, 80°		388

X	R	Time (h)		X	R	Time (h)	
F	H	48	(—)	Cl	6-Me	48	(57)
Cl	H	24	(68)	Cl	7-Me	48	(46)
Cl	5-O_2N	22	(61)	Cl	4-NC	48	(15)
Cl	6-O_2N	48	(17)	Cl	5-NC	42	(32)
Cl	7-O_2N	22	(16)	Cl	4-MeO	48	(56)
F	5-Me	48	(—)	Cl	6-MeO	24	(23)
I	5-CF_3	48	(—)	Cl	6-NH_2CO	28	(50)
Cl	5-CF_3	28	(67)	Cl	6-MeO_2C	48	(15)
Cl	6-CF_3	48	(64)	Cl	5-*t*-Bu	20	(—)
Cl	6-Me	24	(14)	Cl	5-*t*-Bu	48	(67)

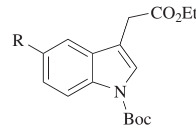
Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11-12} 		1. K_2CO_3, DMF, time 1 2. $Pd(OAc)_2$, PPh_3, additive, K_2CO_3, 60–65°, time 2		173

R^1	R^2	Temp (°)	Time 1 (h)	Additive	Time 2 (h)	
H	Me	0; rt	—; 2	Bu_4NCl	17	(59)
H	Bn	0; rt	—; 2	Bu_4NCl	12	(62)
4-Br	Me	rt	30	—	4	(77)
3-O_2N	Me	rt	30	—	12	(65)
4-O_2N	Bn	rt	30	—	12	(77)
4-MeO	Me	0; rt	—; 2	—	12	(59)





1. K_2CO_3, DMF, rt, time 1
2. $Pd(OAc)_2$, PPh_3,
   rt, 0.5 h; 60–65°, time 2



R	Time 1 (h)	Time 2 (h)	
Br	30	24	(67)
O_2N	3	19	(68)
MeO	94	5	(67)

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TABLE 6C. 3-SUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES

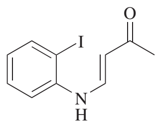
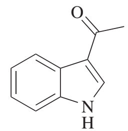
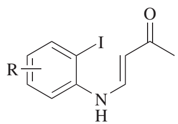
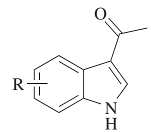
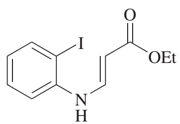
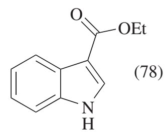
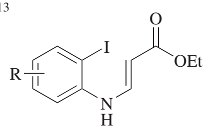
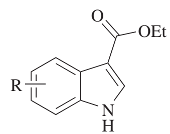
2-Haloarylenamine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}			
	$Pd(OAc)_2$, Et_3N, DMF, 120° (sealed tube), 12 h	 (70)	182
C_{10-12}			
	$Pd(OAc)_2$, $P(o\text{-tol})_3$, Et_3N, MeCN, 100° (sealed tube), 20 h	 R: H (95) 6-OMe (80) 4-CO_2Me (95) 5-CO_2Me (84) 6-CO_2Me (86)	181
C_{11}			
	$Pd(OAc)_2$, Et_3N, DMF, 120° (sealed tube), 2 h	 (78)	182
C_{11-13}			
	$Pd(OAc)_2$, $P(o\text{-tol})_3$, Et_3N, MeCN, 100° (sealed tube), 20 h	 R: H (96) 6-OMe (82) 4-CO_2Me (93) 5-CO_2Me (85) 6-CO_2Me (90)	181

TABLE 6D. 3-SUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES PREPARED IN SITU

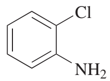
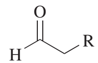
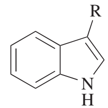
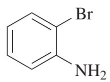
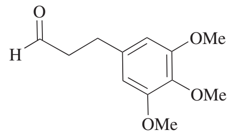
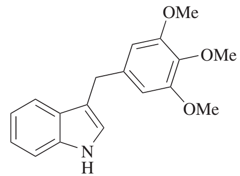
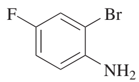
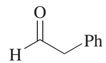
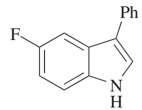
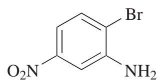
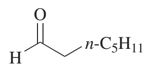
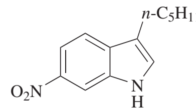
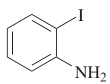
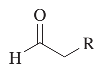
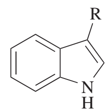
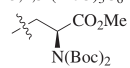
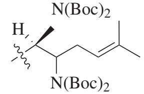
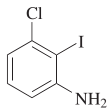
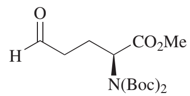
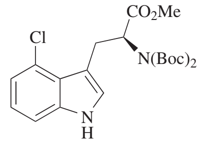
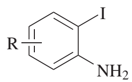
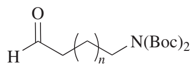
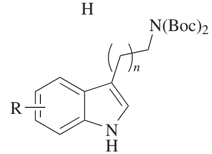
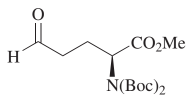
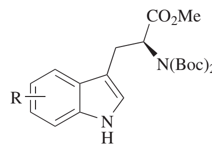
Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6				
		$Pd(dba)_2$, XPhos, AcOK, DMA, 120°, 2–6 h	 R $HO(CH_2)_3$ (63) Ph (70) 3,4,5-$(MeO)_3C_6H_2CH_2$ (85)	183
		$Pd(dba)_2$, XPhos, AcOK, DMA, 120°	 (60)	183
		$Pd(dba)_2$, XPhos, AcOK, DMA, 120°	 (81)	183
		$Pd(dba)_2$, XPhos, AcOK, DMA, 120°	 (15)	183
		$Pd(OAc)_2$, DABCO, DMF, 85°, 6–12 h	 R $(CH_2)_3OH$ (41) n-C_6H_{13} (55) Ph (78) Bn (81) R 3,4,5-$(MeO)_3C_6H_2$ (67)  (81)  (43)	183

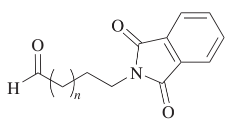
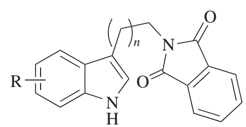
TABLE 6D. 3-SUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES PREPARED IN SITU (*Continued*)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		$Pd(OAc)_2$, DABCO, DMF, 80°, 12 h	 (80)	389
C_{6-7} 		$Pd(OAc)_2$, DABCO, DMF, 85°, 12 h		390

R	*n*		R	*n*	
H	1	(56)	4-Cl	1	(16)
H	2	(52)	6-MeO	1	(49)
5-F	1	(56)	7-MeO	1	(79)
5-O_2N	1	(50)	6-Me	1	(44)
4-O_2N	1	(50)			

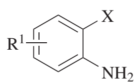
Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$, DABCO, DMF, 85°, 6–12 h		183

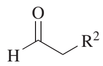
R	
6-Cl	(74)
5-NO_2	(74)
6-NO_2	(64)
4-OMe	(55)
5-OMe	(51)
6-OMe	(58)
7-OMe	(71)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
		$Pd(OAc)_2$, DABCO, DMF, 85°, 12 h		390

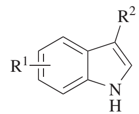
R	n		R	n	
H	1	(52)	4-Cl	1	(23)
H	2	(77)	6-MeO	1	(50)
5-F	1	(49)	7-MeO	1	(66)
5-O_2N	1	(63)	4-MeO	1	(48)
4-O_2N	1	(60)	6-Me	1	(53)

C_{6-8}





$Pd_2(dba)_3$, t-Bu_3P•HBF_4, KOAc, DMA, 120°, 9 h



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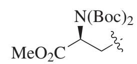
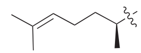
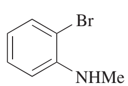
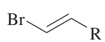
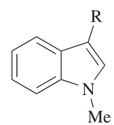
R^1	R^2	X	
5-O_2N	3,4,5-$(MeO)_3C_6H_2CH_2$	Br	(41)
6-O_2N	3,4,5-$(MeO)_3C_6H_2CH_2$	Br	(68)
6-O_2N	3,4,5-$(MeO)_3C_6H_2CH_2$	Cl	(58)
6-O_2N	$Me(CH_2)_4$	Cl	(65)
6-O_2N		Cl	(65)
5-NC	Ph	Br	(61)
6-CF_3	3,4,5-$(MeO)_3C_6H_2CH_2$	Cl	(51)
6-MeCO		Cl	(41)
4-MeO_2C	$Me(CH_2)_4$	Cl	(25)
6-MeO_2C	$Me(CH_2)_5$	Cl	(71)
7-MeO_2C	$Me(CH_2)_5$	Cl	(71)

C_7





$Pd_2(dba)_3$, DavePhos, t-BuONa, toluene, 100°, 20 h



R	
Ph	(70)
4-MeC_6H_4	(69)
n-C_8H_{17}	(64)
CH_2OBn	(63)

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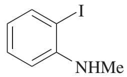
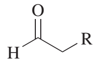
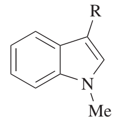
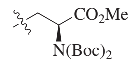
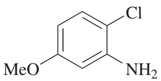
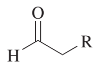
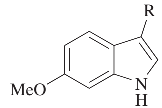
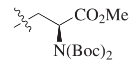
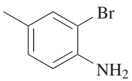
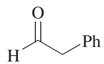
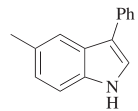
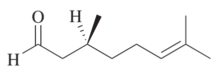
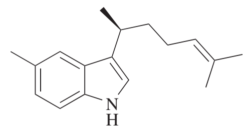
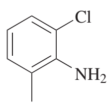
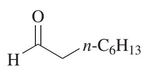
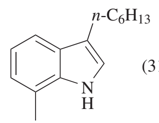
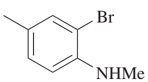
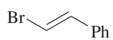
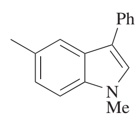
TABLE 6D. 3-SUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES PREPARED IN SITU (*Continued*)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		$Pd(OAc)_2$, DABCO, DMF, 85°, 6–12 h	 R: Bn (76);  (85)	183
		$Pd(dba)_2$, XPhos, AcOK, DMA, 120°, 2–6 h	 R: Bn (56);  (73)	183
		$Pd(dba)_2$, XPhos, AcOK, DMA, 120°	 (46)	183
		$Pd(dba)_2$, XPhos, AcOK, DMA, 120°	 (46)	183
		$Pd(dba)_2$, XPhos, AcOK, DMA, 120°	 (31)	183
C_8				
		$Pd_2(dba)_3$, DavePhos, *t*-BuONa, toluene, 100°, 20 h	 (72)	165

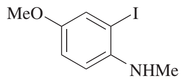
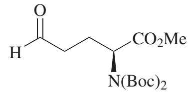
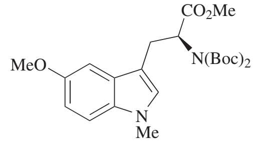
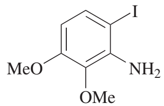
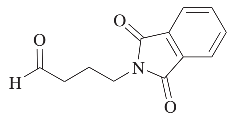
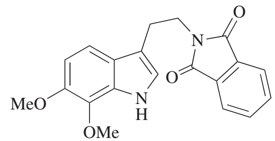
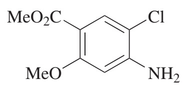
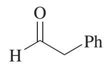
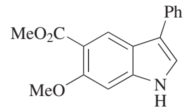
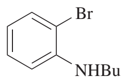
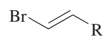
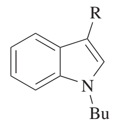
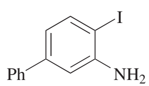
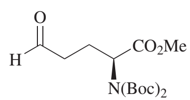
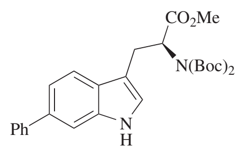
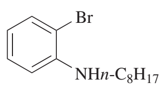
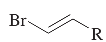
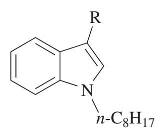
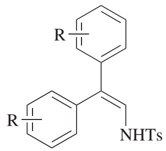
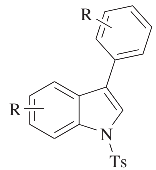
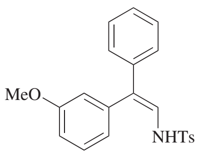
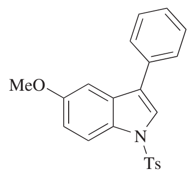
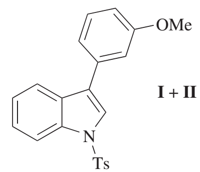
			Pd(OAc)$_2$, DABCO, DMF, 85°	 (84)	183
			Pd(OAc)$_2$, DABCO, DMF, 85°, 24 h	 (60)	390
C_9			Pd(dba)$_2$, XPhos, AcOK, DMA, 120°	 (24)	183
C_{10}			Pd$_2$(dba)$_3$, DavePhos, *t*-BuONa, toluene, 100°, 20 h	 R: Ph (61); 4-MeC$_6$H$_4$ (64); CH$_2$OBn (49)	165
C_{12}			Pd(dba)$_2$, XPhos, AcOK, DMA, 120°	 (42)	183
C_{14}			Pd$_2$(dba)$_3$, DavePhos, *t*-BuONa, toluene, 100°, 20 h	 R: Ph (68); CH$_2$OBn (52)	165

TABLE 6E. 3-SUBSTITUTED INDOLES FROM ARYLENAMINES

Arylenamine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{21-27} 	$Pd(OAc)_2$, $Cu(OAc)_2$, DMSO	 (see below)	208
C_{22} 	$Pd(OAc)_2$, $Cu(OAc)_2$, DMSO, 80°, 24 h	 I +  II; **I + II** (38), **I**:**II** = 4.8:1	208

R	Temp (°)	Time (h)	
4-F	80	24	(42)
4-F	120	6	(51)
4-MeO	80	17	(41)
4-MeO	120	5	(55)
3-MeO	80	22	(45)
3-MeO	120	6	(30)
4-NC	80	22	(29)
4-NC	150	6	(42)
$4-EtO_2C$	80	22	(60)
$4-EtO_2C$	120	6	(68)

TABLE 6F. 3-SUBSTITUTED INDOLES FROM 2-NITROSTYRENES, NITROALKENES, AND NITROARENES

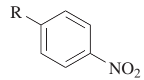
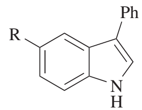
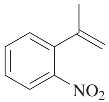
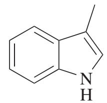
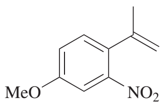
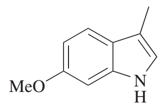
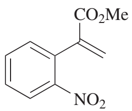
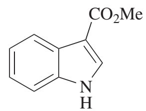
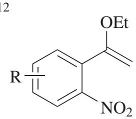
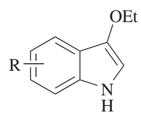
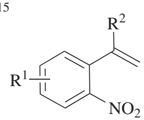
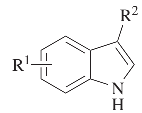
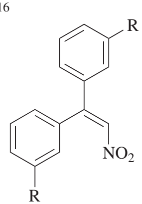
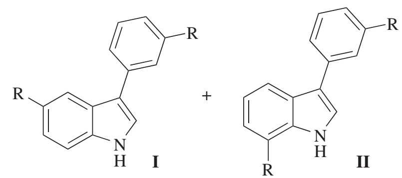
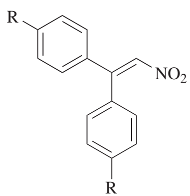
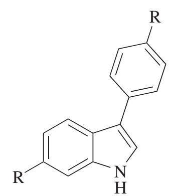
Substrate	Conditions	Product(s) and Yield(s) (%)					Refs.
C_{6-7}							
	$\equiv$—Ph, $[Pd(phen)_2][BF_4]_2$, $Ru_3(CO)_{12}$, additive, DME, CO (59 atm), 170°		R	Additive	Time (h)		392
			H	—	3	(54)	
			H	Me_2CO_3	6	(50)	
			Me	—	1.5	(57)	
			Me	Me_2CO_3	6	(51)	
C_9							
	$PdCl_2(PPh_3)_2$, $SnCl_2$, 1,4-dioxane, CO (20 atm), 100°, 16 h	 (57)					154, 155
C_{10}							
	$Pd(OAc)_2$, PPh_3, MeCN, CO (4 atm), 70°, 24 h	 (81)					156
	$Pd(OAc)_2$, PPh_3, DMF, CO (6 atm), 110°, 72 h	 (91)					393
C_{10-12}							
	$Pd(dba)_2$, phen, dppp, DMF, CO (6 atm), 120°		R	Time (h)			180
			H	96	(72)		
			6-Cl	72	(63)		
			6-NO_2	72	(85)		
			4-Me	48	(84)		
			6-OMe	96	(79)		
			4-CO_2Me	72	(87)		

TABLE 6F. 3-SUBSTITUTED INDOLES FROM 2-NITROSTYRENES, NITROALKENES, AND NITROARENES (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-15} 	$Pd(dba)_2$, dppp, phen, DMF, CO (6 atm), 72 h		393
C_{14-16} 	$Pd(OAc)_2$, phen, DMF, CO (1 atm), 110°	 I + II	209
C_{14-22} 	$Pd(OAc)_2$, phen, DMF, CO (1 atm), 110°		209

Ref. 393:

R^1	R^2	Temp (°)	
6-MeO	CO_2Et	100	(81)
4-MeO_2C	CO_2Et	120	(99)
5-Br	CO_2t-Bu	100	(98)
5-Cl	CO_2t-Bu	120	(92)
5-MeO	CO_2t-Bu	120	(99)
5-MeO	SO_2Ph	120	(74)

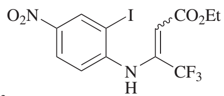
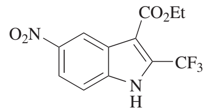
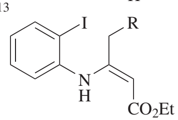
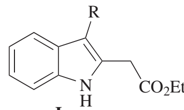
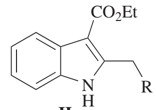
Ref. 209 (I + II):

R	Time (h)	**I + II**	**I:II**
Cl	6	(91)	42:58
CF_3	8	(86)	51:49
MeO	3	(91)	53:47

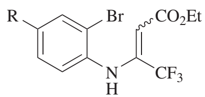
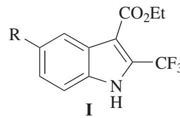
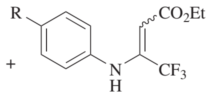
Ref. 209:

R	Time (h)	
H	3	(97)
Cl	6	(98)
CF_3	16	(58)
MeO	3	(93)
Me	3	(87)
t-Bu	3	(92)

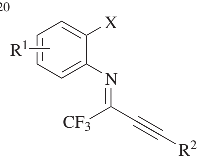
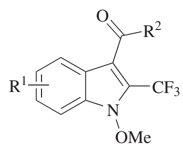
TABLE 7A. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES

2-Haloarylenamine or -imine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12} 	$Pd(OAc)_2$, PPh_3, $NaHCO_3$, DMF, 120°	 (44)	45, 46
C_{12-13} 	$Pd(PPh_3)_4$, Ag_3PO_4, DMSO, 100°	 **I** +  **II**	379

R	Time (h)	**I**	**II**
H	3.5	(17)	(79)
Me	4.5	(6)	(86)

2-Haloarylenamine or -imine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13-15} 	$Pd(OAc)_2$, PPh_3, Pr_3N, DMF, 120°	 **I** +  **II**	45, 46

R	**I**	**II**
CN	(54)	(28)
CO_2Et	(68)	(25)

2-Haloarylenamine or -imine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14-20} 	$PdCl_2(PPh_3)_2$, K_3PO_4, H_2O, DME, 60°		394

X	R^1	R^2	Time (h)	
I	H	2-thienyl	0.5	(85)
I	H	*t*-Bu	0.5	(86)
Br	H	Ph	0.5	(80)
Cl	H	Ph	5	(13)
I	4-F	Ph	1	(76)
I	H	$4\text{-}ClC_6H_4$	0.5	(70)
I	H	$2\text{-}ClC_6H_4$	1	(70)
I	H	$4\text{-}FC_6H_4$	1	(59)
I	H	$4\text{-}MeC_6H_4$	0.5	(82)
I	H	$4\text{-}MeOC_6H_4$	0.5	(85)
I	H	$3\text{-}MeOC_6H_4$	0.5	(81)
I	$4\text{-}CF_3$	Ph	3	(52)
I	4-Me	Ph	0.5	(82)
I	5-MeO	Ph	0.5	(78)
I	H	2-Np	1	(74)

TABLE 7A. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES (*Continued*)

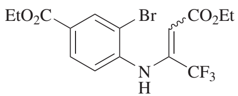
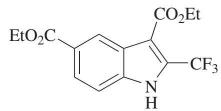
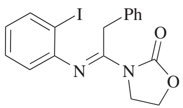
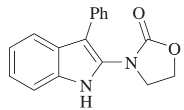
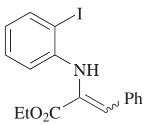
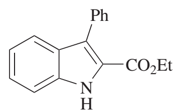
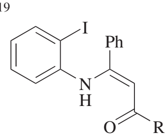
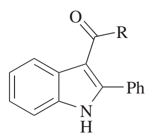
2-Haloarylenamine or -imine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15} 	$Pd(OAc)_2$, PPh_3, $NaHCO_3$, DMF, 120°	 (44)	45, 46
C_{17} 	$Pd(dba)_2$, XPhos, K_3PO_4, 1,4-dioxane, 80°, 23 h	 (86)	395
	$Pd_2(dba)_3$, P(*o*-tol)$_3$, Et_3N, DMF, 120°, 2 h	 (56)	396
$C_{17–19}$ 	$Pd_2(dba)_3$, XPhos, K_3PO_4, 1,4-dioxane, 80°, 23 h	 R: OEt (98); *N*-morpholino (91)	354

TABLE 7B. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES PREPARED IN SITU

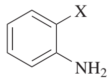
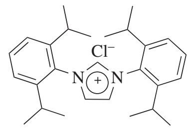
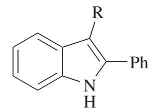
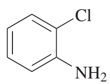
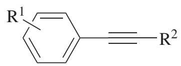
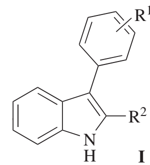
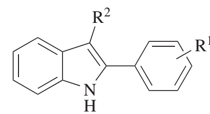
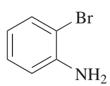
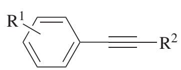
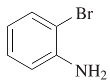
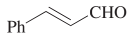
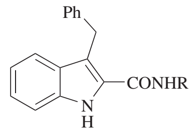
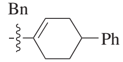
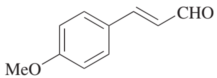
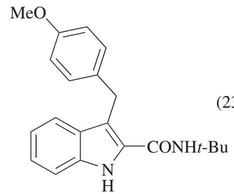
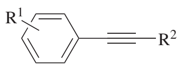
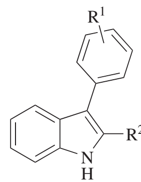
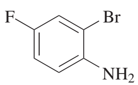
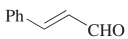
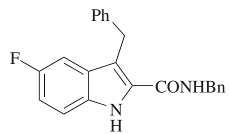
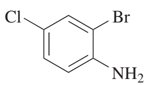
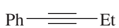
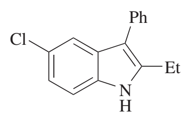
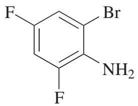
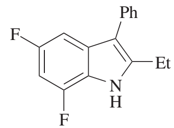
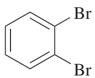
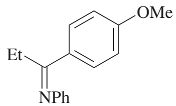
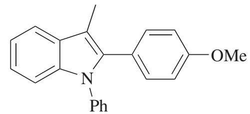
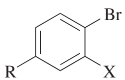
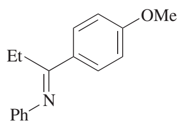
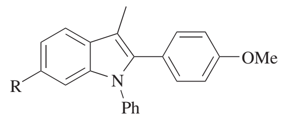
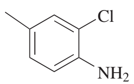
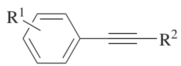
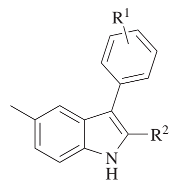
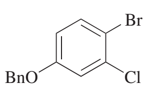
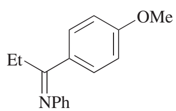
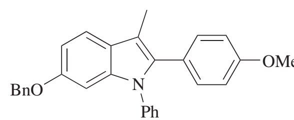
Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 		1. $Ru_3(CO)_{12}$, PF_6NH_4, toluene, 105°, 18 h 2. $Pd(OAc)_2$, **L2**, *t*-BuOK, 105°, 24 h  **L2**	 X / R: Cl / Et (—); Cl / Ph (89); Br / Ph (87)	382
		1. $TiCl_4$, *t*-$BuNH_2$, toluene, 105°, 20 h 2. $Pd(OAc)_2$, HIPrCl, *t*-BuOK, toluene, 105°, 20 h	 **I** +  **II** R^1 / R^2 / **I + II** / **I:II**: H / Bu / (81)[a] / 92:8; 3-CF_3 / Bu / (84)[b] / 97:3; H / Ph / (76) / —; H / *n*-C_6H_{13} / (81)[a] / 92:8; 4-F / *n*-C_6H_{13} / (74)[b] / >99:1; 4-Me / *n*-C_6H_{13} / (81)[a] / 92:8; 4-OMe / *n*-C_6H_{13} / (66) / >99:1; 3-CF_3 / *n*-C_6H_{13} / (82)[b] / 97:3	184
		1. $TiCl_4$, *t*-$BuNH_2$, toluene, 105°, 20 h 2. $Pd(OAc)_2$, HIPrCl, *t*-BuOK, toluene, 105°, 20 h	**I + II** R^1 / R^2 / **I + II** / **I:II**: 4-Cl / *n*-C_6H_{13} / (67) / >99:1; 2-Cl / *n*-C_6H_{13} / (46) / >99:1	184

TABLE 7B. 2,3-DISUBSTITUTED INDOLES FROM 2-HALOARYLENAMINES AND -IMINES PREPARED IN SITU (*Continued*)

Substrate	Reagent	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6				
		1. 2,2,2-trifluoroethanol, rt, 1 h 2. HCO_2H, RNC, rt, 1–3 d, solvent evaporated 3. MeCN, $Pd(OAc)_2$, PPh_3, 80°, 16–24 h	 R CH_2CO_2Me (15) *t*-Bu (17) 1-cyclohexenyl (29) Bn (21)  (32)	187
		1. 2,2,2-trifluoroethanol, rt, 1 h 2. HCO_2H, *t*-BuNC, rt, solvent evaporated 3. MeCN, $Pd(OAc)_2$, PPh_3, 80°	 (23)	187
		1. $TiCl_4$, *t*-$BuNH_2$, toluene, 105°, 14 h 2. $Pd(OAc)_2$, PCy_3, *t*-BuOK, toluene, 105°, 22 h	 R^1 / R^2 H / Ph (74) 4-OMe / n-C_6H_{13} (68) 3-OMe / n-C_6H_{13} (71)	184
		1. 2,2,2-trifluoroethanol, rt, 1 h 2. HCO_2H, BnNC, rt, solvent evaporated 3. MeCN, $Pd(OAc)_2$, PPh_3, 80°	 (38)	187
		1. $TiCl_4$, *t*-$BuNH_2$, toluene, 105°, 14 h 2. $Pd(OAc)_2$, PCy_3, *t*-BuOK, toluene, 105°, 22 h	 (53)	184

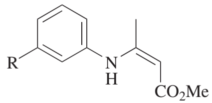
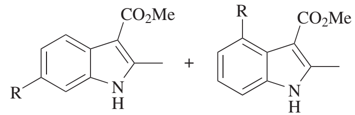
	$PhC\equiv CEt$	1. $TiCl_4$, *t*-$BuNH_2$, toluene, 105°, 14 h 2. $Pd(OAc)_2$, PCy_3, *t*-BuOK, toluene, 105°, 22 h	 (52)	184
		$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 (66)	196
C_{6-13}				
		$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 X — R Br — H — (66) Cl — 6-BnO — (76)	197
C_7				
		1. $TiCl_4$, *t*-$BuNH_2$, toluene, 105°, 14 h 2. $Pd(OAc)_2$, PCy_3, *t*-BuOK, toluene, 105°, 22 h	 R^1 — R^2 H — Et — (71) 3-OMe — Bu — (55)[c] 4-OMe — Bu — (58)[c] H — Ph — (71) 4-F — *n*-C_6H_{13} — (54)[c] 3-OMe — *n*-C_6H_{13} — (51)[c] 3-CF_3 — *n*-C_6H_{13} — (71)[c]	184
C_{13}				
		$Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 (70)	196

[a] Up to 8% of a regioisomer was isolated.

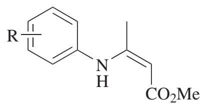
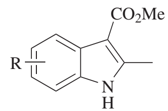
[b] Up to 5% of a regioisomer was isolated.

[c] Up to 4% of a regioisomer was isolated.

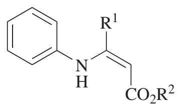
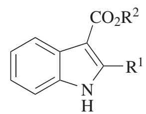
TABLE 7C. 2,3-DISUBSTITUTED INDOLES FROM ARYLENAMINES AND -IMINES

Arylenamine or -imine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11-13} 	$Pd(OAc)_2$, $Cu(OAc)_2$, K_2CO_3, DMF, 12–16 h	 I + II	397

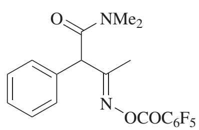
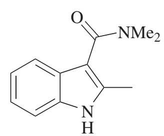
R	Temp (°)	I + II	I:II
Cl	80	(72)	88:12
F	110	(74)	53:47
Me	110	(68)	92:8
MeO	140	(68)	>99:1
MeCO	80	(54)	>99:1

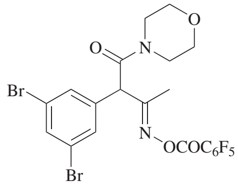
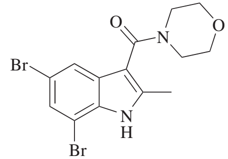
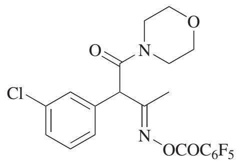
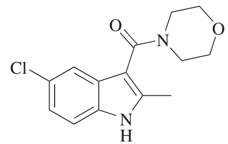
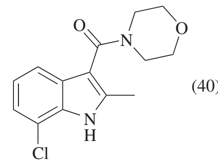
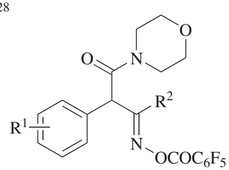
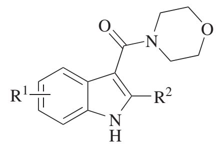
Arylenamine or -imine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11-14} 	$Pd(OAc)_2$, $Cu(OAc)_2$, K_2CO_3, DMF, 12–16 h		397

R	Temp (°)		R	Temp (°)	
H	80	(72)	7-MeO	140	(64)
5-F	110	(74)	5-Me	80	(72)
7-F	140	(78)	7-Me	110	(82)
5-Cl	80	(64)	5-MeCO	140	(52)
7-Cl	80	(53)	4,6-Me_2	140	(62)
5-H_2NCO	140	(70)	5-EtO_2C	140	(64)
5-NC	140	(65)			

Arylenamine or -imine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-17} 	$Pd(OAc)_2$, $Cu(OAc)_2$, K_2CO_3, DMF, 12–16 h		397

R^1	R^2	
Me	Et	(71)
Me	*t*-Bu	(79)
Ph	Et	(68)

Arylenamine or -imine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{19} 	$PdCl_2(MeCN)_2$, MgO, DCE, reflux, 5 h	 (68)	211

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{21} 	$PdCl_2(MeCN)_2$, MgO, DCE, reflux, 10 h	 (68)	211
	$PdCl_2(MeCN)_2$, MgO, DCE, reflux, 6 h	 (59) +  (40)	211
C_{21-28} 	$PdCl_2(MeCN)_2$, MgO, DCE, reflux		211

R^1	R^2	Time (h)	
6-Cl	Me	4	(70)
6-Br	Me	6	(75)
6-F	Me	4	(70)
H	Me	5	(73)
4-Me	Me	6	(46)
H	3-BrC_6H_4	10	(49)
6-Ph	Me	3.5	(72)
H	CH_2-c-C_6H_{11}	9	(91)
H	Bn	9	(63)
H	$(CH_2)_2Ph$	9	(55)

TABLE 7C. 2,3-DISUBSTITUTED INDOLES FROM ARYLENAMINES AND -IMINES (*Continued*)

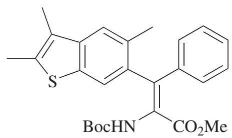
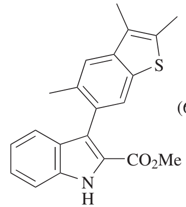
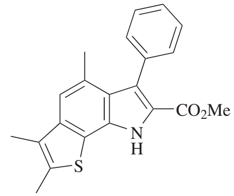
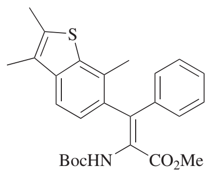
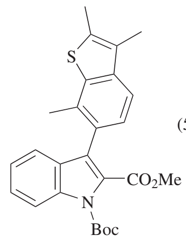
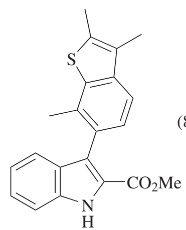
Arylenamine or -imine	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{26}			
	$Pd(OAc)_2$, $Cu(OAc)_2 \bullet H_2O$, DMF, 160°, 0.5 h	 (60) +  (20)	212
	$Pd(OAc)_2$, $Cu(OAc)_2 \bullet H_2O$, DMF, 100°, 2 h	 (50)	212
	$Pd(OAc)_2$, $Cu(OAc)_2 \bullet H_2O$, DMF, 100°, 2 h; 130°, 1 h	 (85)	212

TABLE 7D. 2,3-DISUBSTITUTED INDOLES FROM 2-NITROSTYRENES, 2-ISOCYANOSTYRENE, AND 2-ALLYLANILINES

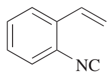
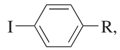
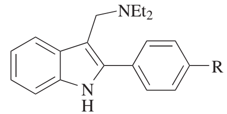
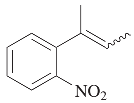
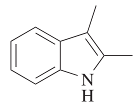
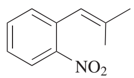
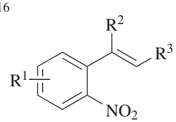
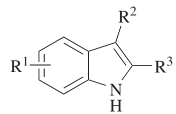
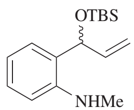
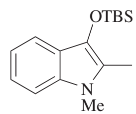
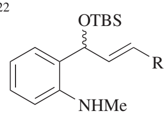
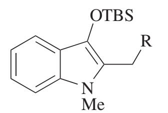
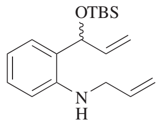
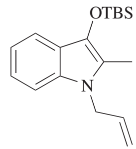
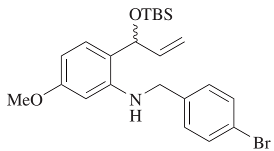
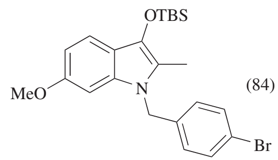
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 	 $Pd(OAc)_2$, dppp, Et_2NH, THF, 40°	 R | Time (h) | H | 3.5 | (42)[a] $4-O_2N$ | 2 | (24) 4-MeO | 21 | (39)	186
C_{10}  *trans:cis* = 1:2	$Pd(OAc)_2$, PPh_3, MeCN, CO (4 atm), 70°, 21.5 h	 (97) **I**	156
	$PdCl_2(PPh_3)_2$, $SnCl_2$, 1,4-dioxane, CO (20 atm), 100°	**I** (52)	155
C_{14-16} 	$Pd(dba)_2$, dppp, phen, DMF, CO (6 atm), 72 h	 R^1 | R^2 | R^3 | Temp (°) | H | EtO_2C | Pr | 120 | (84) 5-MeO | NC | n-C_5H_{11} | 120 | (45) H | MeO_2C | Ph | 100 | (74)	393
C_{16} 	$PdCl_2(MeCN)_2$, K_2CO_3, benzoquinone, THF, rt, 24 h	 (77)	157
C_{17-22} 	$PdCl_2(MeCN)_2$, K_2CO_3, LiCl, benzoquinone, THF, 24 h	 R | Temp | Me | 85° | (50) Ph | rt | (47)	157

TABLE 7D. 2,3-DISUBSTITUTED INDOLES FROM 2-NITROSTYRENES, 2-ISOCYANOSTYRENE, AND 2-ALLYLANILINES (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18} 	$PdCl_2(MeCN)_2$, K_2CO_3, LiCl, benzoquinone, THF, rt, 24 h	 (54)	157
C_{23} 	$PdCl_2(MeCN)_2$, K_2CO_3, benzoquinone, THF, rt, 24 h	 (84)	157

[a] The yield was determined by NMR spectroscopy.

TABLE 8. INDOLES VIA ARENE VINYLATION

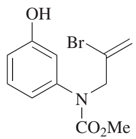
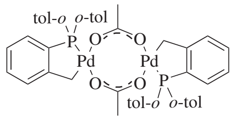
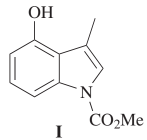
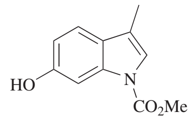
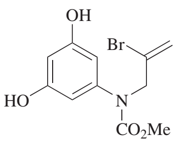
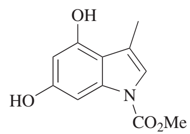
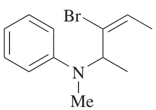
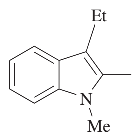
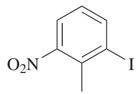
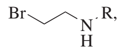
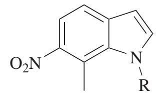
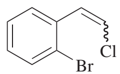
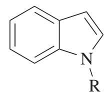
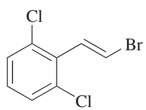
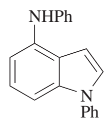
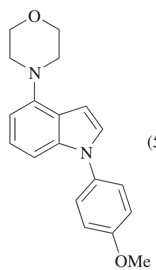
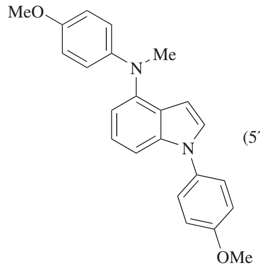
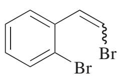
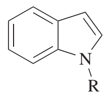
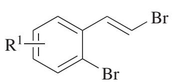
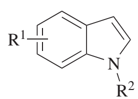
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11} 	Herrmann's catalyst, Cs_2CO_3, DMA, 70°, 1 d  Herrmann's catalyst	 **I** +  **II** **I + II** (79), **I**:**II** = 1:1	47
	Herrmann's catalyst, Cs_2CO_3, DMA, 70°, 1 d	 (71)	47
C_{12} 	$Pd(OAc)_2$, XPhos, Cs_2CO_3, DME, 90°, 3 h	 (12)	398

TABLE 9. 2,3-UNSUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7 	 Pd(OAc)$_2$, (2-furyl)$_3$P, norbornene, Cs_2CO_3, MeCN, 135°, 20 h	 R Ph (53) 4-$O_2NC_6H_4$ (70)	193
C_8 	RNH_2, Pd(OAc)$_2$, HP(*t*-Bu)$_3$BF$_4$, *t*-BuONa, toluene, 130°, 4 h	 R *t*-Bu (65) CMe_2Et (64) C(Me)$_2$CH=CH$_2$ (68) *c*-C_6H_{11} (61) 2-MeC_6H_4 (85) CHMePh (77) 2,6-$Me_2C_6H_3$ (83) 1-adamantyl (66) 1-Np (78) 2,6-(*i*-Pr)$_2C_6H_3$ (73)	191
	$PhNH_2$, Pd$_2$(dba)$_3$, DavePhos, *t*-BuONa, toluene, 100°	 (65)	190
	1. 4-$MeOC_6H_4NH_2$, Pd$_2$(dba)$_3$, DavePhos, *t*-BuONa, toluene, 100°, 30 min 2. Morpholine	 (55)	190

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. 4-$MeOC_6H_4NH_2$, $Pd_2(dba)_3$, DavePhos, *t*-BuONa, toluene, 100°, 30 min 2. 4-$MeOC_6H_4NHMe$	 (57)	190
	RNH_2, $Pd_2(dba)_3$, ligand, *t*-BuONa, toluene	 **I**	190
	RNH_2, $Pd_2(dba)_3$, PhXPhos, Cs_2CO_3, 1,4-dioxane, 110°	**I**	190
	R^2NH_2, $Pd_2(dba)_3$, SPhos, Cs_2CO_3, toluene, 110°, 6 h		192

Product **I** (RNH_2, $Pd_2(dba)_3$, ligand, *t*-BuONa, toluene):

R	Ligand	Temp (°)	Time (h)	
Ph	SPhos	80	5	(85)
c-C_6H_{11}	DPEPhos	100	20	(65)
4-ClC_6H_4	SPhos	80	5	(77)
Bn	DPEPhos	100	20	(70)
4-$MeOC_6H_4$	SPhos	80	6	(75)
N=C(Ph)$_2$	SPhos	80	6	(62)

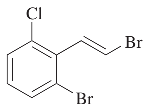
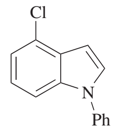
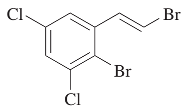
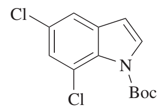
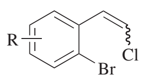
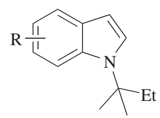
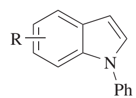
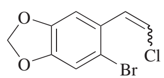
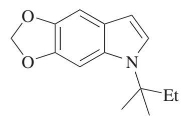
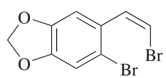
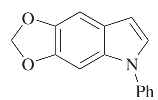
Product **I** (RNH_2, $Pd_2(dba)_3$, PhXPhos, Cs_2CO_3, 1,4-dioxane, 110°):

R	Time (h)	
CO_2Et	24	(54)
CO_2 *t*-Bu	10	(68)

Product (R^2NH_2, $Pd_2(dba)_3$, SPhos, Cs_2CO_3, toluene, 110°, 6 h):

R^1	R^2	
6-Cl	*N*-morpholino	(68)
5-Cl	Boc	(69)
6-Cl	Boc	(84)
7-Cl	Boc	(68)
6-Cl	4-$MeOC_6H_4$	(87)
6-Cl	4-$MeOC_6H_4CH_2$	(67)

TABLE 9. 2,3-UNSUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8			
	$PhNH_2$, $Pd_2(dba)_3$, DavePhos, *t*-BuONa, toluene, 100°	 (80)	190
	$BocNH_2$, $Pd_2(dba)_3$, SPhos, Cs_2CO_3, toluene, 110°, 6 h	 (39)	192
C_{8-9}			
	 H_2N Et, $Pd(OAc)_2$, $HP(t\text{-}Bu)_3BF_4$, *t*-BuONa, toluene, 130°, 4 h	 R: 5-F (65); 5-NO_2 (34); 6-Me (76)	191
	$PhNH_2$, $Pd_2(dba)_3$, SPhos, *t*-BuONa, toluene, 80°	 R: 5-F (59); 6-Me (73)	190
C_9			
	 H_2N Et, $Pd(OAc)_2$, $HP(t\text{-}Bu)_3BF_4$, *t*-BuONa, toluene, 130°, 4 h	 (64)	191
	$PhNH_2$, $Pd(OAc)_2$, SPhos, *t*-BuONa, toluene, 80°	 (67)	190

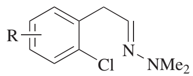
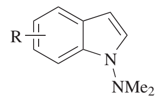
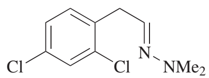
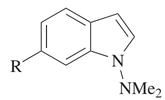
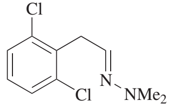
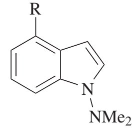
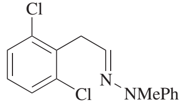
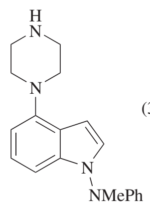
Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} 	$Pd(dba)_2$, dmam-dtbpf, *t*-BuONa, *o*-xylene, 120°, 2–20 h	 **I** R: H (73); 4-F (60); 6-F (74); 4-Cl (48)	189
	$Pd(dba)_2$, $(t\text{-Bu})_3P$, base, *o*-xylene, 120°, 2–20 h	**I** R / Base: H / *t*-BuONa (39); 4-Cl / *t*-BuONa (46); 6-Cl / Rb_2CO_3 (18)	189
	Reagent, $Pd(dba)_2$, ligand, base, *o*-xylene, 120°, 24–48 h	 Reagent / R / Ligand / Base: $PhB(OH)_2$ / Ph / dmam-dtbpf / Cs_2CO_3 (29); pyrrole / 1-pyrrolyl / $(t\text{-Bu})_3P$ / Rb_2CO_3 (24)	189
	Reagent, $Pd(dba)_2$, ligand, base, *o*-xylene, 120°, 24–48 h	 Reagent / R / Ligand / Base: $PhB(OH)_2$ / Ph / dmam-dtbpf / Cs_2CO_3 (56); $PhB(OH)_2$ / Ph / $(t\text{-Bu})_3P$ / Cs_2CO_3 (40); pyrrole / 1-pyrrolyl / $(t\text{-Bu})_3P$ / Rb_2CO_3 (54); indole / 1-indolyl / $(t\text{-Bu})_3P$ / Rb_2CO_3 (40); piperazine / 1-piperazinyl / dmam-dtbpf / *t*-BuONa (30); PhMeNH / PhMeN / dmam-dtbpf / *t*-BuONa (39)	189
C_{15} 	Piperazine, $Pd(dba)_2$, dmam-dtbpf, *t*-BuONa, *o*-xylene, 120°	 (33)	189

TABLE 9. 2,3-UNSUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION (*Continued*)

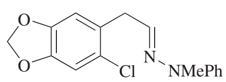
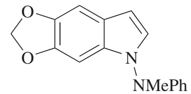
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16}			
	Pd(dba)$_2$, dmam-dtbpf, *t*-BuONa, *o*-xylene, 120°	 (33)	189

TABLE 10. 2-SUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION

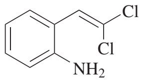
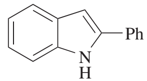
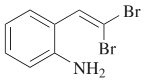
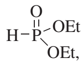
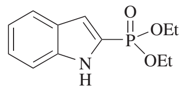
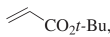
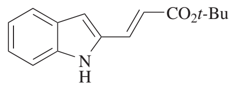
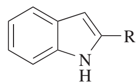
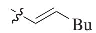
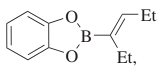
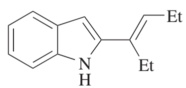
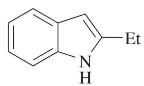
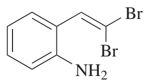
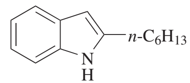
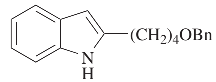
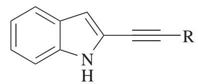
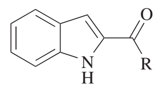
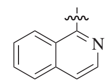
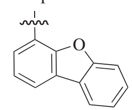
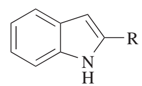
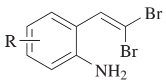
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8 	$PhB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 100°, 2 h	 (95)	200, 202
	 $Pd(OAc)_2$, dppf, Et_3N, toluene, 120°, 12 h	 (63)	198
	 $Pd(OAc)_2$, $P(o\text{-tol})_3$, K_3PO_4•H_2O, Et_3N, toluene, reflux	 (50)	199
	$RB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 90°	 R / Time (h) 3-thienyl 12 (86) Ph 6 (84)  5 (80) 2-MeC_6H_4 4 (82) 4-$CF_3C_6H_4$ 7 (83) 4-$MeOC_6H_4$ 2 (75)	200
	 $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 90°, 6 h	 (73)	200
	Et_3B, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, THF, 60°, 2 h	 (77)	200

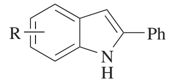
TABLE 10. 2-SUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)					Refs.
C_8 	n-C_6H_{13}BBN, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, THF, 60°, 3 h	 (79)					200
	$BnO(CH_2)_4$BBN, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, THF, 60°, 4 h	 (78)					200
	R, Pd/C, CuI, $P(4\text{-}MeOC_6H_4)_3$, i-Pr_2NH/toluene, 100°		R		R		205
			CH_2OH	(40)	3-pyridyl	(81)	
			$(CH_2)_3OH$	(83)	Ph	(85)	
			TMS	(57)	n-C_6H_{13}	(71)	
			$(CH_2)_3CN$	(50)	$(CH_2)_3OTHP$	(71)	
			$(CH_2)_4Cl$	(70)			
	$RB(OH)_2$, CO (12 atm), $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 100°, 16 h		R		R		203
			3-thienyl	(67)	3,4,5-$(MeO)_3C_6H_2$	(63)	
			4-ClC_6H_4	(70)		(40)	
			2-$MeOC_6H_4$	(40)			
			4-$MeOC_6H_4$	(61)			
			4-$CF_3C_6H_4$	(73)	2-Np	(61)	
			4-$MeCONHC_6H_4$	(29)		(71)	
			(E)-PhCH=CH	(67)			
			2-benzofurayl	(58)			
	$RB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 90°, 4 h		R		R		202
			3-thienyl	(86)	4-$MeOC_6H_4$	(83)	
			$Me(CH_2)_3CH$=CH	(80)	4-$CF_3C_6H_4$	(75)	
			Ph	(84)	4-$MeCOC_6H_4$	(23)	
			3-ClC_6H_4	(57)	(E)-PhCH=CH	(68)	
			4-ClC_6H_4	(60)	2-Me-3-$MeOC_6H_3$	(79)	
			2-MeC_6H_4	(82)	2-Np	(82)	
			4-MeC_6H_4	(88)			

C_{8-15}



$PhB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 90°



I

R	Time (h)	
4-F	14	(88)
5-F	2	(87)
6-F	2.5	(80)
4-Me	2	(77)
6-CF_3	2.5	(90)
4-CO_2Me	8.5	(90)
5-OBn	3	(86)

200

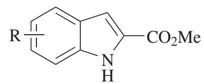
$PhB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 90°, 4 h

I

R		R	
4-F	(88)	6-CF_3	(90)
5-F	(87)	5-MeO_2C	(87)
6-F	(80)	6-MeO_2C	(90)
4-Me	(77)	5-BnO	(86)
7-Me	(89)	6-BnO	(72)

202

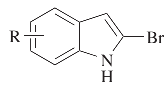
CO (10 atm), $PdCl_2(PPh_3)_2$, PPh_3, *i*-Pr_2NEt, THF/MeOH (1:1), 110°, 20 h



R		R	
H	(70)	6-MeO_2C	(73)
5-Cl	(68)	5,6-$(MeO)_2$	(62)
5-F	(78)	5-BnO	(72)
7-MeO	(75)		

204

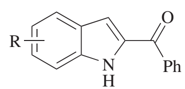
$Pd(OAc)_2$, *t*-Bu_3P•HBF_4, K_2CO_3, toluene, 100°



R	Time (h)		R	Time (h)	
H	14	(81)	6-CF_3	14	(72)
5-I	24	(68)	5-MeO_2C	14	(75)
5-Br	24	(71)	6-MeO_2C	14	(84)
6-F	14	(82)	6-BnO	14	(84)
7-MeO	14	(80)			

207

$PhB(OH)_2$, CO (12 atm), $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 85°, 24 h



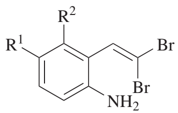
R	
4-Cl	(68)
5-MeO_2C	(50)
5-BnO	(73)

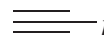
203

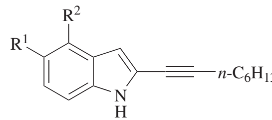
TABLE 10. 2-SUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

$C_{8–16}$



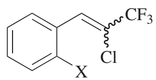
 n-C_6H_{13}, Pd/C, CuI, $P(4\text{-}MeOC_6H_4)_3$, i-Pr_2NH/toluene, 100°



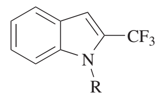
R^1	R^2	
H	F	(72)
MeO_2C	H	(84)
MeO	BnO	(81)

205

C_9



RNH_2, $Pd_2(dba)_3$, DavePhos, t-BuONa, toluene, 140°



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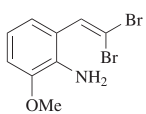
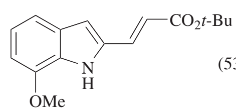
R	X	Time (h)	
Bu	Br	26	(36)
Bu	Cl	14	(32)
4-pyridyl	Br	24	(24)
Ph	Cl	18	(83)
$4\text{-}FC_6H_4$	Br	14	(87)
$4\text{-}FC_6H_4$	Cl	12	(87)
$4\text{-}ClC_6H_4$	Br	32	(64)
$4\text{-}O_2NC_6H_4$	Br	36	(41)
$2\text{-}MeC_6H_4$	Br	12	(76)
$2\text{-}MeC_6H_4$	Cl	18	(72)
$4\text{-}MeC_6H_4$	Br	18	(94)

R	X	Time (h)	
$4\text{-}MeC_6H_4$	Br	26	(96)
$4\text{-}MeC_6H_4$	Cl	16	(76)
$4\text{-}MeOC_6H_4$	Br	10	(84)
$4\text{-}CF_3C_6H_4$	Br	16	(68)
$4\text{-}CF_3C_6H_4$	Cl	24	(57)
Bn	Br	48	(—)
$2,6\text{-}Me_2C_6H_3$	Br	6	(62)
$Ph(CH_2)_2$	Br	10	(44)
1-Np	Br	16	(67)
1-Np	Cl	36	(71)



 CO_2t-Bu, $Pd(OAc)_2$, $P(o\text{-}tol)_3$, K_3PO_4•H_2O, Et_3N, toluene, reflux



(53)

199

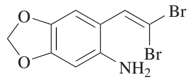
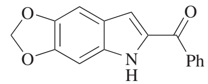
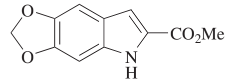
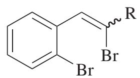
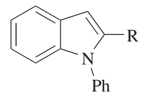
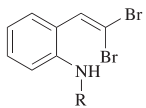
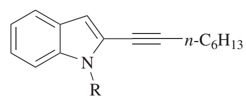
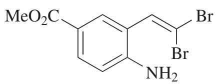
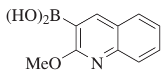
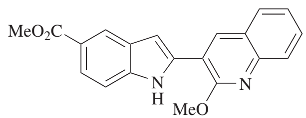
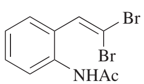
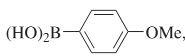
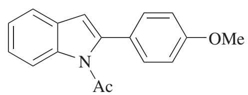
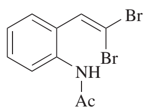
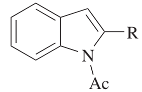
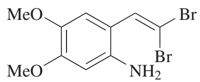
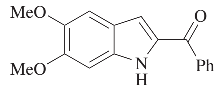
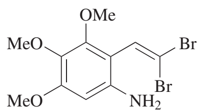
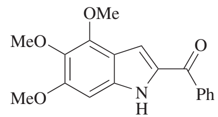
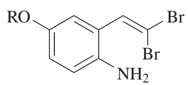
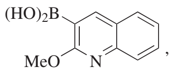
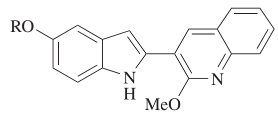
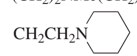
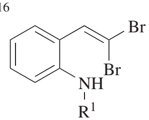
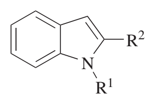
		PhB(OH)$_2$, CO (12 atm), Pd(PPh$_3$)$_4$, K$_2$CO$_3$, 1,4-dioxane, 85°, 24 h	 (56)	203
		PdCl$_2$(PPh$_3$)$_2$, PPh$_3$, CO (10 atm), *i*-Pr$_2$NEt, THF/MeOH (1:1), 110°, 20 h	 (67)	204
C$_{9-15}$		PhNH$_2$, Pd$_2$(dba)$_3$, SPhos, *t*-BuONa, toluene	 R | Temp (°) Me | 80 | (79) 4-ClC$_6$H$_4$ | 100 | (51) 4-MeOC$_6$H$_4$ | 100 | (81)	190
		$\equiv$—*n*-C$_6$H$_{13}$, Pd/C, CuI, P(4-MeOC$_6$H$_4$)$_3$, *i*-Pr$_2$NH/toluene, 100°	 R Me (61) *i*-Pr (60) Ph (65) Bn (51)	205
C$_{10}$		, Pd(OAc)$_2$, SPhos, K$_3$PO$_4$•H$_2$O, toluene, rt, 2 min; 100°, 1.5 h	 (86)	201
		, Pd$_2$(dba)$_3$, dppf, Et$_3$N, toluene, 100°, 12 h	 (52)	198

TABLE 10. 2-SUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} 	$RB(OH)_2$, $Pd_2(dba)_3$, $P(o\text{-tol})_3$, K_2CO_3, toluene, 85°, 18 h	 R: Ph (72); 2-MeC_6H_4 (17); 4-$MeCOC_6H_4$ (23)	202
	$PhB(OH)_2$, CO (12 atm), $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 85°, 24 h	 (55)	203
C_{11} 	$PhB(OH)_2$, CO (12 atm), $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 85°, 24 h	 (65)	203
C_{11-15} 	, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 100°	 R: CH_2CH_2OMe (79); $(CH_2)_2NMe(CH_2)_2OMe$ (88);  (94)	201
C_{11-16} 	$R^2B(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 90–100°, 4 h		202

R^1	R^2		R^1	R^2	
i-Pr	Ph	(71)	4-FC_6H_4	Ph	(71)
Ph	Ph	(92)	Bn	Ph	(82)
Ph	4-FC_6H_4	(86)	4-$CF_3C_6H_4$	2-FC_6H_4	(82)
Ph	3,4-$(MeO)_2C_6H_3$	(60)	3,4-$(MeO)_2C_6H_3$	4-$CF_3C_6H_4$	(81)

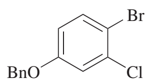
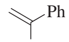
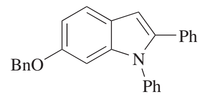
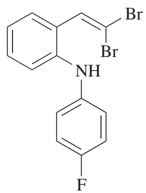
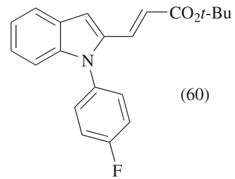
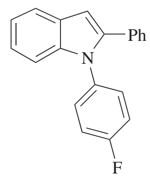
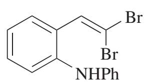
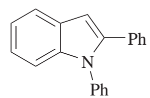
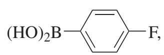
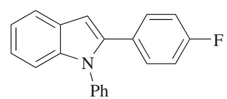
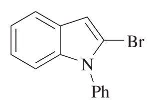
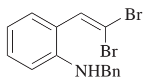
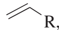
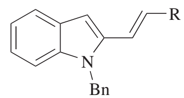
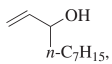
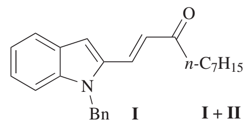
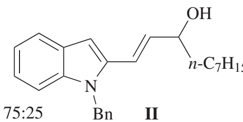
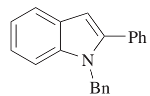
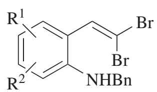
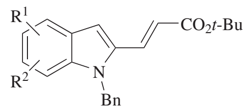
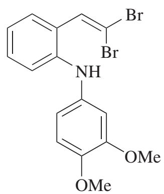
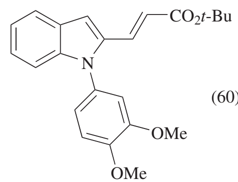
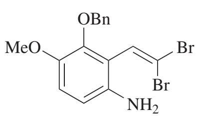
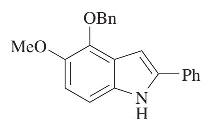
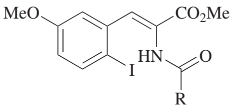
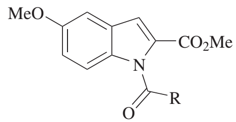
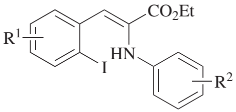
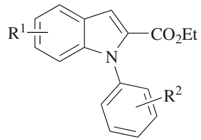
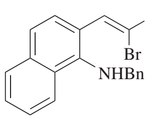
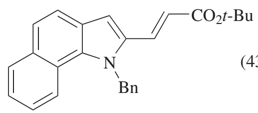
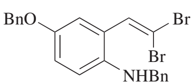
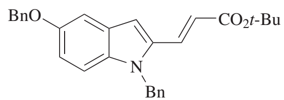
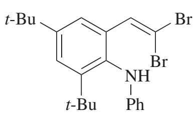
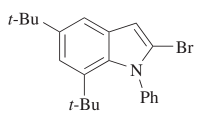
C_{13}		 Br, $PhNH_2$, $Pd_2(dba)_3$, XPhos, *t*-BuONa, 1,4-dioxane, 110°, 14 h	 (57)	196
C_{14}		 CO_2*t*-Bu, $Pd_2(dba)_3$, SPhos, K_3PO_4•H_2O, Et_3N, toluene, reflux	 (60)	199
		$PhB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 100°	 (90)	200
		$PhB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 100°	 (90)	200
		, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 100°	 (86)	200
		$Pd(OAc)_2$, $(t\text{-Bu})_3P$•HBF_4, K_2CO_3, toluene, 100°, 14 h	 (72)	207

TABLE 10. 2-SUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15} 	 R, Pd(OAc)$_2$, P(*o*-tol)$_3$, K$_3$PO$_4$•H$_2$O, Et$_3$N, toluene, reflux	 R: CN (70); 4-MeOC$_6$H$_4$ (73)	199
	 Pd(OAc)$_2$, Me$_4$NCl, K$_3$PO$_4$•H$_2$O, Et$_3$N, toluene, reflux	 **I** +  **II** **I** + **II** (82), **I**:**II** = 75:25	199
	PhB(OH)$_2$, Pd(OAc)$_2$, SPhos, K$_3$PO$_4$•H$_2$O, toluene, 90°, 4 h	 (82)	200
C_{15-23} 	 CO$_2$*t*-Bu, Pd(OAc)$_2$, Me$_4$NCl, K$_3$PO$_4$•H$_2$O, Et$_3$N, toluene, reflux	 R^1 / R^2: H / 6-F (70); H / 6-CO$_2$Me (71); 3-OBn / 4-OMe (39)	199
C_{16} 	 CO$_2$*t*-Bu, Pd$_2$(dba)$_3$, SPhos, K$_3$PO$_4$•H$_2$O, Et$_3$N, toluene, reflux	 (60)	199
	PhB(OH)$_2$, Pd(OAc)$_2$, SPhos, K$_3$PO$_4$•H$_2$O, toluene	 Temp (°) 100, Time (h) 2 (72) Temp (°) 90, Time (h) 4 (72)	200 202

C_{17-19} 	$PdCl_2$(dppf), KOAc, DMF, 90°, 4 h		R: 2-Cl-3-pyridyl (91); Ph (45); OBn (85)	194
C_{17-21} 	$PdCl_2$(dppf), KOAc, DMF, 90°, 4 h		see below	194
C_{19} 	 CO_2t-Bu, $Pd(OAc)_2$, P(*o*-tol)$_3$, K_3PO_4•H_2O, Et_3N, toluene, reflux		(43)	199
C_{22} 	 CO_2t-Bu, $Pd(OAc)_2$, P(*o*-tol)$_3$, K_3PO_4•H_2O, Et_3N, toluene, reflux		(64)	199
	$Pd(OAc)_2$, (*t*-Bu)$_3$P•HBF_4, K_2CO_3, toluene, 100°, 14 h		(81)	207

R	
2-Cl-3-pyridyl	(91)
Ph	(45)
OBn	(85)

R^1	R^2	
5-NO_2	2-Br	(90)
6-NO_2	2-Br	(83)
H	3,4-OCH_2O	(92)
6-NO_2	3,4-OCH_2O	(94)
5-OMe	3,4-OCH_2O	(90)
H	4-CO_2Et	(89)
6-NO_2	4-CH_2CO_2Et	(93)
5-OMe	4-CO_2Et	(94)

TABLE 10. 2-SUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION (*Continued*)

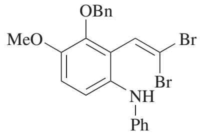
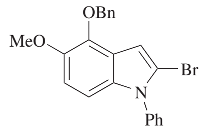
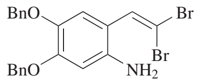
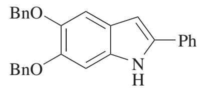
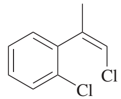
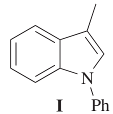
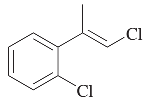
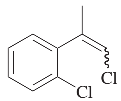
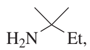
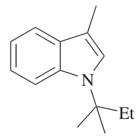
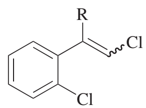
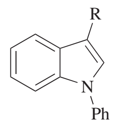
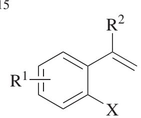
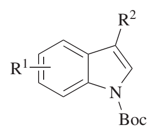
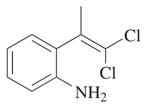
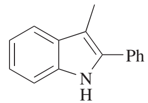
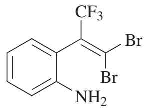
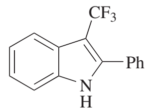
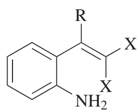
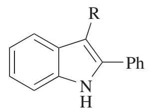
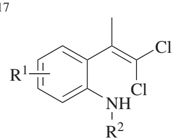
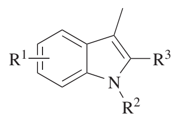
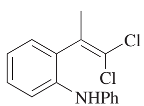
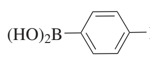
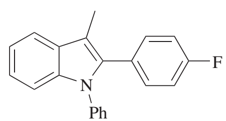
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{22} 	$Pd(OAc)_2$, $(t\text{-}Bu)_3P \bullet HBF_4$, K_2CO_3, toluene, 100°, 14 h	 (73)	207
	$PhB(OH)_2$, $Pd(OAc)_2$, SPhos, $K_3PO_4 \bullet H_2O$, toluene, 90°, 4 h	 (57)	207

TABLE 11. 3-SUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 	$PhNH_2$, $Pd_2(dba)_3$, DavePhos, *t*-BuONa, toluene, 100°, 25 h	 (73)	190
	$PhNH_2$, $Pd_2(dba)_3$, DavePhos, *t*-BuONa, toluene, 100°, 25 h	**I** (82)	190
	, $Pd(OAc)_2$, HP(*t*-Bu)$_3$BF$_4$, *t*-BuONa, toluene, 130°, 4 h	 (66)	191
C_{9-14} 	$PhNH_2$, $Pd_2(dba)_3$, DavePhos, *t*-BuONa, toluene, 100°	 R: Me (78); Ph (94)	190
C_{11-15} 	$BocNH_2$, $Pd_2(dba)_3$, SPhos, Cs_2CO_3, toluene, 110°, 6 h		192

X	R^1	R^2	
Br	4-Cl	CO_2Et	(61)
Cl	4-Cl	3-furyl	(61)
Cl	4-Cl	4-$MeOC_6H_4$	(71)
Br	5-Cl	4-$MeOC_6H_4$	(75)
Br	6-Cl	4-$MeOC_6H_4$	(81)
Br	7-Cl	4-$MeOC_6H_4$	(—)

TABLE 12. 2,3-DISUBSTITUTED INDOLES VIA *N*-VINYLATION AND *N*-ARYLATION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 	$PhB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 100°, 2 h	 (96)	200
	$PhB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 100°, 1 h	 (79)	200
$C_{9–16}$ 	$PhB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 90–100°, 4 h	 R / X CF_3 / Br (79) Me / Cl (96) 4-FC_6H_4 / Br (90) Ph—≡—⌇ / Br (77)	202
$C_{10–17}$ 	$R^3B(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 90–100°, 4 h	 R^1 / R^2 / R^3 5-O_2N / Me / Ph (90) H / Ph / 4-FC_6H_4 (96) H / 4-FC_6H_4 / Ph (94) H / 2-MeC_6H_4 / Ph (77) H / 4-$CF_3C_6H_4$ / 4-$MeOC_6H_4$ (79) H / 4-$MeCOC_6H_4$ / 2-MeC_6H_4 (75)	202
C_{15} 	, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 100°	 (96)	200

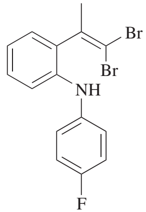
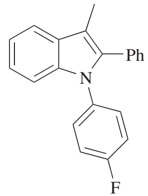
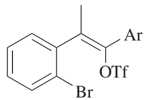
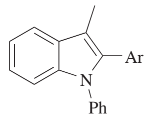
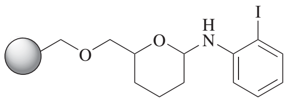
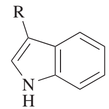
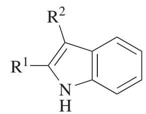
	$PhB(OH)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4•H_2O, toluene, 100°		(94)	200
C_{16}				
	$PhNH_2$, $Pd_2(dba)_3$, DPEPhos, *t*-BuONa, toluene, 100°		Ar: Ph (74); 4-FC_6H_4 (65)	210

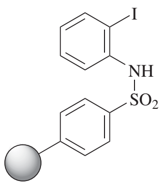
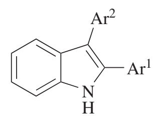
TABLE 13. SOLID-PHASE SYNTHESIS OF INDOLES FROM ALKYNES

Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
C_6 	*Indole formation* TMS—≡—R, $PdCl_2(PPh_3)_2$, TMG, DMF, 110° *Cleavage* TFA, CH_2Cl_2, 15 min		228

R	% Mass Recovery
CH_2CH_2OH	82
Ph	73

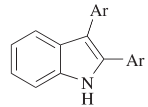
Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
	Indole formation R^1—≡—R^2, $PdCl_2(PPh_3)_2$, TMG, DMF, 110° *Cleavage* TFA, CH_2Cl_2, 15 min		228

R^1	R^2	% Mass Recovery
t-Bu	Me	55
Pr	Pr	55
Ph	Et	63[b]
Ph	Ph	97

Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
	*Indole formation* ≡—Ar^1, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 70° *Bromination (at C3)* NBS, dioxane, 70°, 24 h *Suzuki cross-coupling* $Ar^2B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, DMF, 90°, 5–10 h *Cleavage* Bu_4NF, THF, 70°, 5 h		225

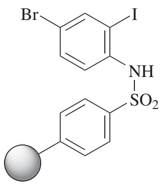
Ar^1	Ar^2		% Purity
$4\text{-}FC_6H_4$	Ph	(87)	91
$4\text{-}FC_6H_4$	$4\text{-}ClC_6H_4$	(86)	92
$4\text{-}FC_6H_4$	$4\text{-}MeOC_6H_4$	(86)	85
$4\text{-}O_2NC_6H_4$	3-thienyl	(93)	96
$4\text{-}O_2NC_6H_4$	$4\text{-}MeOC_6H_4$	(87)	96
$4\text{-}O_2NC_6H_4$	$4\text{-}MeSC_6H_4$	(99)	96
$4\text{-}O_2NC_6H_4$	1-Np	(91)	99
$4\text{-}MeC_6H_4$	4-pyridyl	(92)	84
$4\text{-}MeC_6H_4$	$4\text{-}MeOC_6H_4$	(85)	93
$4\text{-}MeC_6H_4$	$4\text{-}MeO_2CC_6H_4$	(94)	87

Indole formation
≡—TMS, $PdCl_2(PPh_3)_2$,
CuI, Et_3N, DMF, 70°
Bromination (at C2 and C3)
NBS, dioxane, 70°, 24 h
Suzuki cross-coupling
$ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3,
DMF, 90°, 5–10 h
Cleavage
Bu_4NF, THF, 70°, 5 h

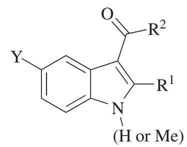


Ar		% Purity
4-MeC_6H_4	(81)	90
4-$MeOC_6H_4$	(84)	86

225



Indole formation
≡—R^1, $PdCl_2(PPh_3)_2$,
CuI, Et_3N, DMF, rt, 24 h
Acylation (at C3)
R^2COCl, $AlCl_3$, CH_2Cl_2, 12 h
Sonogashira cross-coupling (at C5)
≡—R^3, $PdCl_2(PPh_3)_2$,
CuI, Et_3N, DMF, 70°, 24 h
or *Suzuki cross-coupling*
$ArB(OH)_2$, $PdCl_2(dppf)$, K_2CO_3,
dioxane, 90°, 24 h
Cleavage
t-BuOK, rt
Alkylation after cleavage
MeI



(10–20)

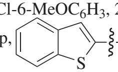
Y: R^3—≡—, Ar
R^1: Pr, Ph, 2-FC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4
R^2: Me, *i*-Pr, *c*-Pr, Cy, Ph, 3-FC_6H_4, 4-FC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-PhC_6H_4, 4-(*i*-Pr)C_6H_4, 1-Np
R^3: Pr, CH_2=C(Me), Ph, 2-FC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, Bn
Ar: Ph, 2-MeC_6H_4, 3,4-$Cl_2C_6H_3$, 3-F-4-MeC_6H_3, 2,3-$Me_2C_6H_3$, 4-(*i*-Pr)C_6H_4, 2-Cl-6-$MeOC_6H_3$, 2-NCC_6H_4, 4-$PhOC_6H_4$, 3,4-$F_2C_6H_3$, 2-Np, 

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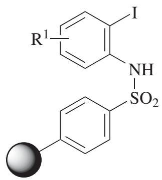
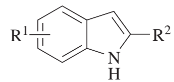
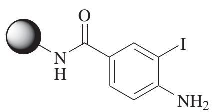
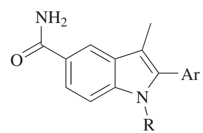
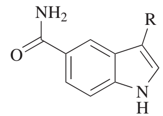
TABLE 13. SOLID-PHASE SYNTHESIS OF INDOLES FROM ALKYNES (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)[a]					Refs.
			R^1	R^2		% Purity	
C_{6-8} 	*Indole formation* ≡—R^2, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 60–70°, 5–16 h *Cleavage* Bu_4NF, THF, 70°, 5 h		H	Bu	(89)	92	229
			H	$MeOCH_2$	(97)	93	
			H	$HOCH_2CH_2$	(90)	—	
			H	$(EtO)_2CH$	(94)	—	
			H	Ph	(100)	95	
			H	$4\text{-}MeC_6H_4$	(97)	95	
			H	$4\text{-}FC_6H_4$	(100)	98	
			H	$4\text{-}MeOC_6H_4$	(95)	97	
			6-F	$PhSCH_2$	(85)	98	
			6-F	6-MeO-2-Np	(97)	95	
			6-OMe	$MeOCH_2$	(94)	86	
			6-OMe	$4\text{-}O_2NC_6H_4$	(90)	96	
			6-OMe	$4\text{-}MeC_6H_4$	(98)	85	
			6-OMe	$4\text{-}MeOC_6H_4$	(85)	91	
			$5\text{-}CO_2Me$	Bu	(87)	94	
			$5\text{-}CO_2Me$	2-pyridyl	(87)	100	
			$5\text{-}CO_2Me$	$PhSCH_2$	(85)	100	
			R	Ar		% Purity	
C_7 	*Indole formation* TMS—≡—, $Pd(OAc)_2$, PPh_3, Bu_4NI, Na_2CO_3, DMF, 80°, 5 h *Iodination (at C2)* NIS, CH_2Cl_2, rt, 2 h *N-Alkylation* RBr, Cs_2CO_3, DMF *Suzuki cross-coupling* $ArB(OH)_2$, $Pd_2(dba)_3$ or $Pd(PPh_3)_4$, K_2CO_3, DMF or DMF/H_2O, 80°, 6–20 h *Cleavage* TFA		H	Ph	(87)	—	225
			H	$4\text{-}MeC_6H_4$	(65)	—	
			H	$4\text{-}MeOC_6H_4$	(94)	85	
			H	1-Np	(96)	96	
			4-F-Bn	$4\text{-}MeC_6H_4$	(75)[c]	—	
			4-F-Bn	$4\text{-}MeOC_6H_4$	(74)[c]	—	

Indole formation
R—≡—TMS, $Pd(OAc)_2$,
PPh_3, Bu_4NI, Na_2CO_3,
DMF, 80°, 6–16 h
Cleavage
TFA, CH_2Cl_2, 1 h



R		% Purity[c]
Me	(77)	—
CH_2CH_2OH	(95)	85
CH_2CH_2Cl	(88)	96
Ph	(56)	—
CH_2OCH_2-3-$MeOC_6H_4$	(90)	92

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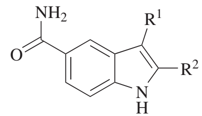
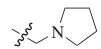
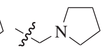
Indole formation
R^1—≡—R^2, $Pd(OAc)_2$,
PPh_3, LiCl, K_2CO_3,
DMF, 80°, 15–22 h
Cleavage
TFA, CH_2Cl_2, 1 h



R^1	R^2		% Purity[c]
Me	*t*-Bu	(87)	84
Pr	Pr	(91)	82
Me	Ph	(86)	72
CO_2Et	Ph	(38)[c]	—
		(63)[d]	—

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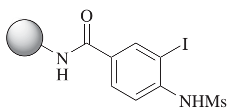
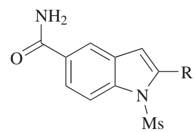
C_8



Indole formation
≡—R, $PdCl_2(PPh_3)_2$,
CuI, Et_3N,
DMF, 80°, 5–16 h
Cleavage
TFA, CH_2Cl_2, 1 h



R		% Purity
CH_2NMe_2	(86)	98
n-C_5H_{11}	(90)	79
Ph	(87)	90
Bn	(96)	90

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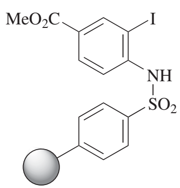
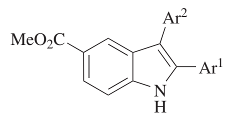


Indole formation
≡—Ar^1, $PdCl_2(PPh_3)_2$,
CuI, Et_3N, DMF, 70°
Bromination (at C3)
NBS, dioxane, 70°, 24 h
Suzuki cross-coupling
$Ar^2B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3,
DMF, 90°, 5–10 h
Cleavage
Bu_4NF, THF, 70°



Ar^1	Ar^2	
Ph	3,4-OCH_2O-C_6H_3	(86)
Ph	2-Np	(85)

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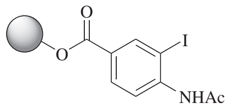
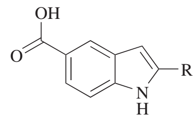
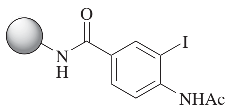
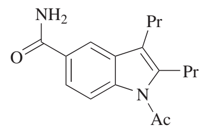
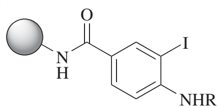
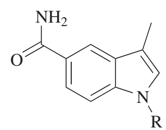
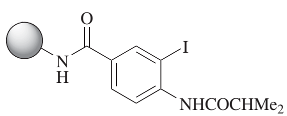
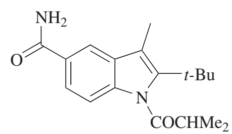
TABLE 13. SOLID-PHASE SYNTHESIS OF INDOLES FROM ALKYNES (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
C_9 	*Indole formation* ≡—R, $PdCl_2(PPh_3)_2$, CuI, TMG, dioxane, 90°, 18 h *Cleavage* NaOH, *i*-PrOH, 50°, 5 h	 R [c] Pr (55) $(CH_2)_3OH$ (95) *i*-Bu (82) Ph (72) 4-ClC_6H_4 (52) 4-$MeOC_6H_4$ (48) CH_2SPh (81)	222
	*Indole formation* Pr—≡—Pr, $Pd(OAc)_2$, PPh_3, Bu_4NCl, KOAc, DMF, 80°, 16 h *Cleavage* TFA, CH_2Cl_2, 1 h	 (95)	226
C_{9-11} 	*Indole formation* —≡—TMS, $Pd(OAc)_2$, PPh_3, Bu_4NCl, Na_2CO_3, DMF, 80°, 7–120 h *Cleavage* TFA, CH_2Cl_2, 1 h	 R Ac (93) $COCHMe_2$ (100)	226
C_{11} 	*Indole formation* —≡—*t*-Bu, $Pd(OAc)_2$, PPh_3, LiCl, K_2CO_3, DMF, 80°, 120 h *Cleavage* TFA, CH_2Cl_2, 1 h	 (75)	226

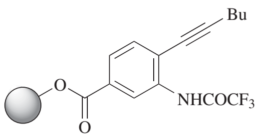
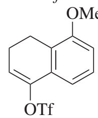
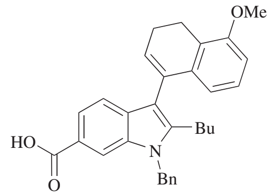
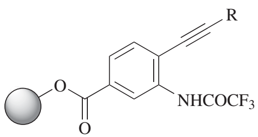
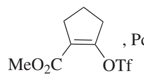
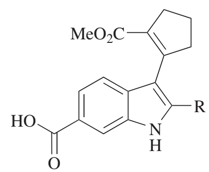
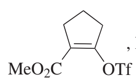
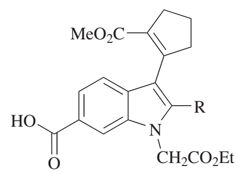
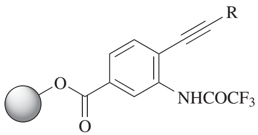
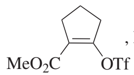
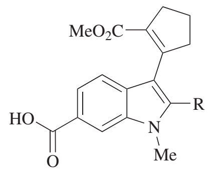
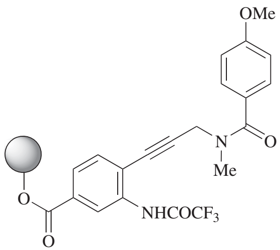
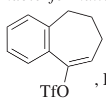
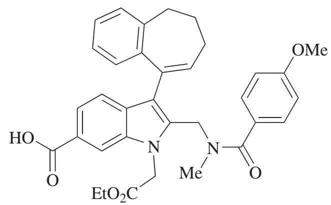
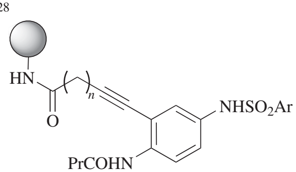
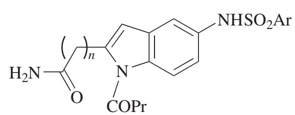
C_{15} 	*Indole formation*  , $Pd(PPh_3)_4$, K_2CO_3, DMF, rt, 24 h *N-Alkylation* BnBr, NaH, DMF, rt, 4 h *Cleavage* TFA, CH_2Cl_2, 1 h		(81)	223
$C_{15–22}$ 	*Indole formation*  , $Pd(PPh_3)_4$, K_2CO_3, DMF, rt, 24 h *Cleavage* TFA, CH_2Cl_2, 1 h		R Bu (65) *c*-C_5H_9 (75) Ph (60) CH_2CH_2Ph (60) $CH_2N(Me)COC_6H_44$-OMe (76) $CH_2CH_2CH_2OC_6H_43$-CO_2Me (68)	223
	Indole formation  , $Pd(PPh_3)_4$, K_2CO_3, DMF, rt, 24 h *N-Alkylation* $BrCH_2CO_2Et$, NaH, DMF, rt, 4 h *Cleavage* TFA, CH_2Cl_2, 2 h		R Bu (55) *c*-C_5H_9 (38) Ph (71) CH_2CH_2Ph (67) $CH_2N(Me)COC_6H_44$-OMe (73) $CH_2CH_2CH_2OC_6H_43$-CO_2Me (40)	223

TABLE 13. SOLID-PHASE SYNTHESIS OF INDOLES FROM ALKYNES (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
C_{15-22} 	*Indole formation* , $Pd(PPh_3)_4$, K_2CO_3, DMF, rt, 24 h *N-Alkylation* MeI, NaH, DMF, rt, 4 h *Cleavage* TFA, CH_2Cl_2, 2 h	 R Bu (33) c-C_5H_9 (41) Ph (58) CH_2CH_2Ph (62) $CH_2N(Me)COC_6H_4$4-OMe (70) $CH_2CH_2CH_2OC_6H_4$3-CO_2Me (58)	223
C_{21} 	*Indole formation* , $Pd(PPh_3)_4$, K_2CO_3, DMF, rt, 24 h *N-Alkylation* $BrCH_2CO_2Et$, NaH, DMF, rt, 4 h *Cleavage* TFA, CH_2Cl_2, rt, 1 h	 (55)	223
C_{22-28} 	*Indole formation* $PdCl_2(MeCN)_2$, THF, MW, 160°, 10 min *Cleavage* TFA, CH_2Cl_2, rt, 2 h	 n Ar 2 2-$CF_3C_6H_4$ (79) 4 2-$CF_3C_6H_4$ (71) 4 3-$CF_3C_6H_4$ (71) 8 2-$CF_3C_6H_4$ (65) 8 3-$CF_3C_6H_4$ (68) 8 4-$CF_3C_6H_4$ (75)	227

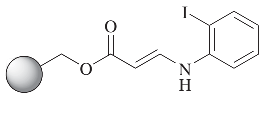
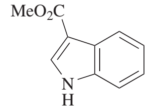
[a] The number is the crude yield given for all steps.

[b] The product was isolated as an 84:16 isomeric mixture.

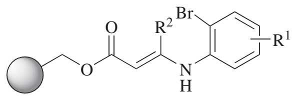
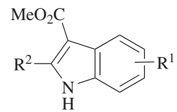
[c] The number was determined by HPLC.

[d] The product was purified by preparative TLC.

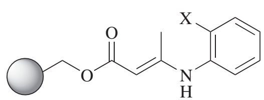
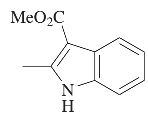
TABLE 14. SOLID-PHASE SYNTHESIS OF INDOLES FROM ALKENES

Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
C_9 	*Indole formation* $Pd_2(dba)_3$, ligand, Et_3N, DMF, 110°, 15 h *Cleavage* MeONa, MeOH/THF, 60°, 12 h		234

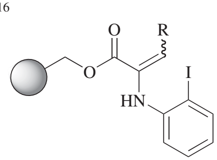
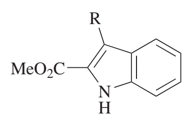
Ligand		% Purity
—	(74)	83
P(*o*-tol)$_3$	(78)	87

Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
$C_{9–11}$ 	*Indole formation* $Pd_2(dba)_3$, P(*o*-tol)$_3$, Et_3N, DMF, 110°, 15 h *Cleavage* MeONa, MeOH/THF, 60°, 12 h		234

R^1	R^2		% Purity
H	H	(69)	90
6-NO_2	H	(39)	90
H	Me	(53)	92
5-Me	H	(57)	—
5-CF_3	H	(65)	—
6-CF_3	H	(66)	82
5-Me	Me	(43)	93
6-CF_3	Me	(32)	93

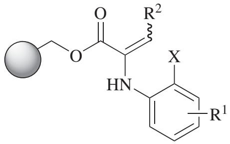
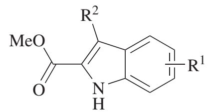
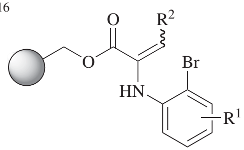
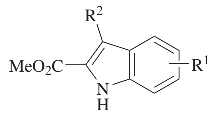
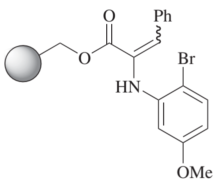
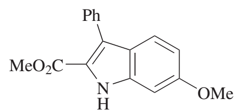
Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
C_{10} 	*Indole formation* $Pd(OAc)_2$, ligand, Et_3N, DMF, 110°, 15 h *Cleavage* MeONa, MeOH/THF, 60°, 12 h		234

X	Ligand		% Purity
I	—	(27)	91
I	P(*o*-tol)$_3$	(63)	90
Br	P(*o*-tol)$_3$	(35)	93

Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
$C_{13–16}$ 	*Indole formation* $Pd_2(dba)_3$, P(*o*-tol)$_3$, Et_3N, DMF, 110°, 12 h *Cleavage* MeONa, MeOH/THF, rt, 6–12 h		234

R		% Purity
2-thienyl	(31)	55
n-C_5H_{11}	(60)	—
c-C_6H_{11}	(72)	—
Ph	(48)	70
4-$MeOC_6H_4$	(40)	52

TABLE 14. SOLID-PHASE SYNTHESIS OF INDOLES FROM ALKENES (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
$C_{13\text{-}16}$			
	1. Pd_2dba_3, P(*o*-tol)$_3$, Et_3N, DMF, 120°, 2 h 2. MeONa, THF/MeOH		396
$C_{14\text{–}16}$			
	*Indole formation* $Pd_2(dba)_3$, P(*o*-tol)$_3$, Et_3N, DMF, 110°, 12 h *Cleavage* MeONa, MeOH/THF, rt, 6–12 h		234
C_{16}			
	*Indole formation* $Pd_2(dba)_3$, ligand, base, DMF, 110°, 12 h *Cleavage* MeONa, MeOH/THF, rt, 6–12 h		234

Products for $C_{13\text{-}16}$ (ref. 396):

X	R^1	R^2	
I	H	2-thienyl	(31)
Br	H	2-pyridyl	(54)
Br	H	Ph	(52)
I	H	Ph	(48)
I	H	4-$MeOC_6H_4$	(40)
Br	4-Me	Ph	(62)

Products for $C_{14\text{–}16}$ (ref. 234):

R^1	R^2		% Purity
H	2-pyridyl	(54)	65
H	Ph	(52)	82
5,7-F_2	Ph	(40)	69
6-NO_2	Ph	(60)	—
5-Me	Ph	(62)	88
5-CF_3	Ph	(56)	—
6-CF_3	Ph	(62)	—

Products for C_{16} (ref. 234):

Ligand	Base		% Purity
P(*o*-tol)$_3$	Et_3N	(25)	—
HP(*t*-Bu)$_3BF_4$	(*c*-$C_6H_{11})_2NMe$	(67)	—

[a] The number is the crude yield given for all steps.

TABLE 15. SOLID-PHASE SYNTHESIS VIA *N*-ARYLATION

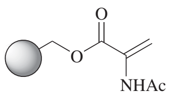
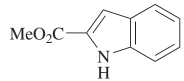
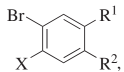
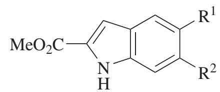
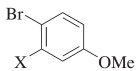
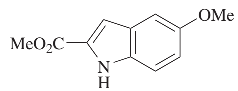
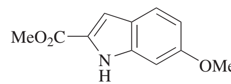
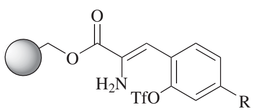
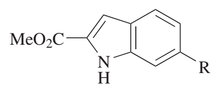
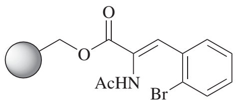
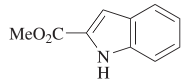
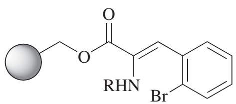
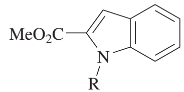
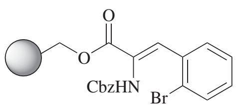
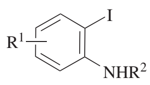
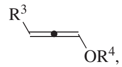
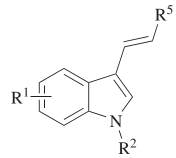
Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
C_5 	*Domino Heck reaction/Indole formation* 1-Br-2-XC_6H_4, $Pd_2(dba)_3$, $(t\text{-}Bu)_3P$, $(c\text{-}C_6H_{11})_2NMe$, toluene, 100°, 24 h *Cleavage* MeONa, MeOH/THF, rt, 12 h	 X: I (46) X: Br (78)	234 235
	Domino Heck reaction/Indole formation  , $Pd_2(dba)_3$, $HP(t\text{-}Bu)_3BF_4$, $(c\text{-}C_6H_{11})_2NMe$ *Cleavage* MeONa, MeOH/THF, rt, 12 h	 X / R^1 / R^2 / Solvent: OTf / H / H / DME (48) Br / Me / Me / toluene (82)	234, 235
	Domino Heck reaction/Indole formation  , $Pd_2(dba)_3$, $HP(t\text{-}Bu)_3BF_4$, $(c\text{-}C_6H_{11})_2NMe$, toluene *Cleavage* MeONa, MeOH/THF, rt, 12 h	 (39) +  (31)	234, 235
C_{10-11} 	*Indole formation* $Pd_2(dba)_3$, $HP(t\text{-}Bu)_3BF_4$, $(c\text{-}C_6H_{11})_2NMe$, DME, 100°, 38 h *Cleavage* MeONa, MeOH/THF, rt, 12 h	 R: H (48) R: MeO (43)	234

TABLE 15. SOLID-PHASE SYNTHESIS VIA *N*-ARYLATION (*Continued*)

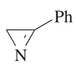
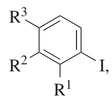
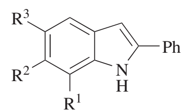
Substrate	Conditions	Product(s) and Yield(s) (%)[a]	Refs.
C_{11} 	*Indole formation* $Pd_2(dba)_3$, $(t\text{-}Bu)_3P$, $(c\text{-}C_6H_{11})_2NMe$, toluene, 80°, 12 h *Cleavage* MeONa, MeOH/THF, rt, 12 h	 **I** (99)	234
C_{16} 	*Indole formation* $Pd_2(dba)_3$, $(t\text{-}Bu)_3P$, $(c\text{-}C_6H_{11})_2NMe$, toluene, 80°, 12 h *Cleavage* MeONa, MeOH/THF, rt, 12 h	 **I** R: 2-MeC_6H_4 (44); 4-$CF_3C_6H_4$ (48)	234
C_{17} 	*Indole formation* $Pd_2(dba)_3$, $(t\text{-}Bu)_3P$, $(c\text{-}C_6H_{11})_2NMe$, toluene, 80°, 12 h *Cleavage* MeONa, MeOH/THF, rt, 12 h	**I** (62)	234

[a] The number is the crude yield given for all steps.

TABLE 16. MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{7-13} 	 $Pd(OAc)_2$, Bu_4NBr, NaOAc, DMSO, 110°		400

R^1	R^2	R^3	R^4	R^5	Time (h)		(E):(Z)
H	Me	Me	THP	H	1.5	(90)	—
H	Me	Pr	CH_2OEt	Et	1.5	(80)	>99:1
6-Cl	Me	Pr	MEM	Et	1.5	(77)	>99:1
H	Ac	Me	CH_2OEt	CO_2Me	3	(85)	—
5-NC	Me	Pr	MEM	Et	1.5	(87)	>99:1
H	Bn	Pr	MEM	Et	2.5	(84)	>99:1

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8 	 $Pd(OAc)_2$, $(3\text{-}ClC_6H_4)_3P$, norbornene, Cs_2CO_3, MeCN, reflux, 16 h[a]		401

R^1	R^2	R^3	
Cl	H	H	(64)
MeO	H	H	(54)
Me	H	H	(55)
Me	F	H	(55)
Me	CF_3	H	(64)
Me	H	NHAc	(68)

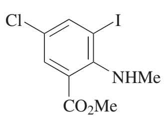
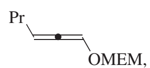
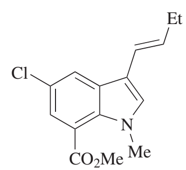
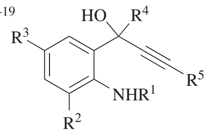
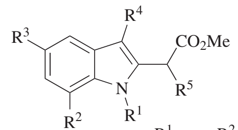
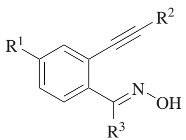
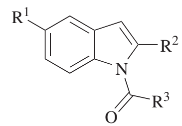
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 	 $Pd(OAc)_2$, Bu_4NBr, NaOAc, DMSO, 110°, 1.5 h	 (76), (E):(Z) = 99:1	400

TABLE 16. MISCELLANEOUS (*Continued*)

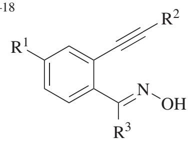
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13-19} 	PdI_2, KI, CO (90 atm), MeOH, 100°, 2 h		402

R^1	R^2	R^3	R^4	R^5	
H	H	H	Me	TMS	(88)
H	H	H	Me	*t*-Bu	(66)[b]
H	H	H	Me	*t*-Bu	(75)
H	MeO	H	Me	TMS	(42)
H	H	Cl	Me	*t*-Bu	(68)
Me	H	H	Me	*t*-Bu	(44)
H	MeO	H	Me	*t*-Bu	(45)
H	H	H	Ph	TMS	(63)
H	H	H	Ph	*t*-Bu	(60)

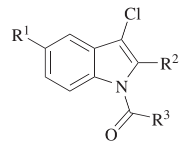
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13-21} 	1. cyanuric chloride, $InCl_3$, MeCN, reflux 2. $PdCl_2(MeCN)_2$, reflux, overnight		403

R^1	R^2	R^3	
H	*c*-C_3H_5	Me	(53)
H	TMS	Me	(—)
H	Bu	Me	(62)
H	Bu	Et	(53)
H	Ph	Me	(80)
Cl	Ph	Me	(52)
H	4-MeC_6H_4	Me	(74)
H	4-$MeOC_6H_4$	Me	(62)
H	Ph	Et	(74)
Me	Ph	Me	(66)
H	4-MeC_6H_4	Et	(70)
H	4-$MeOC_6H_4$	Et	(60)
Me	4-MeC_6H_4	Me	(70)
H	Ph	Ph	(—)

C_{16-18}



1. cyanuric chloride, $InCl_3$, MeCN, reflux
2. $PdCl_2(MeCN)_2$, $CuCl_2$, reflux, overnight



R^1	R^2	R^3	
H	Ph	Me	(66)
Cl	Ph	Me	(50)
H	Ph	Et	(70)
Me	Ph	Me	(50)
H	4-MeC_6H_4	Et	(61)
Me	4-MeC_6H_4	Me	(63)

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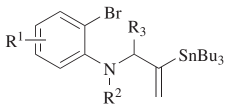
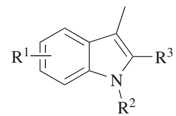
C_{23-29}



$PdCl_2(allyl)_2$, PPh_3, THF, 60°



R^1	R^2	R^3	Time (h)	[c]
5-Br	COMe	H	20	(82)
H	Bn	Me	48	(65)

404

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[a] 2*H*-Azirine was added at the rate of 0.26 mL/min.

[b] The reaction was performed under 60 atm of CO.

[c] The corresponding indolines were isolated in variable amounts.

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