Transition Metal-Catalyzed Direct Arylation of Substrates with Activated sp^3-Hybridized C−H Bonds and Some of Their Synthetic Equivalents with Aryl Halides and Pseudohalides

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Received March 2, 2009

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1. Introduction

Transition metal-catalyzed cross-coupling reactions of alkyl metals and aryl halides or pseudohalides have emerged as a powerful methodology for the formation of Csp^3-Csp^2 bonds over the past decades.[1] However, significant attention has also been focused on Pd- and Ni-catalyzed Csp^3-Csp^2 bond-forming reactions that involve aryl metals and haloalkyl compounds lacking β-hydrogen atoms as cross-coupling partners.[2] In contrast, until a few years ago, few examples were reported in the literature concerning transition metal-catalyzed reactions of aryl metals with functionalized alkyl halides including α-halocarbonyl compounds and α-bromosulfones bearing β-hydrogen atoms,[3] and a single example of Pd-catalyzed cross-coupling reaction of aryl metals and unfunctionalized alkyl halides bearing β-hydrogen atoms had been described.[4] Only in recent years, successful procedures for the Pd-,[5] Ni-,[6] Rh-,[7] Fe-,[8] V-,[9] Co-,[10] and Cu-catalyzed[11] cross-coupling reactions of aryl metals and unfunctionalized alkyl halides bearing β-hydrogen atoms have been developed.[12] Nevertheless, new, effective, and more environmentally benign methodologies for the formation of (cyclo)alkyl−aryl bonds, which require a reduced number of synthetic operations, have emerged as valuable alternatives to the conventional cross-coupling reactions.

These methodologies (Scheme 1) are based on transition metal-catalyzed simple or 2-fold C−H bond functionalization according to the following approaches: (a) highly regioselective Pd-catalyzed direct arylation reactions of unactivated sp^3-hybridized C−H bonds with aryl halides (eq a, Scheme 1);[13] (b) Pd-catalyzed direct alkylation reactions of aryl C−H bonds with alkyl metals (eq b, Scheme 1);[14] Au-[15] or Pd-catalyzed[16] direct alkylation reactions of aryl C−H bonds with alkyl halides or pseudohalides (eq c, Scheme 1); (d) Pd-catalyzed arylations of unactivated sp^3-hybridized C−H bonds with aryl metals (eq d, Scheme 1);[14c] (e) Pd-, Ru-, or Cu-catalyzed cross-coupling reactions of sp^3-hybridized C−H bonds with arylboronic acids using air as oxidant (eq d, Scheme 1);[17] and (f) cross-dehydrogenative coupling of alkyl and aryl C−H bonds (eq e, Scheme 1).[18] Finally, great attention, particularly in the past decade, has also been focused on the design, development, and application of transition metal-catalyzed coupling reactions of aryl halides and pseudohalides with a wide variety of substrates containing activated sp^3-hybridized C−H bonds (eq f, Scheme 1). A mini-review on this topic was published by Scolastico and Poli in 1999,[19] and three excellent reviews that concern the results obtained in this rapidly growing area of extensive research by the groups of Miura, Natsume, Hartwig, and Buchwald up to the end of 2002 were published by Miura,[20] Hartwig,[21] and Lloyd-Jones[22] a few years later. However, the reviews by Miura[20] and Hartwig[21] were limited in that they fundamentally emphasized the author's own work and

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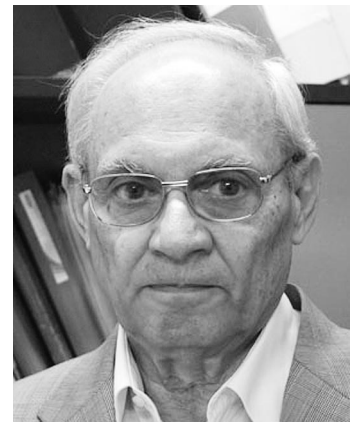
10.1021/cr9000836
Published on Web 07/17/2009

Fabio Bellina was born in Catania (Italy) in 1964. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in 1990. In 1992 he joined the University of Pisa as an Organic Chemistry Researcher at the Department of Chemistry and Industrial Chemistry. In October 2003 he was appointed by the Faculty of Science of the University of Pisa as an Associate Professor of Organic Chemistry. His research interests were initially mainly devoted to the total synthesis of naturally occurring compounds of biological and/or pharmacological interest and to the synthesis of structural analogues of naturally occurring fungicidal derivatives of agrochemical interest. More recently, Prof. Bellina focused his attention on new and efficient protocols for regioselective transition metal-mediated carbon−carbon and carbon−heteroatom bond-forming reactions, with a particular interest towards the selective functionalization of oxygen-containing unsaturated heterocycles such as 2(5*H*)-furanones and 2(2*H*)-pyranones. Currently, he is working on the development of novel and efficient protocols for the transition metal-catalyzed direct C−H and N−H arylations of heteroarenes and for the direct functionalization of active C(sp^3)−H bonds, and on the applications of these new procedures to the selective preparation of bioactive natural and synthetic compounds.



Renzo Rossi was born in Pisa (Italy) and graduated in Organic Chemistry with first-class honours at the University of Pisa defending a thesis performed under the guidance of Professor Piero Pino. In 1969 he became Assistant Professor and in 1971 he earned the libera docenza in Organic Chemistry. After holding other intermediate positions at the University of Pisa and the Scuola Normale Superiore of Pisa, in 1980 he became Full Professor of Organic Chemistry at the University of Calabria. In 1982, he joined again the University of Pisa where he has held the Chair of Chemistry of Naturally Occurring Compounds. In 1999, the University of Pisa awarded him the *Ordine del Cherubino*. His current research interests include (i) the preparation of substances that exhibit significant cytotoxicity against human tumor cell lines and antivascular properties; (ii) the study of new methodologies for carbon−carbon bond formation that involve the use of organometallic reagents, transition metal-catalyzed direct arylation reactions of substrates with activated sp^3-hybridized C−H bonds with aryl halides and pseudohalides; (iii) the design and development of new, highly chemo- and regioselective methods for the transition metal-catalyzed direct C- and N-arylation of electron-rich heteroaromatic systems, including free (NH)-azoles, with aryl halides and pseudohalides; and (iv) the application of these methods to the synthesis of direct precursors to compounds with relevant biological properties. In recent years, several successful studies have also been performed by his research group in the field of the synthesis and evaluation of the biological properties of naturally occcurring compounds of marine origin and their structural analogues, which are characterized by the 2(5*H*)-furanone ring. Professor Rossi, who has coauthored over 220 research publications and a number of highly cited review articles and patents, is a fellow of the Royal Society of Chemistry, the American Chemical Society, and the Società Chimica Italiana.

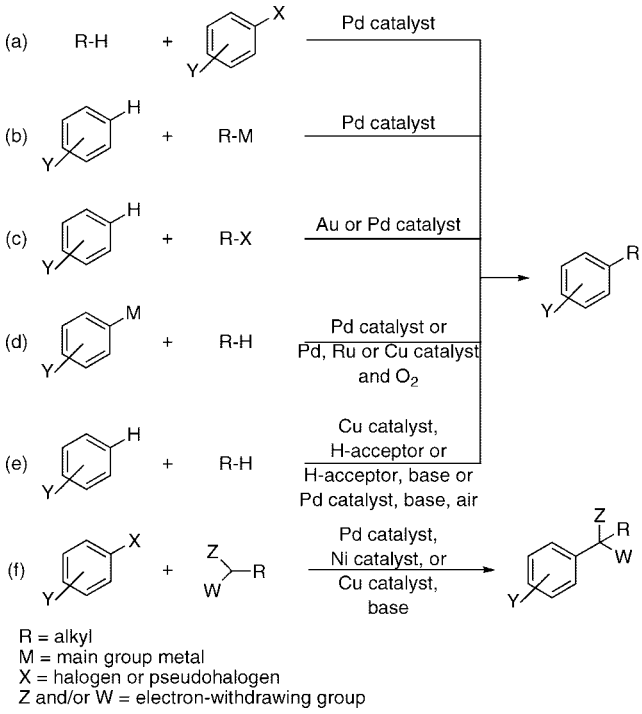
the review by Lloyd-Jones[22] gave only a general overview of this highly attractive research area.

The present review aims to give a complete picture of these direct arylation reactions of substrates with activated sp^3-hybridized C−H bonds, which, because of their general efficiency and high atom economy, represent a very useful and convenient tool for the formation of Csp^3-Csp^2 bonds in the α-position to electron-withdrawing functional groups, including keto, imino, formyl, cyano, nitro, alkoxycarbonyl, sulfonyl, and sulfoximino groups. The review is also focused on the catalyst systems and experimental conditions used for the regioselective synthesis of α-arylated compounds via transition metal-catalyzed arylation of synthetic equivalents of carbonyl compounds, including silyl enol ethers and enol esters of ketones and silyl ketene acetals, using aryl halides or pseudohalides as electrophiles. Finally, a further aim of the review is to highlight the utility of all these experimentally simple reactions, which do not require the preparation of stoichiometric amounts of organometallics, as tools of paramount importance for the regiocontrolled, chemoselective, and efficient synthesis of fine chemicals, comprising compounds of pharmacological interest, bioactive natural products, and their precursors. Limitations and problems associated with the use of some protocols of the direct arylation reactions will also be illustrated and discussed.

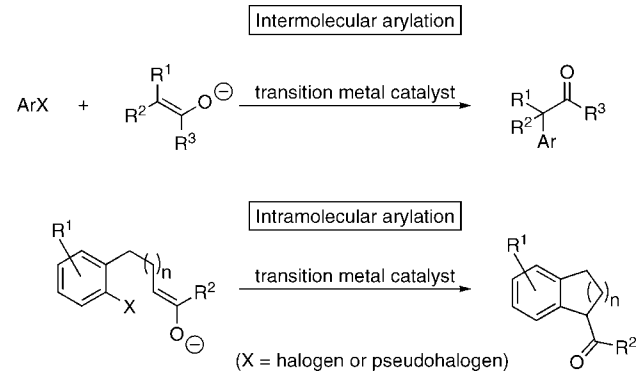
The literature on these topics with 563 references has been covered up to the end of June 2008 and includes in large part that concerned with the results obtained in Miura's, Natsume's, Hartwig's, and Buchwald's seminal work on the α-arylation of substrates with acidic sp^3-hybridized C−H bonds, which have already been the subject of the reviews by Miura,[20] Hartwig,[21] and Lloyd-Jones,[22] as well as the data on this subject area published up to the end of 2002, but not reported and commented in these reviews. In fact, our aim is to give an exhaustive and clear picture of all the literature data concerning the transition metal-catalyzed direct arylation of substrates with activated sp^3-hybridized C−H bonds and some their relevant synthetic equivalents. Nevertheless, much more attention has been directed to summarize and comment the literature data published from the beginning of 2003 up to the end of June 2008 on the significant developments achieved for improving the scope of these transition metal-catalyzed intra- and intermolecular arylation reactions and for increasing the reactivity and chemo- and regioselectivity of their catalyst systems. These data comprise those concerned with asymmetric versions of arylation reactions that enable the highly enantioselective synthesis of carbonyl derivatives bearing arylated quaternary stereocenters.

For the sake of clarity, the scientific literature concerning the topics covered in this review has been subdivided into eight sections: (i) synthesis of α-aryl substituted ketones by α-arylation of ketones with aryl halides or pseudohalides; (ii) synthesis of α-aryl substituted ketones by coupling of silyl enol ethers of ketones with aryl halides or pseudohalides; (iii) synthesis of α-aryl substituted ketones by coupling of enol esters of ketones with aryl halides or pseudohalides;

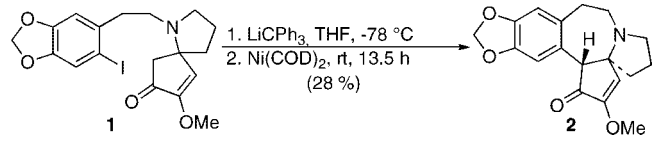
Scheme 1. New Methodologies for the Formation of Csp^3-Csp^2 Bonds



Scheme 2. Transition Metal-Catalyzed Inter- and Intramolecular Arylation Reactions of Ketone Enolates



Scheme 3. Ni-Catalyzed Intramolecular Arylation of Iodoketone 1



(iv) synthesis of α-aryl substituted ketones via α-arylation of ketimines with aryl halides; (v) synthesis of α-arylated aldehydes by α-arylation of aldehydes; (vi) direct α-arylation of carboxylic acid esters, azlactones, lactones, and silyl ketene acetals; (vii) α-arylation of nitriles, carboxyamides, lactams, and trimethylsilyl enolates of imides; and (viii) α-arylation of β-dicarbonyl compounds, ethyl cyanoacetate, malononitrile, ethyl phenylsulfonylacetate, methanesulfonamides, *N*-sulfoximines, and nitroalkanes. However, this review does not cover data reported in the patent literature.

2. Synthesis of α-Aryl Substituted Ketones by α-Arylation of Ketones with Aryl Halides or Pseudohalides

The synthesis of α-aryl substituted ketones has been the subject of intense research over the past 35 years. Reaction of an enolate with a derivative of benzyne is one of the several methods developed to construct a bond between an arene and a carbon at the α-position of a carbonyl compound.[23,24] Unfortunately, intermolecular reactions involving substituted benzynes have often been shown to be nonregioselective.[24] A seemingly more straightforward method to prepare α-arylated ketones is the $S_{RN}1$ reaction of ketone enolates with electronically neutral aryl halides and aryl halides bearing electron-withdrawing or -donating substituents.[25] Unfortunately, this procedure, in which a limited number of solvents can be used, suffers from regioselectivity problems for ketones having both enolizable methyl and methylene groups.[25c,g]

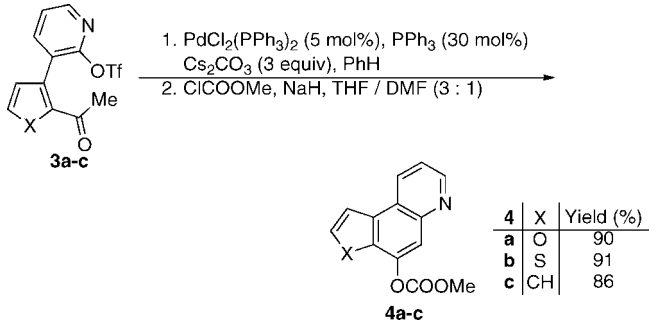
A number of specific main group aryl reagents including organobismuth,[26] organocadmium,[27] organocopper,[28] organolead,[29] and organoboron compounds,[30] (π-halogenobenzene)chromium tricarbonyls,[31] aryldiazonium salts in the presence of catalytic amounts of CuCl,[32] diaryliodonium salts,[33] arylmagnesium halides,[34] and arylazo-*tert*-butyl sulfides[35] have also been used to prepare α-arylated ketones. However, the application of procedures involving the use of these reagents is limited by the cost and time needed to prepare stoichiometric amounts of the arylating reagents. Moreover, many of these procedures do not involve arylation of ketones, but instead of their less readily available derivatives including α-haloketones[28d,30,34] or silyl enol ethers.[28c,31,33a,d]

Other methods to prepare α-arylated ketones rely on intramolecular nucleophilic addition of silyl enol ethers of ketones to electron-transfer generated arene radical cations,[36] regiospecific reaction of arylalkenes with [hydroxy(tosyloxy)iodo]benzene,[37] direct nucleophilic acylation of *o*-quinone methides,[38] arylation of lithium enolates of cycloalkanones with diphenyliodonium triflate in the presence of stoichiometric quantities of CuCN,[39] and reaction of isopropenyl acetate with aryldiazonium tetrafluoroborates in aqueous acetone in the presence of KOAc.[40] The latter methodology was applied to the multigram scale preparation of 1-(3-bromo-4-methylphenyl)propan-2-one.[40] On the other hand, optically active α-aryl substituted ketones have recently been synthesized with high enantioselectivities by organocatalytic addition of dicyanoalkylidenes to quinones using cinchona alkaloid catalysts, followed by reaction with carboxy anhydrides and oxidative degradation of the resulting α-aromatic compounds.[41]

A more general and effective strategy that emerged over the last three decades to connect inter- and intramolecularly aryl units to sp^3-hybridized C−H bonds in the α-position to carbonyl keto groups involves the transition metal-catalyzed direct coupling of aryl halides or pseudohalides with enolates obtained in situ from the corresponding ketones under basic conditions (Scheme 2).

An early example of application of this synthetic strategy was reported by Semmelhack et al. in 1975, who found that $Ni(COD)_2$ mediates the intramolecular reaction of the iodoenolate, obtained by treatment of compound **1** with lithium triphenylmethylide, to give racemic cephalotaxinone **2** in 28% yield (Scheme 3).[42]

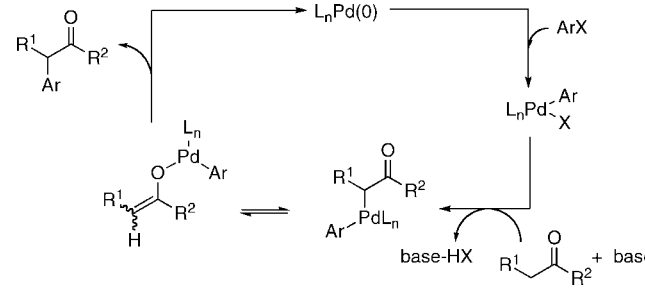
Scheme 4. Intramolecular Arylation of Methyl Ketones Bearing a 3-(2-Trifluoromethanesulfonyloxy)pyridyl Group in the β-Position



Twenty-two years after this report, Natsume et al. synthesized the heteroaromatic derivatives **4a**−**c** via palladium-catalyzed intramolecular arylation of (hetero)arylmethyl ketones **3a**−**c** bearing a 3-(2-trifluoromethanesulfonyloxy) pyridyl group in the β-position to the carbonyl group (Scheme 4).[43]

Various bases, including NaH, KO*t*-Bu, and K_2CO_3, were tested for this intramolecular process, and it was found that Cs_2CO_3 performed best.[44] It was also observed that a less polar solvent was more useful because polar solvents seemed to accelerate intermolecular aldol reactions.[44]

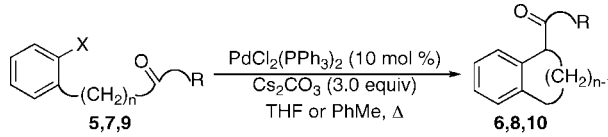
Scheme 5. Catalytic Cycle for the Pd-Catalyzed α-Arylation of Ketones with Aryl Halides



Interestingly, reaction conditions similar to those used to prepare compounds **4a**−**c** enabled the synthesis of the bridged 2-tetralones **6** from the 2-bromobenzyl substituted cycloalkanones **5** in 26−83% yield and the preparation of spirocompounds **8** and **10** from the 2-bromophenethyl- and 3-(2-bromophenyl)propyl-substituted cycloalkanones **7** and **9**, respectively (Table 1).[45]

Practical palladium-catalyzed intermolecular α-arylations of ketones with aryl halides were independently introduced by Buchwald,[46] Hartwig,[47] and Miura[48] in 1997. The reactions were conducted in the presence of a base and a catalyst system consisting of a combination of $Pd(OAc)_2$ or a Pd(0) compound such as $Pd_2(dba)_3$ or $Pd(dba)_2$ and a suitable phosphine ligand. The catalytic cycle of these reactions, summarized in Scheme 5, involves three key steps: (i) the

Table 1. Pd-Catalyzed Intramolecular Arylation of Substrates Bearing Keto Groups



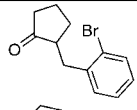
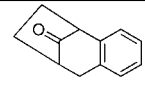
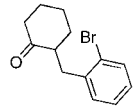
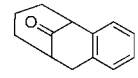
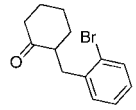
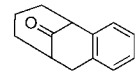
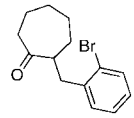
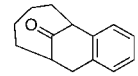
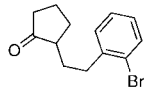
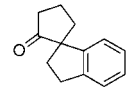
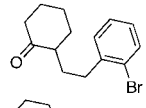
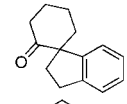
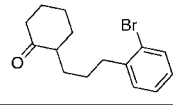
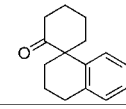
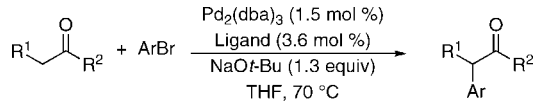
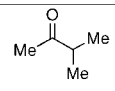
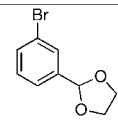
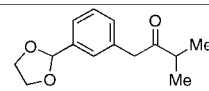
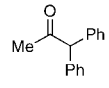
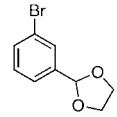
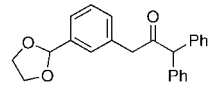
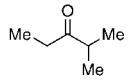
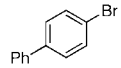
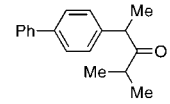
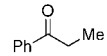
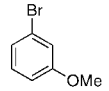
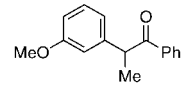
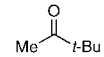
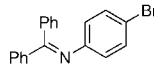
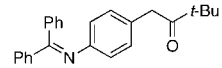
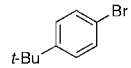
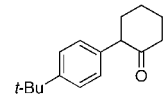
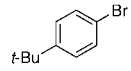
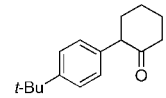
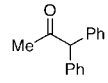
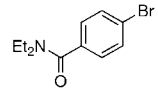
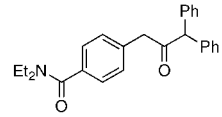
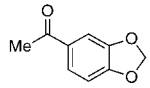
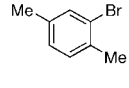
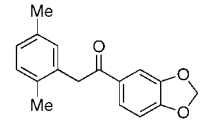
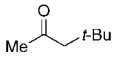
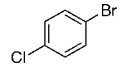
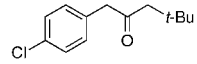
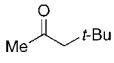
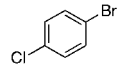
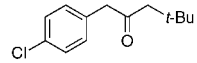
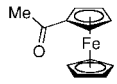
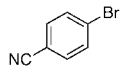
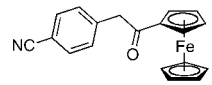
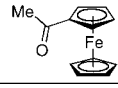
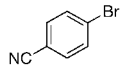
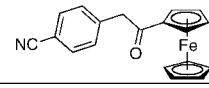
Entry		Substrate	Solvent	Reaction conditions (°C / h)		Product	Yield (%)
1	**5a**		THF	100 / 16	**6a**		26
2	**5b**		THF	100 / 13	**6b**		83
3	**5b**		PhMe	110 / 6	**6b**		63
4	**5c**		THF	100 / 14	**6c**		61
5	**7a**		THF	100 / 14	**8a**		71
6	**7b**		PhMe	110 / 12	**8b**		57
7	**9**		THF	100 / 14	**10**		35

Table 2. $Pd_2(dba)_3$/Tol-BINAP or BINAP-Catalyzed Coupling of Ketones with Aryl Bromides



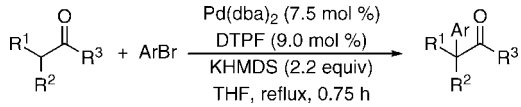
Entry	Ketone	ArBr	Ketone / ArBr molar ratio	Ligand	Product	Yield (%)
1			1.2	Tol-BINAP		76[a]
2			1.2	Tol-BINAP		72
3			1.2	Tol-BINAP		93
4			1.2	BINAP		91
5			1.2	Tol-BINAP		78
6			1.2	Tol-BINAP		67[b]
7			2.0	Tol-BINAP		83[c]
8			1.2	Tol-BINAP		69
9			1.2	BINAP		84
10			1.2	Tol-BINAP		71[d]
11			2.0	Tol-BINAP		88[e]
12			1.2	BINAP		64[f]
13			2.0	BINAP		63[g]

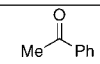
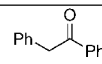
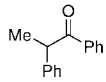
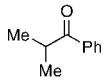
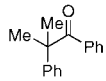
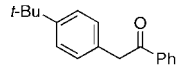
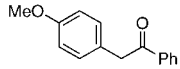
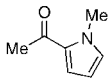
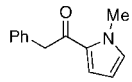
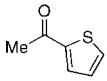
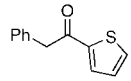
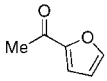
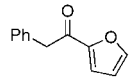
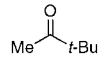
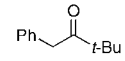
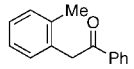
[a] Mono/diarylation = 13:1. [b] Mono/diarylation = 30:1. [c] Mono/diarylation = 33:1. [d] Mono/diarylation = 7:1. [e] Mono/diarylation = 16:1. [f] Mono/diarylation = 20:1. [g] Mono/diarylation = 27:1.

oxidative addition of the aryl halide to a Pd(0) species; (ii) the substitution of the halide in the oxidative addition complex by the enolate formed from the ketone bearing an α-hydrogen atom in the presence of a base; and (iii) a reductive elimination reaction involving the resulting palladium−enolate complex. However, this schematic catalytic cycle does not account for the role played from the nature of the base, ligand, and solvent used in the arylation reaction.

The regioselective protocol disclosed by Buchwald specifically involves treatment of an aryl bromide with a ketone bearing an α-hydrogen atom in the presence of NaO*t*-Bu and a catalyst system composed of a combination of $Pd_2(dba)_3$ and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) or 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl (Tol-BINAP) in refluxing tetrahydrofuran (THF) (Table 2).[46] Ketones bearing α,α′-hydrogens were found to be preferentially arylated at the least hindered side, and arylation of

Table 3. Pd(dba)$_2$/DTPF-Catalyzed α-Arylation of Ketones with Aryl Bromides



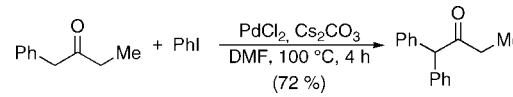
Entry	Ketone	Aryl Bromide	Product	Yield (%)
1		PhBr		84
2		PhBr		71
3[a]		PhBr		55
4		4-*t*-BuC$_6$H$_4$Br		85
5		4-MeOC$_6$H$_4$Br		69
6		PhBr		79
7		PhBr		68
8		PhBr		57
9		PhBr		51
10		2-MeC$_6$H$_4$Br		94

[a] This reaction was run using 10 mol % Pd(dba)$_2$, 15 mol % DTPF, and 1.5 equiv of KHMDS in refluxing THF for 5 h.

methine groups was not observed under these conditions. Diarylation was noticed only for methyl ketones relatively unhindered at the α′-position. High yields were obtained with some dialkyl ketones when a BINAP-ligated palladium catalyst was used, but ligandless catalysts proved to be advantageous for large-scale processes.[46]

The procedure independently developed by Hartwig for the α-arylation of ketones with aryl bromides involves the use of KHMDS or NaO*t*-Bu as the base and a catalytic system consisting of a combination of Pd(dba)$_2$ and a chelating ligand such as 1,1′-bis(diphenylphosphino)ferrocene (dppf)[49] or 1,1′-bis(di-*o*-tolylphosphino)ferrocene (DTPF).[47] It was indeed expected that the use of a chelating ligand would inhibit β-hydrogen elimination of the arylpalladium enolates by rendering four-coordinate the intermediate Pd(II) complex and inhibiting the generation of open coordination sites necessary for the β-hydrogen elimination. Representative examples of Pd(dba)$_2$/DTPF-catalyzed α-arylation reactions are reported in Table 3.[47] Arylations involving electron-rich or electron-neutral aryl bromides were found to be more selective for monoarylation when KHMDS was used as the base, but good selectivity was observed for arylations involving electron-poor aryl bromides when NaO*t*-Bu was the base.[47]

Scheme 6. PdCl$_2$−Catalyzed α-Arylation of Benzyl Ethyl Ketone with Iodobenzene



Remarkably, fast rates were observed using 1,1′-bis(di-*tert*-butylphosphino)ferrocene (DTBPF) as the supporting ligand, and in some cases the turnover numbers reached 20.000 in a few hours at 70 °C.[21,47]

Protocols involving Pd-catalyzed arylation of ketones under ligandless conditions were described by Miura et al.[48,50a] and Prashad et al.[50b] The reaction conditions used by Miura et al. are illustrated in the arylation reaction reported in Scheme 6, which was conducted by treatment of a benzyl ketone with an aryl iodide. Nevertheless, these authors demonstrated that a phosphine ligand should be used for the arylation of benzyl ketones with aryl bromides.[50a]

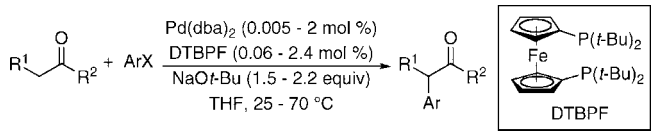
Ligandless conditions were also used by Prashad et al.[50b] for an efficient and large-scale synthesis of 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone by chemoselective α-arylation of pinacolone with 1-bromo-4-chlorobenzene in the presence of Pd(OAc)$_2$ and NaO*t*-Bu in toluene. Interesting elements regarding this reaction are the fact that an increase in the concentration of NaO*t*-Bu to 2.5−3.0 equiv proved to suppress the formation of overarylated products and that, under these conditions, 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone was obtained in a yield comparable to those obtained using a ligand.[50b]

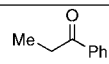
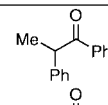
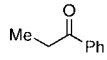
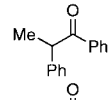
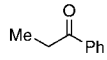
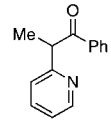
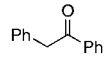
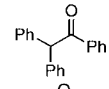
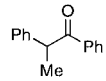
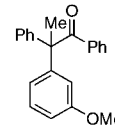
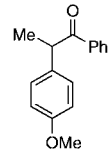
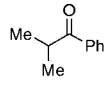
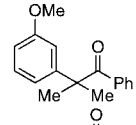
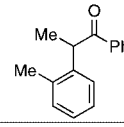
In 1999, aryl chlorides were used for the first time as electrophiles by Kawatsura and Hartwig in the α-arylation of ketones.[51] These authors established that a catalyst system consisting of a combination of Pd(dba)$_2$ and DTBPF permits the mild α-arylation of ketones with aryl chlorides and furnishes yields similar to those obtained when aryl bromides are used as electrophiles (Table 4).[51] It is noteworthy that this catalyst system led to high reaction rates for arylations of ketones with aryl bromides, and in some cases, the reactions could be performed at room temperature.[51] It was also found that the diphosphine ligand DTBPF is ligated to palladium in a η^1-fashion in the arylpalladium enolate intermediates. Hence, it was thought right to test sterically hindered monophosphines as supporting ligands, and it was discovered that P(*t*-Bu)$_3$ gives exceptionally fast rates and high turnover numbers for the α-arylation of ketones with aryl chlorides (Table 5).[21,51]

On the other hand, the highly efficient arylation of acetophenones with non- and deactivated aryl chlorides was performed by Beller et al. in 2002 using a Pd(OAc)$_2$/*n*-butyldi(1-adamantyl)phosphine catalyst system.[52] Depending on the structure of the ketone, the aryl chloride-to-ketone molar ratio, and the type of base, mono- or diarylation could be effected selectively.[52] Moreover, by applying NaO*t*-Bu as the base, a very high catalyst turnover number for the arylation with nonactivated aryl chlorides was obtained.[52]

In 2007, well-defined and air-stable (DTBPF)PdX$_2$ complexes (X = Cl, Br), in which the P−Pd−P bite angle of the bidentate ligand is the largest (104.22°) in the series of bisphosphinoferrocene complexes, were identified by Grasa

Table 4. $Pd(dba)_2$/DTBBF-Catalyzed α-Arylation of Ketones with Aryl Chlorides and Bromides



Entry	Ketone	Aryl Halide	Mol % $Pd(dba)_2$	Conditions (°C / h)	Product	Yield (%)
1		PhBr	2	25 / 2		99
2		PhBr	0.005	60 / 2		99
3		2-bromopyridine	2	50 / 5		87
4		PhBr	2	25 / 12		90
5		3-$MeOC_6H_4Cl$	2	70 / 12		92
6		PhCl	2	70 / 12		70
7		4-$MeOC_6H_4Cl$	2	70 / 12		91
8		3-$MeOC_6H_4Cl$	2	70 / 12		78
9		2-MeC_6H_4Cl	2	70 / 12		80

and Colacot as active catalysts for the arylation of various ketones with aryl chlorides and bromides in excellent yields (Table 6).[53] Under the experimental conditions reported in this table, sterically crowded aryl halides gave only monoarylated products, but sterically less hindered aryl halides, such as 4-chloroanisole, furnished both mono- and diarylated products even when stoichiometric amounts of the reagents were used.[53] Nevertheless, the selectivity of the monoarylation reaction could be improved by increasing the amount of base.[53] ^{31}P NMR monitoring of the $(DTBPF)PdCl_2$-catalyzed reaction of propiophenone with 4-chlorotoluene indicated that DTBPF remained coordinated in a bidentate mode during the catalytic cycle.[53]

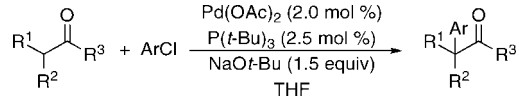
Highly active and selective catalyst systems for the α-arylation of ketones with aryl bromides and chlorides have also been shown to consist of bulky, electron-rich phosphines with a biphenyl backbone that are combined with $Pd(OAc)_2$.

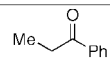
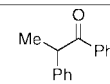
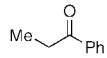
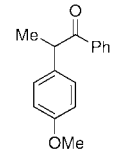
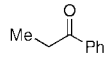
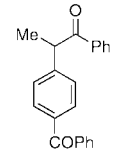
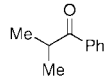
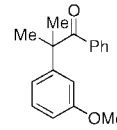
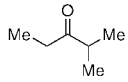
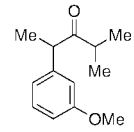
In 2000, Buchwald observed that the ligand 2-dicyclohexylphosphino-2′-methylbiphenyl (MeDCHB) is particularly effective, and with 0.1−1.0 mol % Pd, a large variety of ketones and functionalized aryl chlorides and bromides were shown to react efficiently and with high selectivity (Table 7).[54a]

The aryl halides included compounds substituted with an alkyl, methoxy, hydroxy, dimethylamino, 1,3-dioxolane, nitrile, and ester functions. Both aromatic and cyclic or acyclic ketones were used, but an exception was cyclopentanone, which was diverted to an aldol condensation, instead undergoing α-arylation. However, despite the usefulness of the ligand MeDCHB for the α-arylation of a variety of ketones, not all types of substrates were found to react effectively. The α-arylation of ketones that have both enolizable methyl and methylene groups was in fact not selective.

In addition, the experimental conditions summarized in Table 7, which allow one to perform the α-arylation of aromatic ketones with aryl halides with ester or nitrile functional groups, failed to give the required α-arylation products when they were used for the α-arylation of aliphatic ketones with aryl halides possessing an electron-withdrawing group.[54a] Nevertheless, these reactions could

Table 5. $Pd(OAc)_2/P(t\text{-}Bu)_3$-Catalyzed α-Arylation of Ketones with Aryl Chlorides



Entry	Ketone	Aryl Chloride	Conditions (°C / h)	Product	Yield (%)
1		PhCl	70 / 4		90
2		4-$MeOC_6H_4$	70 / 12		91
3		4-$(PhCO)C_6H_4Cl$	70 / 24		95
4		3-$MeOC_6H_4Cl$	70 / 12		82
5		3-$MeOC_6H_4Cl$	70 / 12		69

successfully be carried out using a Pd catalyst system based on the bidentate ligand XantPhos [9,9-dimethyl-4,6-bis-(diphenylphosphino)xanthene] in combination with NaHMDS or NaO*t*-Bu.[54a] Remarkably, the Pd/XantPhos catalyst system enabled arylation reactions where palladium catalysts involving the use of other monophosphine ligands failed, and this catalyst system also furnished good yields and high mono/diarylation selectivity in the α-arylation of ketones with enolizable methyl and methylene groups (Table 8).[54a]

It is noteworthy that the scope of the process could be enlarged to substrates possessing base-sensitive groups when the milder base K_3PO_4 was used in place of NaHMDS or NaO*t*-Bu (Table 9).[54a] Table 9 also shows that MeDCHB could be used as the supporting ligand in conjunction with K_3PO_4 to perform high yielding α-arylation reactions of cycloalkanones (entries 3−5). It should also be noted that the α-arylation of entry 3 of this table was found to occur selectively at the benzyl position of the carbonyl substrate.[54a]

In 2008, Doherty, Knight, Smyth et al. described that α-arylations of ketones with a variety of aryl bromides can also be performed in THF at 70 °C in the presence of NaO*t*-Bu as the base and a catalyst system composed of a mixture of $Pd_2(dba)_3$ and the bidentate ligand CATPHOS, the 1,3-butadiene-bridged diphosphine generated via double Diels−Alder cycloaddition between anthracene and bi(diphenylphosphino)buta-1,3-diyne.[54b]

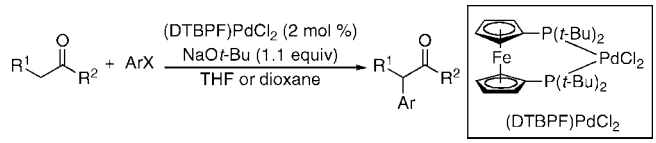
Recently, a catalyst system consisting of a combination of $Pd(OAc)_2$ and XantPhos was also employed for the α-arylation of *N*-tosyl-2′-aminoacetophenone with *ortho*-dibromobenzene in toluene and water at 120 °C in the presence of Cs_2CO_3 (Scheme 7).[55a] This reaction was then used as a key step in a new route to oxcarbazepine (Trileptal), the most widely prescribed drug for the treatment of epilepsy both in children and adults. It is noteworthy that the addition of a small amount of water to the toluene solution of the reactants proved to cause enhancement of the selectivity of the arylation reaction but decreased the rate of the process.[55a] This result was quite surprising, but now it is well-known that the addition of either catalytic or stoichiometric amounts of water to a significant number of organic reactions can positively affect the reaction outcome also in terms of improved selectivity.[55b]

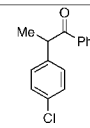
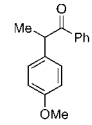
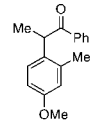
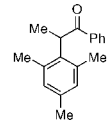
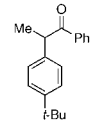
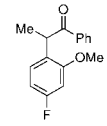
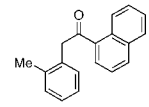
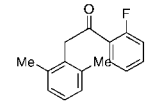
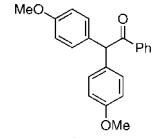
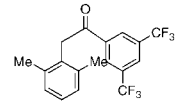
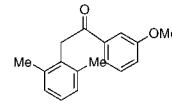
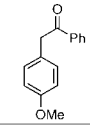
In 2006, Griebenow et al. adapted the palladium-catalyzed α-arylation of ketones to solid support using modified Buchwald−Hartwig conditions (Table 10).[56]

The protocol developed to prepare compounds **11** entailed treatment of immobilized 4-bromobenzamide, prepared from polystyrene Rink amide resin and 4-bromobenzoic acid chloride, with a very large molar excess of (hetero)aryl or alkyl methyl ketones in dioxane at 70 °C in the presence of NaO*t*-Bu, $Pd_2(dba)_3$, and BINAP, followed by reaction with trifluoroacetic acid in CH_2Cl_2.[56]

A variety of 2,3-diarylbenzofurans **12** were synthesized in fair-to-excellent yields by Miura et al. in 1999 via reaction of aryl benzyl ketones with *o*-dibromobenzenes in refluxing *o*-xylene in the presence of Cs_2CO_3 as the base and catalytic quantities of $Pd(OAc)_2$ and PPh_3.[57a] More recently, com-

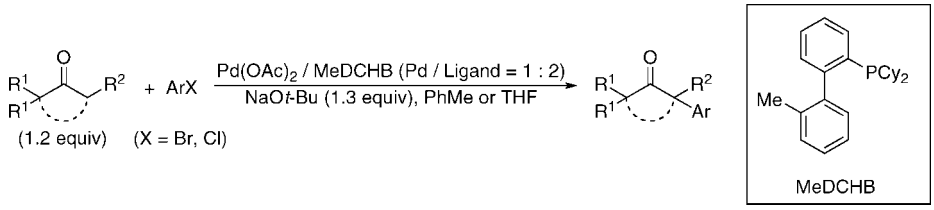
Table 6. (DTBPF)$PdCl_2$−Catalyzed α-Arylation of Ketones with Aryl Bromides and Chlorides



Entry	R^1	R^2	ArX	Solvent	Reaction temp (°C)	Product	Isolated Yield (%)
1	Me	Ph	4-ClC_6H_4Br	THF	rt		92
2	Me	Ph	4-$MeOC_6H_4Br$	THF	rt		97
3	Me	Ph	2-MeO,4-$MeOC_6H_3Br$	THF	rt		97
4	Me	Ph	2,4,6-$Me_3C_6H_2Br$	THF	rt		80
5	Me	Ph	4-*t*-BuC_6H_4Br	THF	rt		96
6	Me	Ph	2-MeO,4-FC_6H_3Br	THF	rt		65
7	H	1-Naph	2,6-$Me_2C_6H_3Cl$	dioxane	100		95
8	H	2-FC_6H_4	2,6-$Me_2C_6H_3Cl$	dioxane	100		95
9	4-$MeOC_6H_4$	Ph	4-$MeOC_6H_4Cl$	dioxane	100		90
10	H	3,5-$(CF_3)_2C_6H_3$	2,6-$Me_2C_6H_3Cl$	dioxane	100		60
11	H	3-$MeOC_6H_4$	2,6-$Me_2C_6H_3Cl$	dioxane	100		91
12	H	Ph	4-$MeOC_6H_4Cl$	dioxane	100		(53)[a,b]

[(a)] GLC yield. [(b)] 47% bisarylation product determined by GLC.

Table 7. $Pd(OAc)_2$/MeDCHB-Catalyzed α-Arylation of Ketones with Aryl Bromides and Chlorides



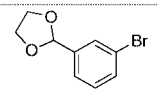
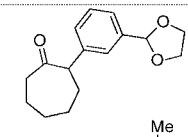
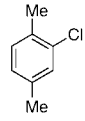
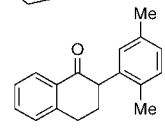
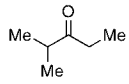
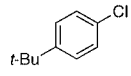
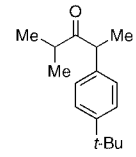
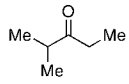
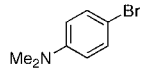
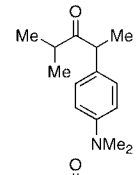
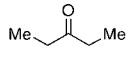
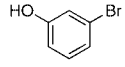
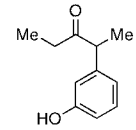
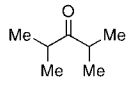
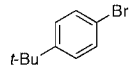
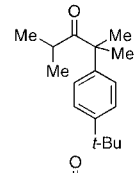
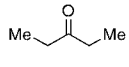
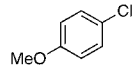
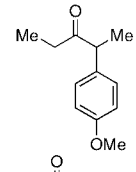
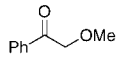
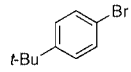
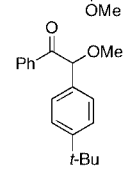
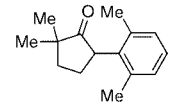
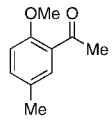
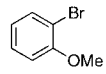
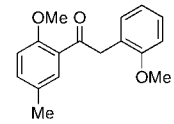
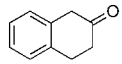
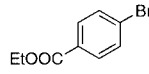
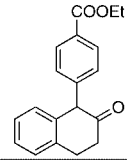
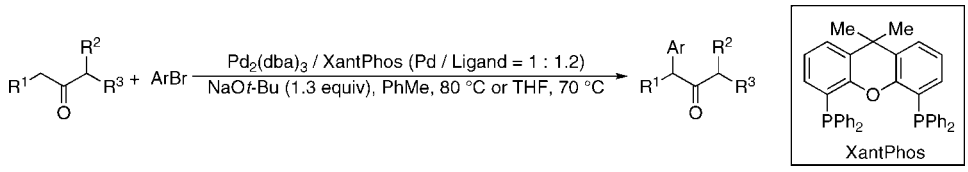
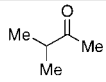
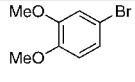
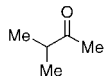
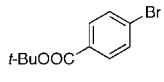
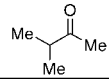
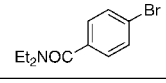
Entry	Ketone	ArX	Solvent	Conditions (°C / T)	Mol % Pd	Product	Yield (%)
1			PhMe	45 / 20	0.1		80
2			PhMe	80 / 5	0.1		93
3			PhMe	90 / 16	0.1		79
4			PhMe	85 / 24	0.1		70
5			THF	70 / 24	0.1		88
6			PhMe	65 / 24	0.5		61
7			PhMe	70 / 24	0.1		74
8			THF	70 / 17	0.5		83
9			PhMe	70 / 23	0.5		64
10			PhMe	80 / 16	1.0		91
11			THF	80 / 24	0.2		85

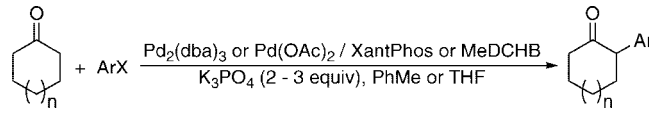
Table 8. $Pd_2(dba)_3$/XantPhos-Catalyzed α-Arylation of Acyclic Ketones with Aryl Bromides

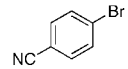
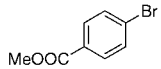
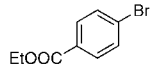
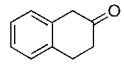
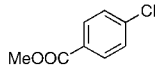
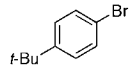


Entry	Ketone	ArBr	Solvent	Reaction time (h)	Mol % Pd	Yield (%)	Mono / Diarylation ratio
1			THF	17.5	0.5	72	12 :1
2			THF	12	1.0	74	25 :1
3[a]			PhMe	16	0.2	67	n.d.
4[b]			PhMe	15	0.2	74	n.d.

[a] NaHMDS (2.0 equiv) was the base. Regioisomers were formed in a 50:1 ratio. [b] NaO*t*-Bu (2.0 equiv) was the base.

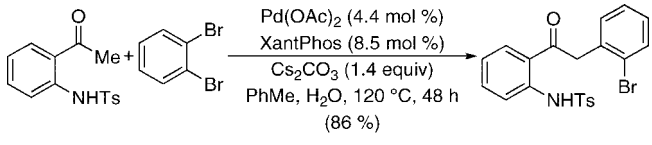
Table 9. Pd-Catalyzed α-Arylation of Cycloalkanones with Aryl Halides in the Presence of K_3PO_4 as the Base

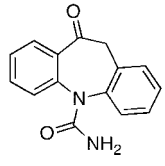


Entry	ArX	Ketone	Ligand	Mol % Pd	Solvent	Reaction conditions (°C / h)	Yield (%)	Mono/ Diarylation ratio
1[a]			XantPhos	1.0	THF	60 / 16	72	8:1
2[a]			XantPhos	1.0	PhMe	80 / 13	74	n.d.
3[b]			MeDCHB	0.2	PhMe	100 / 23	91	6.5:1
4[b]			MeDCHB	1.0	PhMe	100 / 15	70	4.9:1
5[b]			MeDCHB	1.0	THF	80 / 17	81	15:1

[a] $Pd_2(dba)_3$ was the Pd source, and the ratio ligand/$Pd_2(dba)_3$ was 2.2:1. [b] $Pd(OAc)_2$ was the Pd source, and the ratio ligand/$Pd(OAc)_2$ was 2.2:1.

Scheme 7. Pd-Catalyzed α-Arylation of *N*-Tosyl-2′-Aminoacetophenone with *o*-Dibromobenzene



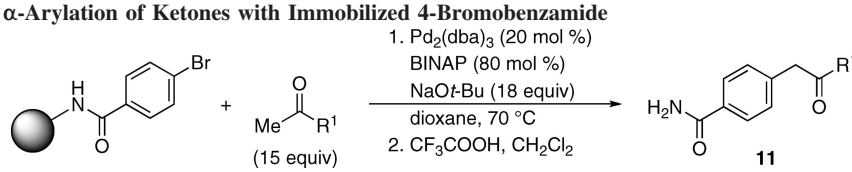

oxcarbazepine

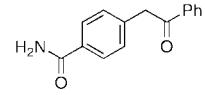
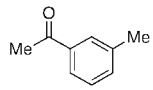
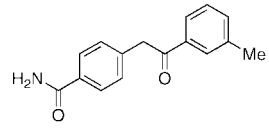
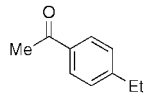
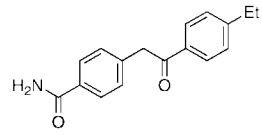
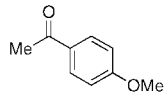
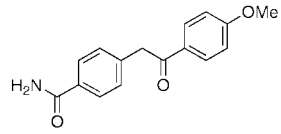
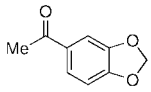
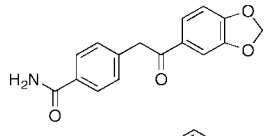
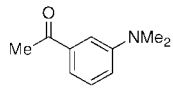
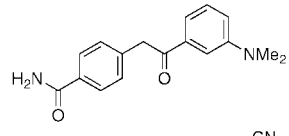
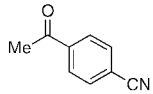
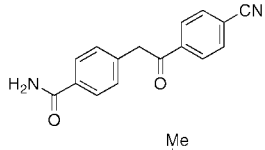
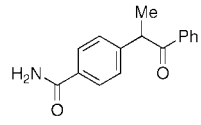
pounds **12** have also been synthesized in good yields by means of polymer-anchored FiberCat1026 catalyst (Scheme 8).[58]

A plausible reaction sequence for these palladium-catalyzed reactions involves arylation at the benzylic position of the aryl benzyl ketone, followed by the C−O bond formation, as shown in Scheme 9.[57a]

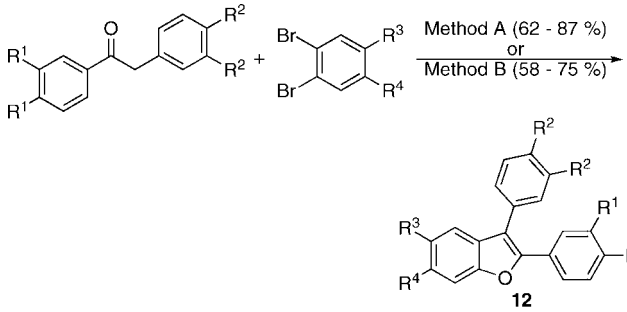
In 2007, SanMartin, Dominguez et al. prepared *o*,*o*′-dihalodeoxybenzoins **13** in modest-to-satisfactory yields by

Table 10. Pd-Catalyzed α-Arylation of Ketones with Immobilized 4-Bromobenzamide



Entry	Methyl Ketone	Product	Yield (%)	Purity (%)
1			56	> 95
2			35	> 95
3			69	85 – 90
4			66	> 95
5			62	> 95
6			77	55 – 60
7			Trace	20 – 30
8			0	

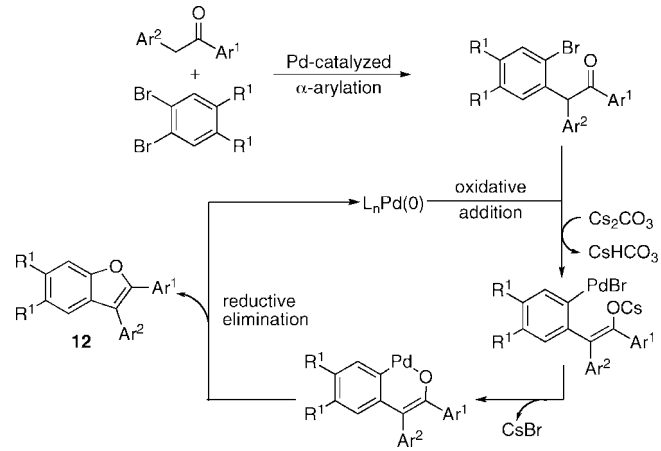
Scheme 8. Synthesis of 2,3-Diarylbenzofurans 12 by Means of a Homogeneous or a Heterogeneous Catalyst System



palladium-catalyzed reaction of *o*-dibromobenzenes with *o*-chloroacetophenones (Scheme 10).[59]

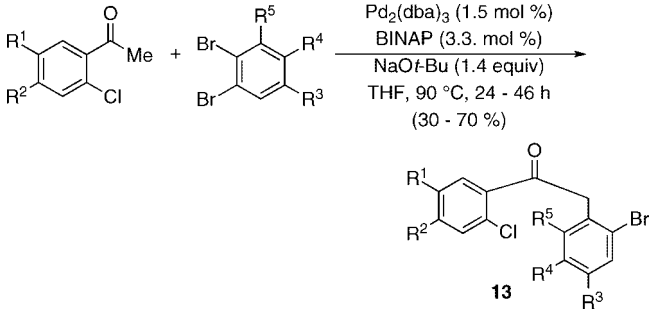
Willis et al.[60a] had previously reported that treatment of cyclohexanone with 1,2-dibromobenzene in toluene at 80 °C in the presence of Cs_2CO_3 and catalytic quantities of $Pd_2(dba)_3$ and XantPhos results in no reaction. However, these authors were pleased to observe that the use of

Scheme 9. Plausible Reaction Mechanism for the Synthesis of 2,3-Diarylbenzofurans 12



1-bromo-2-iodobenzene under identical reaction conditions allowed for an efficient arylation reaction that delivered 2-(2-bromophenyl)cyclohexanone in 78% yield.[60a,b]

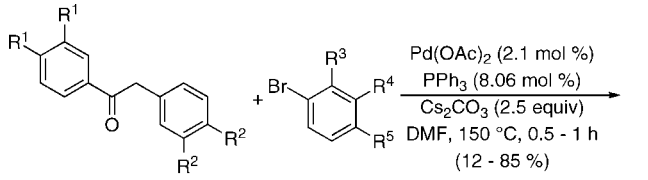
Scheme 10. Pd-Catalyzed α-Arylation of *o*-Chloroacetophenones with *o*-Dibromobenzenes



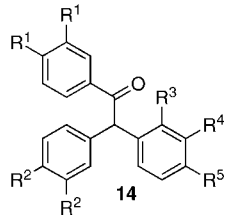
A wide variety of tamoxifen-related 1,2,2-triarylethanones **14** were synthesized in moderate-to-high yields by SanMartin, Dominguez et al. in 2002 by arylation of aryl benzyl ketones at the benzylic position with aryl bromides in DMF solution in the presence of Cs_2CO_3 as the base and a catalyst system composed of a mixture of $Pd(OAc)_2$ and PPh_3 (Scheme 11).[61] Tamoxifen is an orally active selective estrogen receptor modulator that is used in the treatment of breast cancer. Remarkably, the arylation protocol illustrated in Scheme 11 allowed side-reactions such as *ortho*-arylation of the ketone substrate and dehydrohalogenation of the aryl bromide reagent to be avoided.

More recently, 1,2,2-triarylethanones have also been synthesized using acetophenones as starting materials.[62] Specifically, two methods have been developed for the α,α-diarylation of acetophenones that avoided side reactions. The first one was based on the use of the system $Pd(OAc)_2/PPh_3/Cs_2CO_3$,[59,62] and the second method entailed the use of the commercially available polymer-bound catalyst FiberCat1026 (Scheme 12).[62]

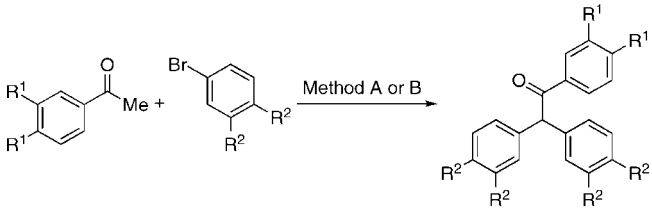
Scheme 11. Pd-Catalyzed Synthesis of 1,2,2-Triarylethanones 14 from Aryl Benzyl Ketones



R^1 = H, OMe; R^2 = H, OMe; R^3 = H, OMe
R^4 = H, OMe, OCH_2O; R^5 = H, OMe, NO_2

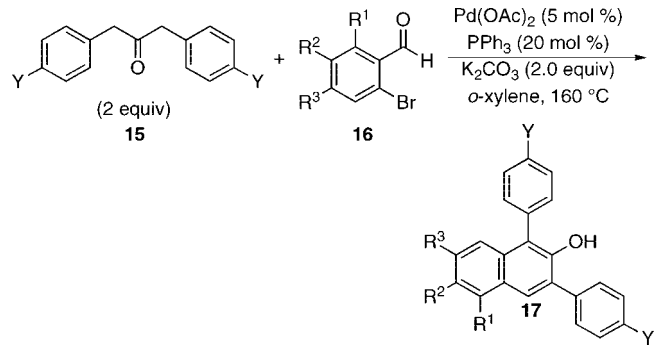


Scheme 12. Pd-Catalyzed Synthesis of 1,2,2-Triarylethanones from Acetophenones



Method A: $Pd(OAc)_2$, PPh_3, Cs_2CO_3, DMF, 153 °C, 1-7h (35-91%)
Method B: FibreCat 1026, Cs_2CO_3, DMF, 153 °CX, 0.8-1h (20-93%)

Table 11. Pd-Catalyzed Annulation Reaction of *o*-Bromobenzaldehydes with 1,3-Diaryl-2-propanones



entry	R^1	R^2	R^3	Y	reaction time (h)	yield[(a)] (%)
1	H	H	H	H	5	72 (59)
2	H	OMe	H	H	7	57 (45)
3	H	OMe	OMe	H	4	51 (43)
4	OMe	OMe	H	H	3	90 (75)
5	H	H	H	Me	3	60 (44)
6	H	H	H	Cl	8	48 (45)

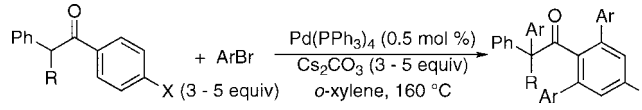
[(a)] GLC yield based on the amount of **16** used. Values in parentheses indicate isolated yields.

As regards the arylation reactions of benzyl ketones, it is worth noting that, in 2000, Miura et al. attempted the use of the $Pd(OAc)_2/PPh_3$ catalyst system for the arylation of dibenzyl ketones **15** with *o*-bromobenzaldehyde **16**, but they found that the reaction produced unexpectedly 1,3-diaryl-2-naphthols **17** in moderate yields (Table 11).[63]

Compounds **17**, which are of interest as bulky oxygen ligands,[64] were supposed to be formed via intermolecular α-arylation of ketones **15**, followed by a base-catalyzed condensation or via dehydrative condensation of the substrates, followed by palladium-catalyzed intramolecular α-arylation of the resulting compounds.[63] Remarkably, benzyl phenyl ketones were found to undergo triarylation at the benzyl position and the two *ortho*-positions of the phenyl group upon treatment with a molar excess of aryl bromides in refluxing *o*-xylene in the presence of Cs_2CO_3 as the base and a catalytic quantity of $Pd(PPh_3)_4$ (Table 12).[57b,65]

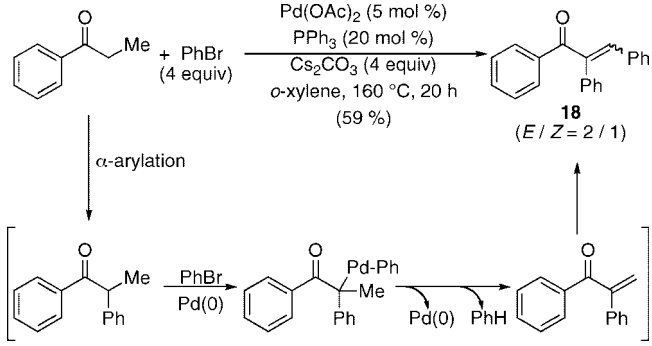
Miura et al. also observed that alkyl aryl ketones are able to undergo multiple arylations on the alkyl chain, accompanied by oxidative unsaturation, by treatment with a molar excess of aryl bromides in refluxing toluene or xylene

Table 12. $Pd(PPh_3)_4$-Catalyzed Triarylation of Benzyl Phenyl Ketones with Aryl Bromides



	benzyl phenyl ketone				
entry	R	X	aryl bromide	reaction time (h)	isolated yield (%)
1	H	H	3-$CF_3C_6H_4Br$	44	41
2	H	H	3-ClC_6H_4Br	23	54
3	H	H	4-ClC_6H_4Br	24	25
4	H	Cl	PhBr	6	59
5	H	H	4-PhC_6H_4Br	21	30
6	Ph	H	2-NaphBr	23	43

Scheme 13. Synthesis of 1,2,3-Triphenyl-2-propen-1-one



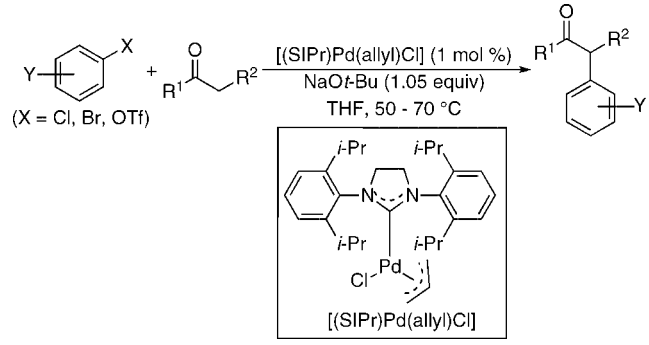
in the presence of Cs_2CO_3 and a combination of $Pd(OAc)_2$ and a phosphine ligand such as P(*o*-tolyl)$_3$, PPh_3, P(*t*-Bu)$_3$, or P(4-FC_6H_4)$_3$.[57b,66] In fact, when propiophenone was reacted with 4 equiv of bromobenzene in the presence of the $Pd(OAc)_2/PPh_3$ catalyst system and Cs_2CO_3 as the base in refluxing *o*-xylene, 1,2,3-triphenyl-2-propen-1-one was obtained in 59% yield (Scheme 13).[66]

The formation of this ketone was explained by the reaction sequence illustrated in Scheme 13 that involves oxidative unsaturation. Specifically, it was supposed that, after the α-arylation reaction of propiophenone, the enolate of the resulting α-arylated ketone may react with phenylpalladium bromide to form an alkyl phenylpalladium intermediate. Then, *β*-elimination of PhPdH should give a Pd(0) species and benzene together with 1,2-diphenyl-2-propen-1-one. Finally, this α,*β*-unsaturated ketone should undergo phenylation via carbopalladation to give 1,2,3-triphenyl-2-propen-1-one.[64]

It was also observed that, when butyrophenone was reacted with a large excess of bromobenzene using the experimental condition reported in Scheme 13, a mixture of mono-, tri-, tetra-, and pentaphenylated products was obtained (Scheme 14).[66]

Until 2001 inclusive, tertiary phosphines were the palladium catalyst supporting ligands used for the α-arylation of ketones. However, difficulties associated with removal of these ligands from the final reaction mixtures, formation of degradation byproducts of these phosphines, and the high price of bulky tertiary phosphines encouraged researchers to evaluate the possibility of using *N*-heterocyclic carbenes (NHCs) as ancillary ligands in the arylation reactions of ketones. On the other hand, in the last few years, *N*-heterocyclic carbenes have proven to be excellent supporting ligands in numerous palladium-catalyzed reactions and

Table 13. [(SIPr)Pd(allyl)Cl]-Catalyzed α-Arylation of Ketones



entry	X	Y	R^1	R^2	conditions (°C/h)	isolated yield
1	Cl	4-CF_3	Ph	Me	70/1	81
2	Cl	4-MeO	Ph	H	70/1	78
3	Cl	H	Ph	Me	70/1	93
4	Cl	3-MeO	Ph	Me	70/1	86
5	Br	2,4,6-$(Me)_3$	Ph	Me	60/6	72
6	Cl	2-MeO	*t*-Bu	H	60/1	(91)[(a)]
7	Br	2,4,6-$(Me)_3$	Et	Me	60/0.5	68
8	OTf	4-MeO	Ph	H	60/1	87
9	OTf	4-Me	Ph	H	60/1.5	86
10	OTf	4-Me	Ph	Me	60/1	93
11	OTf	4-MeO	Ph	Me	60/1	90
12	Cl	2-MeO	Ph	H	60/1	80
13	Cl	2-MeO	Ph	Me	60/1	80
14	Cl	H	Et	Me	70/0.2	88

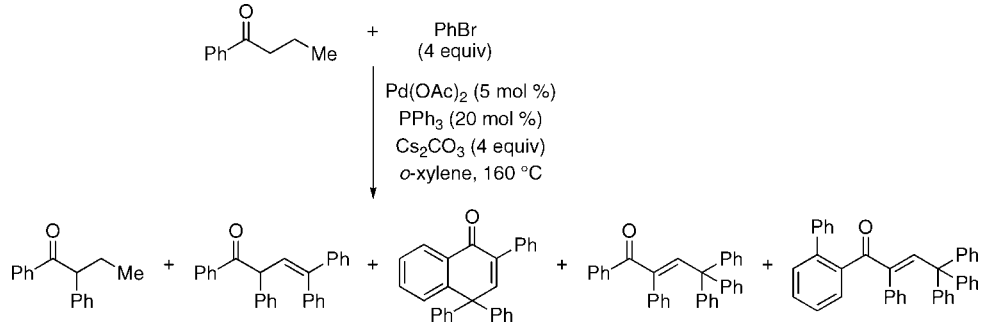
[(a)] GLC yield.

serious alternatives to the tertiary phosphines.[67] Their strong *σ*-electron-donating ability enables the formation of stable active metal species and facilitates oxidative insertion even in challenging substrates, while their steric bulk is responsible for fast reductive elimination.

In 2002, Nolan et al. tested a number of Pd−NHC complexes and found that allylchloro[1,3-bis(2,6-di-*i*-propylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium [(SIPr)Pd(allyl)Cl] is an air-stable, active catalyst for the high yielding α-arylation of ketones with activated, neutral, and nonactivated aryl chlorides, bromides, and triflates in short reaction times with low catalyst loading, using NaO*t*-Bu as the base in THF at 50−70 °C (Table 13).[68]

In 2005, Singh and Nolan significantly improved these reactions.[69] They found that the α-arylation of aryl−alkyl, dialkyl, and cyclic ketone enolates with nonactivated aryl chlorides could be performed at room temperature in moderate-to-high yields using 1 mol % of complex (IPr)$Pd(OAc)_2$ [IPr = 1,3-bis(2,6-di-*i*-propylphenyl)imidazol-2-ylidene] (Figure 1).[69]

Scheme 14. Multiple Arylation of Butyrophenone Accompanied by Oxidative Unsaturation



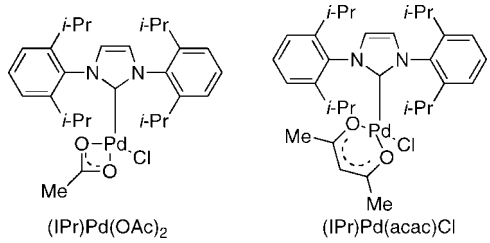
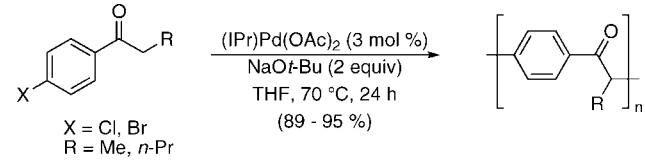


Figure 1. Chemical structures of (IPr)Pd(OAc)$_2$ and (IPr)Pd(acac)Cl.

Ketone enolates were generated in situ via use of a slight molar excess of NaO*t*-Bu as base. The arylation reactions could also be carried out under microwave irradiation, and it was observed that a variety of functional groups with the exception of aldehyde and nitrile were tolerated on the aryl moiety and that substituents in the α-position to the carbonyl group had a detrimental effect on the arylation reaction.[70] In fact, unsymmetrically substituted ketones were preferentially arylated at the least sterically hindered carbon atom in the α-position. As expected, aryl bromides proved to be suitable substrates for reactions under these experimental conditions, and ketones could undergo α-arylation with unactivated and sterically demanding aryl bromides in excellent yields and shorter reaction times compared to those for the analogous aryl chlorides.[70]

Scheme 15. (IPr)Pd(OAc)$_2$-Catalyzed Polymerization of 4-Haloaryl Alkyl Ketones

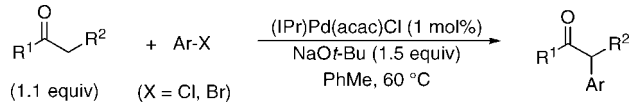


Nolan et al. also discovered that air-stable complex (IPr)Pd(acac)Cl (Figure 1), which was prepared from Pd(acac)$_2$ and IPr·HCl [1,3-bis(2,6-di-*i*-propylphenyl)imidazolium chloride],[71] shows excellent activity in the α-arylation of ketones with unactivated, sterically hindered heteroaryl chlorides under mild reaction conditions.[72,73] Table 14 illustrates some representative examples of (IPr)Pd(acac)Cl-catalyzed α-arylation reactions of ketones with aryl chlorides.

In 2006, complex (IPr)Pd(OAc)$_2$ and other Pd-complexes bearing NHC ligands were shown to be active catalyst precursors able to produce poly-α-arylketones by α-arylation of the corresponding 4-haloaryl alkyl ketones (Scheme 15).[74]

Nolan et al.[75] had previously demonstrated that a new class of well-defined and air-stable catalysts consisting of a palladacycle scaffold[76] stabilized by the presence of a highly donating sterically demanding NHC ligand is active in the

Table 14. (IPr)Pd(acac)Cl-Catalyzed α-Arylation Reactions of Ketones with Aryl Chlorides and Bromides



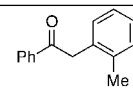
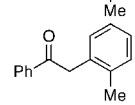
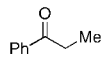
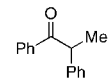
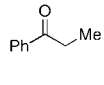
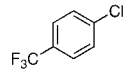
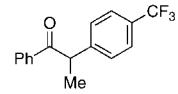
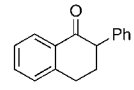
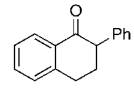
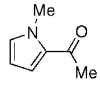
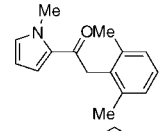
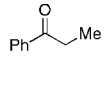
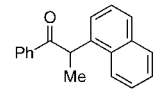
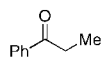
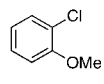
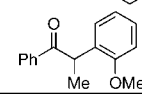
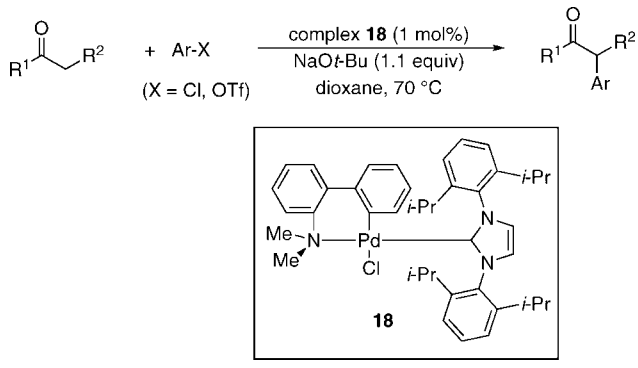
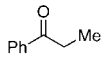
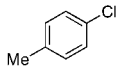
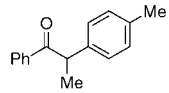
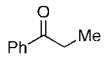
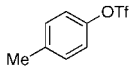
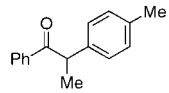
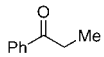
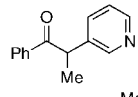
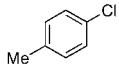
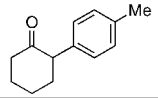
Entry	Ketone	ArX	Reaction time (h)	Product	Isolated yield (%)
1			3.5		89
2			2		90
3		PhCl	1		98
4			0.75		93
5		PhCl	4		62
6		PhBr	3.5		72
7			3		96
8			2		96
9			2.5		91

Table 15. α-Arylation of Ketones with Aryl Chlorides and Triflates in the Presence of a Catalytic Amount of Complex 18



Entry	Ketone	ArX	Product	Yield (%)
1				89
2				78
3				90
4				97

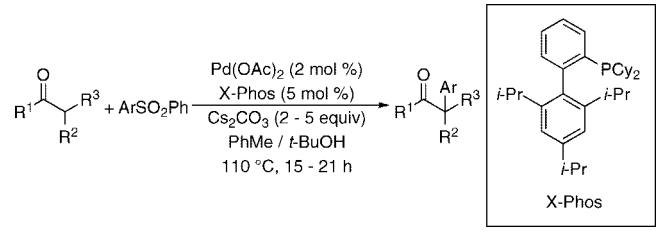
α-arylation of ketones with (hetero)aryl chlorides and triflates. Table 15 summarizes the excellent results of four α-arylations performed using the *N*-NHC−palladacycle complex **18**.[75]

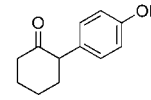
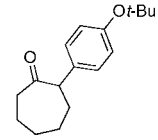
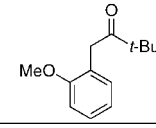
On the other hand, the first and, until now, sole examples of the use of aryl benzenesulfonates as arylating species in α-arylation reactions of acyclic and cyclic ketones were reported by Buchwald et al. in 2003.[77] These synthetically important reactions did not involve the use of Pd−NHC complexes but were performed in a mixture of toluene and *tert*-butanol in the presence of Cs_2CO_3 and a catalyst system composed of a mixture of $Pd(OAc)_2$ and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (X-Phos), a bulky electron-rich monophosphine, as the ligand. Remarkably, the $Pd(OAc)_2$/X-Phos catalyst system allowed for the synthesis of the required α-arylated ketones in very good yields (Table 16) and proved also to be highly efficient for the α-arylation of *β*-dicarbonyl compounds.[77]

The α-arylation of ketones with aryl chlorides using a class of air-stable complexes consisting of a palladacycle[76] stabilized by coordination with a secondary phosphine was explored by Indolese, Studer et al. in 2002.[78] As depicted in Scheme 16, aminopalladacycle **19**, which is a member of this class, allowed for the α-arylation of propiophenone with 4-chlorotoluene in a quantitative yield.[78]

More recently, the α-arylation of propiophenone with aryl chlorides has been successfully performed using complexes **20**[79] and **21**[80] (Figure 2) as catalyst precursors.

Table 16. $Pd(OAc)_2$/X-Phos-Catalyzed α-Arylation of Ketones with Aryl Benzenesulfonates



Entry	Reaction time (h)	α-Arylated ketone	Isolated yield (%)
1	15		81
2	18		85
3	20		75

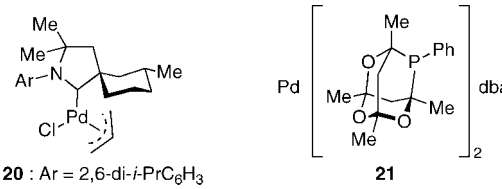


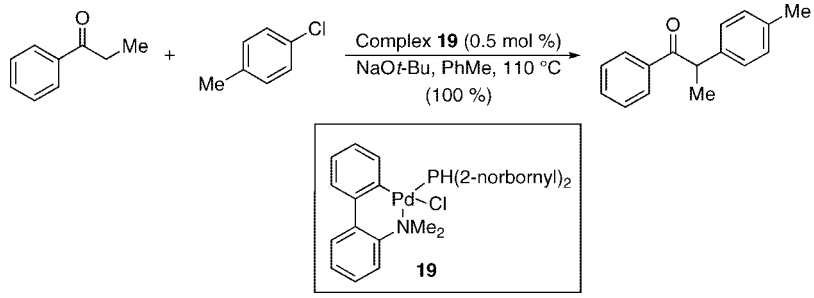
Figure 2. Chemical structures of complexes **20** and **21**.

Complex **20**, bearing a stable cyclic (alkyl)(amino)carbene as strong *σ*-donor ligand, proved to be particularly efficient for the α-arylation of propiophenone with 2-chloro-1,3-dimethylbenzene,[79] and the Pd complex **21** of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane was found to be an efficient catalyst for the α-arylation of propiophenone with aryl chlorides and bromides, including 2-substituted and 2,6-disubstituted derivatives.[80]

In 2006, the PCP−bis(phosphinite) pincer complexes **22** and **23**, which appear to combine in one molecule the advantages of palladacycles and a modulation of the catalyst properties by the phosphinite ligands, were reported to provide higher yields compared with those using the homogeneous $Pd(OAc)_2/PPh_3$ or heterogeneous FiberCat catalysts[59,61,62] in the α-arylation of ketones with both activated and deactivated aryl bromides, even decreasing the catalyst amounts from 2−5 mol % to 0.1 mol %.[81,82] Representative examples of α-arylations performed using these powerful catalyst precursors are shown in Table 17.[81]

In the same year, it was also demonstrated by Ackermann et al. that bulky substituents on the nitrogen atoms of secondary chlorophosphines facilitate the efficient palladium-catalyzed α-arylation of ketones bearing sp^3-hybridized C−H bonds in the α-position with electron-

Scheme 16. α-Arylation of Propiophenone with 4-Tolyl Chloride Catalyzed by Aminopalladacycle 19

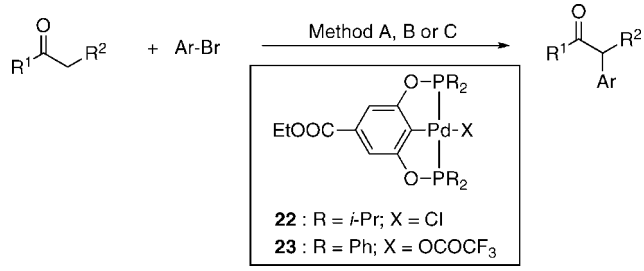


rich aryl chlorides (Table 18).[83] The active catalyst for these reactions was generated from $Pd(OAc)_2$ and the bulky ligand **24**.[84]

More recently, Matsubara et al. have reported that propiophenones can efficiently be α-arylated with aryl bromides and chlorides using the air-stable nickel(II) halide complex **25** bearing both PPh_3 and bulky NHC ligands as a catalyst precursor (Scheme 17).[85]

Anyway, palladium catalysts have generally been preferred for performing α-arylations of ketones with aryl halides, and

Table 17. α-Arylation of Ketones by the PCP Palladium Complexes 22 and 23



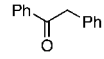
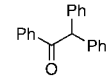
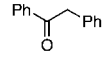
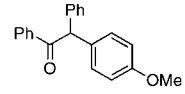
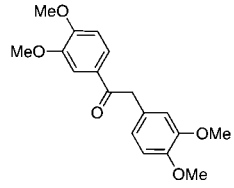
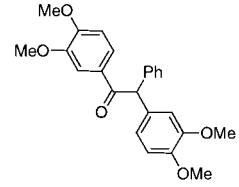
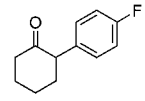
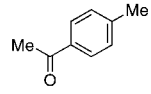
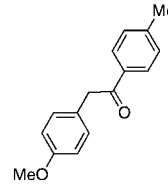
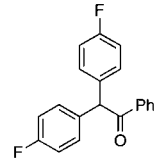
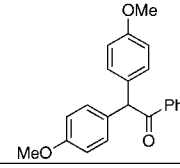
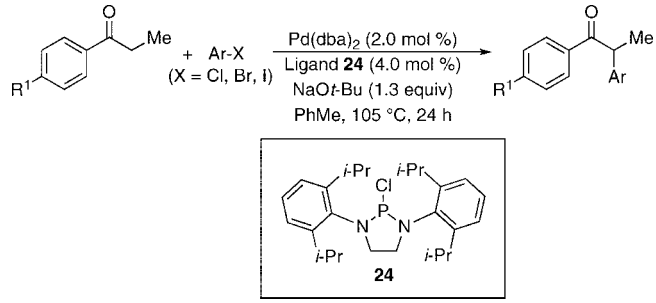
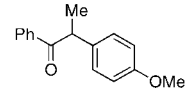
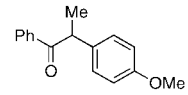
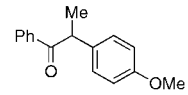
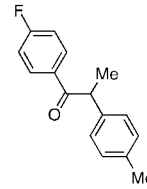
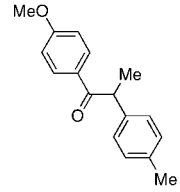
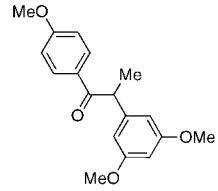
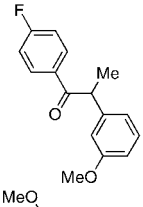
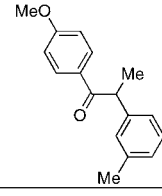
Entry	Method	Ar	Ketone	Product	Yield (%) using 22	Yield (%) using 23
1	A	Ph			78	84
2	A	4-$MeOC_6H_4$			95	96
3	A	Ph			93	92
4	A	4-FC_6H_4			85	86
5	B	4-$MeOC_6H_4$			>99	90
6	C	4-FC_6H_4			84	85
7	C	4-$MeOC_6H_4$			86	88

Table 18. α-Arylation of Ketones with Aryl Halides in the Presence of Catalytic Amounts of $Pd(dba)_2$ and Ligand 24

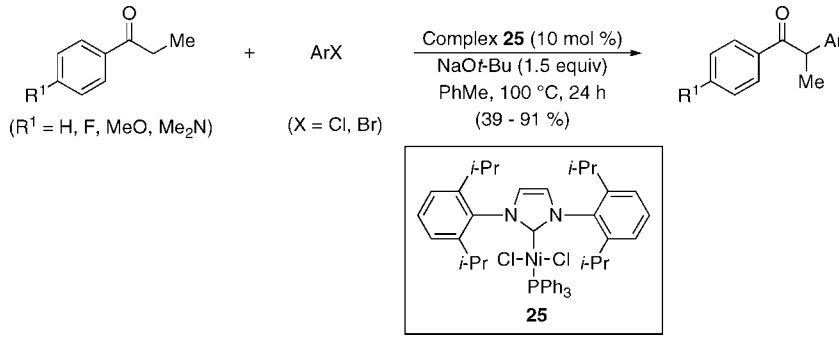


Entry	R^1	ArX	Product	Yield (%)
1	H	4-$MeOC_6H_4Cl$		90
2	H	4-$MeOC_6H_4Br$		98
3	H	4-$MeOC_6H_4I$		96
4	F	4-MeC_6H_4Cl		92
5	OMe	4-MeC_6H_4Cl		90
6	OMe	3,5-$(MeO)_2C_6H_3Cl$		87
7	F	3-$MeOC_6H_4Cl$		80
8	OMe	3-MeC_6H_4Cl		89

the palladium-catalyzed reactions have proven to be a valid tool for the synthesis of a variety of substrates. In fact, they have been validated both in the preparation of building blocks for the synthesis of rocaglamide analogues[86] and *N*-substituted indoles[87] and as key steps for the synthesis of highly substituted free (NH)-indoles **26**,[88] rocaglaols **27**,[89] which are biologically active natural products first isolated from the leaves of *Aglaia odorata*,[90] and the isoindolo benzazepine alkaloids lennoxamine **28**, 13-deoxychilenine **29**, and chilenine **30**[91] (Figure 3).

The synthetic utility of the palladium-catalyzed intermolecular α-arylations of ketones has also been highlighted in a study by Wills et al. on the palladium-catalyzed reaction of ketones **31** with *tert*-butyldimethyl-[3(2-bromophenyl)a-

Scheme 17. α-Arylation of Propiophenones Catalyzed by the Ni(II) Complex 25



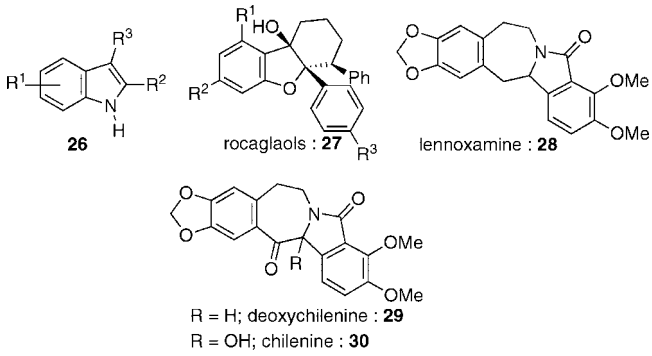
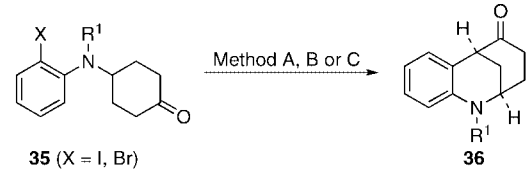


Figure 3. Chemical structures of compounds **26**−**30**.

llyloxy]silane **32**[92] where it was shown that, through an appropriate selection of the phosphine ligand and solvent, the reaction can furnish selectively the cyclized isochromene products **34** or the noncyclized intermediates **33** (Scheme 18).[92] The direct formation of isochromenes **34** was interpreted as the result of a ketone α-arylation followed by an intramolecular cyclization of the resulting enolate with the allyl system via allylic substitution. The presence of the *tert*-butyldimethylsilyl protecting group in the substrate **32** proved to be essential for this palladium-catalyzed tandem reaction as the use of more effective leaving groups, such as acetate, resulted in reaction of the allyl system and no α-arylation was observed.[92]

Recently, attention has also been paid to the palladium-catalyzed intramolecular coupling reaction of amino-tethered aryl halides and ketones,[93] and it has been found that *ω*-(2-haloanilino) alkanones can undergo two different and competitive reaction pathways. Hence, 2-haloanilino cyclohexanones **35** were shown to undergo arylation under the experimental conditions of methods A−C reported in Table 19 to give hexahydro-2,6-methano-1-benzazicines **36** in modest-to-good yields.

Table 19. Pd-Catalyzed Cyclization of 2-Haloanilino Cyclohexanones 35



Method A: $Pd(PPh_3)_4$ (0.2 equiv), KO-tBu (3.0 equiv), THF, reflux, 3-5h
Method B: $PdCl_2(PPh_3)_2$ (0.2 equiv), Cs_2CO_3 (3.0 equiv), THF, 100-110 °C, sealed tube, 24 h
Method C: $Pd(PPh_3)_4$ (0.2 equiv), K_3PO_4 (3.0 equiv), THF, 100-110 °C, sealed tube, 24 h

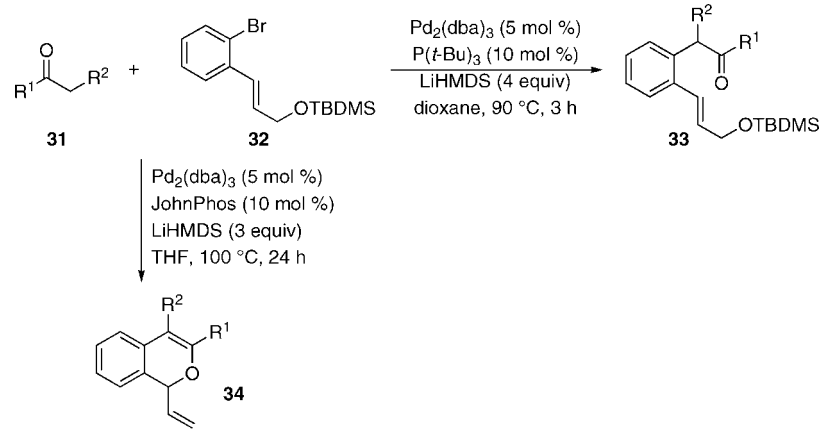
entry	X	R^1	method	yield (%)
1	I	Bn	A	84
2	I	Bn	B	68
3	I	Bn	C	76
4	Br	Bn	A	67
5	Br	Bn	B	60
6	Br	Bn	C	78
7	I	Ac	B	33
8	I	Ac	C	38
9	I	COOMe	A	48
10[(a)]	I	COOMe	B	92
11	I	COOMe	C	35

[(a)] The reaction was run for 48 h using 0.3 equiv of $PdCl_2(PPh_3)_2$.

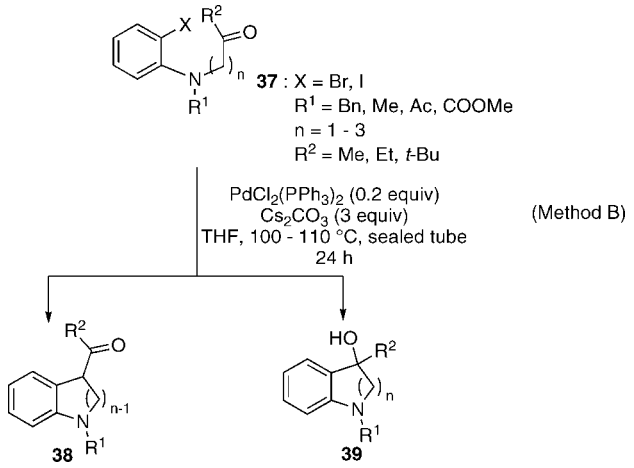
On the other hand, 2-haloanilino ketones **37**, on treatment with a catalytic amount of $PdCl_2(PPh_3)_2$ using the reaction conditions of method B of Table 19, underwent α-arylation or the addition to the carbonyl group depending on their structure (Scheme 19).[93]

For example, the palladium-catalyzed cyclization of **37a** gave **39a** in 40% yield (Scheme 20). However, purification

Scheme 18. Synthesis of Isochromenes 34 and the Noncyclized Intermediates 33



Scheme 19. Pd-Catalyzed Reactions of 2-Haloanilino Ketones 37



of this alcohol was hampered by the formation of considerable amounts of γ-butyrolactone, but interestingly, addition of 2 equiv of Et_3N to a toluene solution of the substrate resulted in a very clean reaction, avoiding the formation of γ-butyrolactone. On the other hand, the $PdCl_2(PPh_3)_2$-catalyzed cyclization of **37b** in toluene in the presence of Et_3N gave a mixture of compounds **39b** and **40a**, which were isolated in 44 and 29% yield, respectively (Scheme 20).[93]

Intramolecular palladium-catalyzed α-arylation reactions of ketones have also been used by Khartulyari and Maier in 2007 for the synthesis of benzomorphan analogues.[94] Specifically, tricyclic compounds **42a** and **42b** were synthesized in 35 and 36% yield, respectively, by cyclization of bromoketoesters **41a** and **41b** in refluxing toluene using K_3PO_4 as the base and a combination of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ as the catalyst system (Scheme 21).[94]

From 1998 until nowadays, efforts have also been focused on asymmetric versions of the transition metal-catalyzed α-arylation of ketone with aryl halides.[95−98] In 1998, Buchwald et al. reported that the intermolecular asymmetric arylation of 2-methyl-α-tetralones can be performed with good levels of the yield using the $Pd_2(dba)_3$/(*S*)- or (*R*)-BINAP catalyst system.[95] The enantioenriched products **43**, in which a quaternary stereocenter was installed,[99] were obtained in 61−88% enantiomeric excess (ee) (Table 20).

Interestingly, 5-benzylidene-2-methylcyclopentanone **44** proved to be arylated with higher enantioselectivity compared with the other investigated ketones, and the required 2-aryl-5-benzylidene-2-methylcyclopentanones **45** (Figure 4) were obtained with ee up to 98% using aryl bromides with *meta*- and *para*-substituents as arylating reagents.[95]

Scheme 21. Synthesis of the Benzomorphan Derivatives 42a and 42b

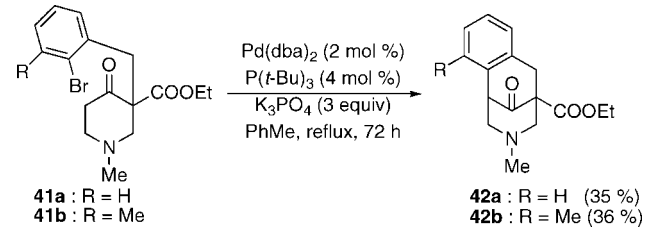
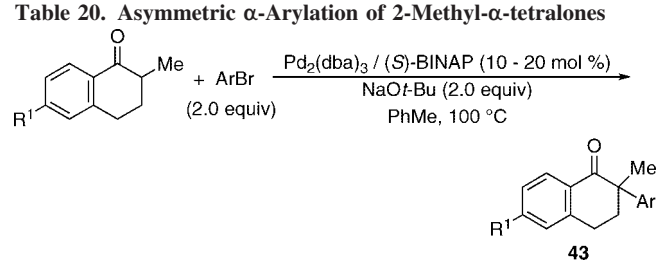


Table 20. Asymmetric α-Arylation of 2-Methyl-α-tetralones



entry	R^1	Ar	yield (%)	ee (%)
1	H	Ph	66	73
2	H	4-*t*-BuC_6H_4	73	88
3	MeO	4-*t*-BuC_6H_4	56	77
4	H	3-(1,3-dioxolan-2-yl)C_6H_4	74	84
5[(a)]	H	4-NC-C_6H_4	40	61

[(a)] The reaction was run at 70 °C using 5 equiv of aryl halide and 5 equiv of NaO*t*-Bu.

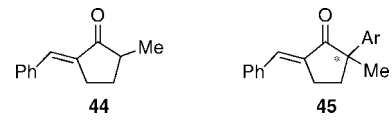


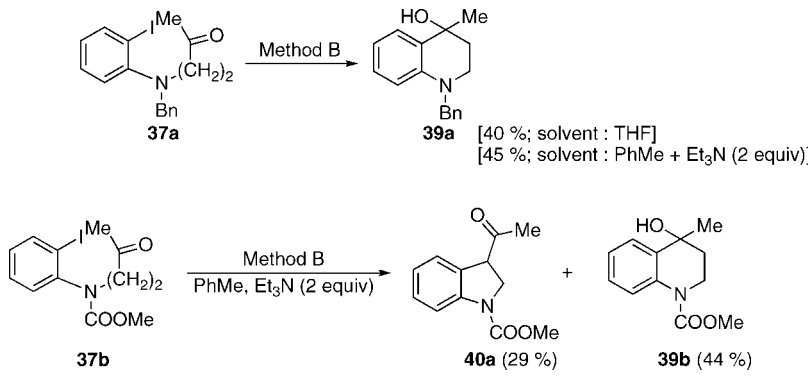
Figure 4. Chemical structures of compounds **44** and **45** .

Four years later, Buchwald et al. reported that the catalyst systems prepared from $Pd_2(dba)_3$ and homochiral dialkylphosphinobinaphthyl ligands **47a−c** are able to effect the asymmetric arylation of the α-alkyl-α′-protected cyclopentanones **46** at room temperature using NaO*t*-Bu as the base and only 2 mol % of the Pd catalyst (Scheme 22).[96]

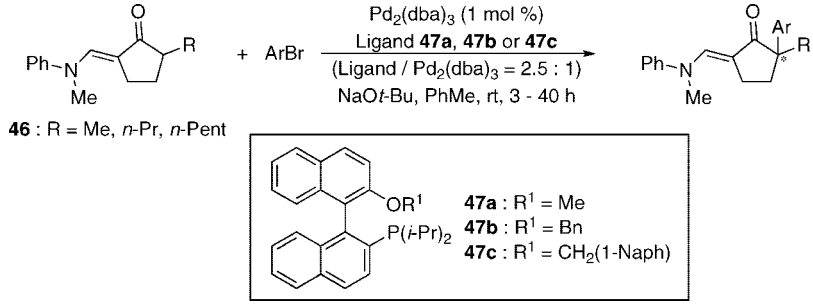
These catalysts proved significantly more reactive than previous systems. Ligand **47c**, which was the best of the ligands used in this study, allowed the installation of an all-carbon quaternary stereogenic center in compounds **46** in high isolated yields and up to 94% ee.[96]

In 2006, Kwong, Chan et al.[98] described that the atropoisomeric dipyridylphosphine (*R*)-P-Phos[100] can effect highly enantioselective nickel-catalyzed α-arylation of cycloalkanone enolates with aryl chlorides, bromides, and iodides

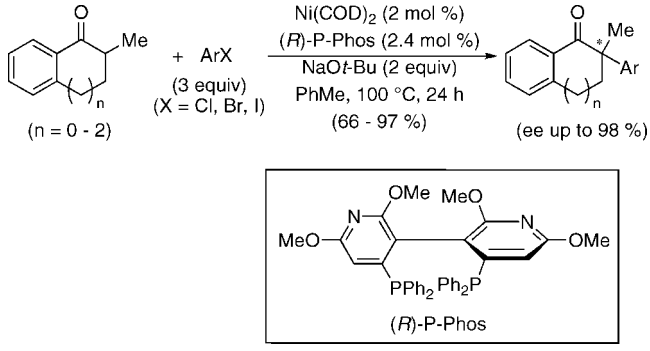
Scheme 20. Pd-Catalyzed Cyclization Reactions of Compounds 37a and 37b



Scheme 22. Enantioselective Arylation of Cyclopentanones 46



Scheme 23. Ni(COD)$_2$/(*R*)-P-Phos-Catalyzed Enantioselective α-Arlation of Cycloalkanones



to install an all-carbon quaternary stereogenic center in excellent yields and up to 98% ee (Scheme 23).

Two years later, the first examples of catalytic enantioselective α-arylation of ketones with aryl triflates were described by Hartwig et al.[97] The palladium-catalyzed reactions were conducted with Difluorphos,[101] an electron-poor diphosphine ligand possessing a small dihedral angle. In fact, the magnitude of the ee values was found to increase with decreasing dihedral angles of the ligands.

The combination of Pd(dba)$_2$ and Difluorphos catalyzed the α-arylation of ketones, including α-methyltetralone, 2-methyl-6-benzylidenecyclohexanone, and 5-benzylidene-2-methylcyclopentanone, with a variety of electron-neutral and electron-rich aryl triflates in excellent yields and ee values up to 95%. Representative examples of these enantioselective reactions are reported in Table 21.

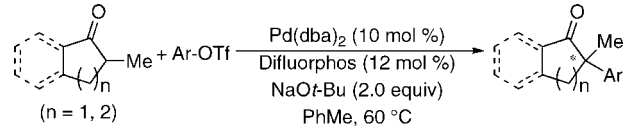
Unfortunately, the reaction conditions illustrated in this table proved to be unsuitable for the arylation reaction with electron-poor aryl triflates, but this limitation could be overcome by using a nickel catalyst containing Difluorphos as the ligand. As shown in Table 22, the Ni(COD)$_2$/Difluorphos catalyst system allowed for the synthesis of α-arylated ketones in 40−84% yield and ee values up to 98%.[97]

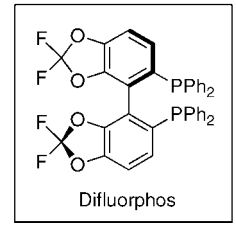
3. Synthesis of α-Aryl Substituted Ketones by Coupling of Silyl Enol Ethers of Ketones with Aryl Halides or Psudohalides

Despite the palladium- and nickel-catalyzed direct α-arylation reactions of ketones with aryl halides or pseudohalides that appear to be a very useful methodology to access α-arylated ketones in a simple way, these reactions suffer from some drawbacks. In fact, some substrates do not tolerate the strongly basic reaction conditions often required by this process and, for instance, 4-chromanones undergo ring-opening to phenolate anions under basic conditions (Scheme 24).[102]

Another limitation is that the α-arylation reaction generally occurs at the less substituted α-position of ketones with two

Table 21. Pd-Catalyzed Enantioselective α-Arylation of Ketones with Aryl Triflates





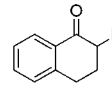
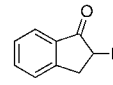
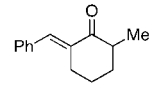
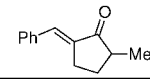
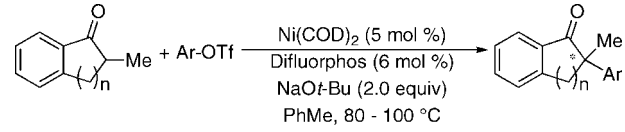
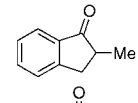
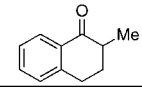
Entry	Ketone	Ar	Yield (%)	ee (%)
1		Ph	81	90
2		4-*t*-BuC$_6$H$_4$	85	92
3		4-MeC$_6$H$_4$	79	92
4		3,5-(*t*-Bu)$_2$C$_6$H$_3$	83	95
5		Ph	77	70
6		4-MeC$_6$H$_4$	79	78
7		3,5-(*t*-Bu)$_2$C$_6$H$_3$	84	89
8		Ph	80	78
9		3,4-(MeO)$_2$C$_6$H$_3$	70	77
10		Ph	70	95

Table 22. Ni-Catalyzed Enantioselective α-Arylation of Ketones with Electron-Poor Aryl Triflates

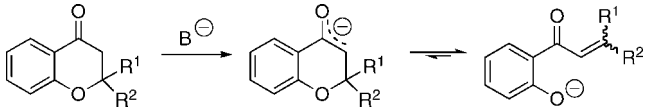


Entry	Ketone	Ar	Yield (%)	ee (%)
1		4-NCC$_6$H$_4$	84	95
2		4-CF$_3$C$_6$H$_4$	69	96
3		3-CF$_3$C$_6$H$_4$	70	86
4		4-NCC$_6$H$_4$	55	97
5		4-CF$_3$C$_6$H$_4$	40	98

enolizable α-positions. Hence, the palladium- or nickel-catalyzed reactions with aryl halides cannot be used for arylations at the more substituted α-position of ketones with two enolizable positions. Moreover, sometimes multiple arylation is possible, and in order to prevent this side-reaction, it is often necessary to block one α-position of the ketone.

A method that does not suffer from these shortcomings and offers several advantages over the direct α-arylation of

Scheme 24. Base-Promoted Ring-Opening of 4-Chromanones

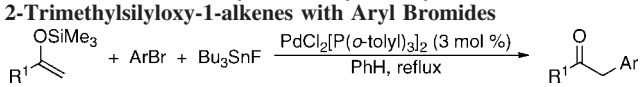


ketones is the palladium-catalyzed coupling of silyl enol ethers of ketones with aryl halides or pseudohalides. The advantages due to the use of silyl enol ethers, which represent masked ketone enolates, include the following: (i) Their reduced basicity in comparison to the corresponding ketone enolates improves functional group compatibility. (ii) The use of structurally well-defined silyl enol ethers[103] can allow the insertion of an aryl group at the more substituted α-position of a ketone with two enolizable α-positions. (iii) The experimental conditions for the arylation of silyl enol ethers of ketones do not generally involve the use of a strong base. Accordingly, these conditions can allow for the development of enantioselective protocols to install an acidic tertiary stereocenter in the α-position to a carbonyl group without meeting with racemization or epimerization issues. However, it must be taken into account that silyl enol ethers of ketones are not commercially available usually and that, in the case of the palladium-catalyzed arylation reaction that involves structurally well-defined ketones with two enolizable α-positions, a nontrivial regioselective synthesis of the silyl derivatives is required.[103]

An early example of palladium-catalyzed arylation of silyl enol ethers of ketones with aryl halides was reported by Kuwajima and Uribe in 1982.[104,105] These authors demonstrated that treatment of silyl enol ethers of methyl *n*-alkyl and methyl *sec*-butyl ketones with aryl bromides bearing an electron-donating, an electron-withdrawing, or an *ortho*-substituent and tributyltin fluoride as an additive in refluxing benzene, in the presence of a catalytic amount of $PdCl_2[P(o\text{-tolyl})_3]_2$, provides α-arylated ketones in modest-to-satisfactory yields.[104] Organotin enolates, generated in situ from the corresponding silyl enol ethers, were the proposed reactive species. Among the following palladium complexes, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2$(dppe), and $PdCl_2[P(o\text{-tolyl})_3]_2$, use of the last one proved to be the most effective. However, silyl enol ethers of methyl *tert*-alkyl ketones and diethyl ketones survived the reaction conditions to be recovered.[104] Representative results of $PdCl_2[P(o\text{-tolyl})_3]_2$-catalyzed arylations of 2-trimethylsilyloxy-1-alkenes with aryl bromides are reported in Table 23.

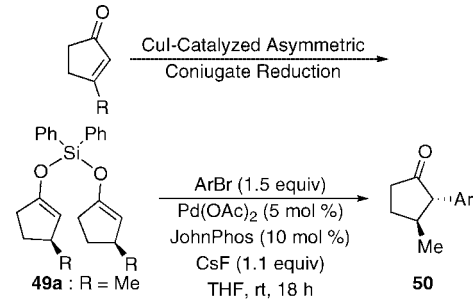
A powerful method for the palladium-catalyzed arylation at room temperature of enantiomerically enriched silyl enol ethers of cyclopentanones in the presence of CsF was devised by Buchwald's group in 2004.[106] The protocol, which

Table 23. $PdCl_2[P(o\text{-tolyl})_3]_2$-Catalyzed Arylation of 2-Trimethylsilyloxy-1-alkenes with Aryl Bromides



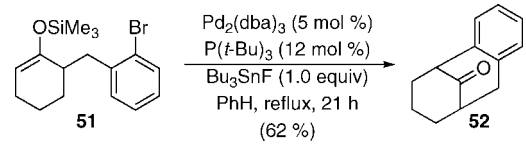
entry	R^1	Ar	silyl ether/ArBr molar ratio	reaction time (h)	yield (%)
1	n-C_7H_{15}	Ph	1/2	4	65
2	n-C_7H_{15}	4-$MeOC_6H_4$	1/1.1	3	62
3	i-$Pr(CH_2)_2$	Ph	1/2	4	65
4	i-$Pr(CH_2)_2$	4-MeC_6H_4	1/1.1	3	62
5	i-$Pr(CH_2)_2$	4-AcC_6H_4	1.5/1	3	70
6	*sec*-Bu	Ph	1/1.1	10	47
7	*t*-Bu	Ph	1/1.1	24	29
8	Ph	Ph	1/2	5	35

Table 24. Arylation of Diphenylsilyl Enol Ether 49a with Aryl Bromides



		compound **50**	
entry	Ar	yield (%)	de (%)
1	Ph	91	93
2	4-*t*-BuC_6H_4	93	93
3	4-$MeOC_6H_4$	84	94
4	4-$MeOC_6H_4$	74	91
5	4-$EtOOCC_6H_4$	70	95
6	2-MeC_6H_4	68	88

Scheme 25. Synthesis of Compound 52 by Intramolecular Pd-Catalyzed Reaction of Silyl Enol Ether 51



provides a simple route to α-arylated cyclopentanones **50** with excellent levels of enantiomeric and diastereomeric purity, involves treatment of enantiomerically enriched *β*-substituted diphenylsilyl enol ethers **49** with a molar excess of aryl bromides in THF in the presence of CsF and a catalytic system consisting of a combination of $Pd(OAc)_2$ and 2-(di-*tert*-butylphosphino)biphenyl (JohnPhos).[106] Compounds **49** were prepared by copper-catalyzed conjugate asymmetric reduction of the corresponding cyclopentenones **48**.[107] Remarkably, this protocol could also be applied to cyclohexenone substrates. Table 24 summarizes the results of arylation reactions of silyl enol ether **49a** with aryl bromides.

In 2006, Iwama and Rawal showed that inter- and intramolecular arylation reactions of trimethylsilyl enol ethers

Scheme 26. Plausible Mechanism for the Intermolecular Pd-Catalyzed Arylation of Silyl Enol Ethers in the Presence of Bu_3SnF

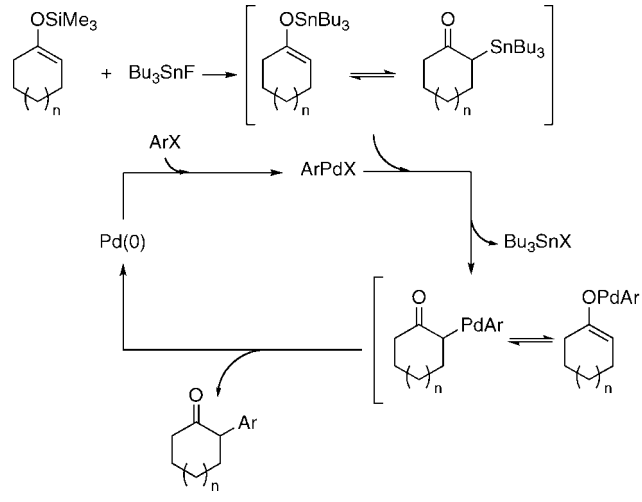
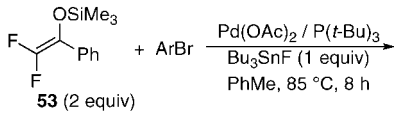
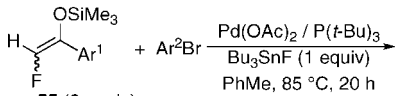


Table 25. Pd-Catalyzed Arylation of Difluoroenol Silyl and Monofluoroenol Silyl Ethers 53 and 55



53 (2 equiv) 54

Ar	Yield (%)
Ph	91
4-MeC_6H_4	86
4-*t*-BuC_6H_4	82
4-$MeOC_6H_4$	84
4-$CF_3C_6H_4$	81
3,5-$(CF_3)_2C_6H_3$	70
3-$MeOOCC_6H_4$	89
4-NCC_6H_4	90
4-$O_2NC_6H_4$	70
4-AcC_6H_4	82
2-thienyl	82



55 (2 equiv) 56

Ar^1	Ar^2	Yield (%)
4-*t*-BuC_6H_4	3-$MeOOCC_6H_4$	94
4-*t*-BuC_6H_4	2-thienyl	75
4-$MeOC_6H_4$	4-NCC_6H_4	75
4-$MeOC_6H_4$	4-$O_2NC_6H_4$	68
4-$CF_3C_6H_4$	Ph	45
2-thienyl	Ph	75

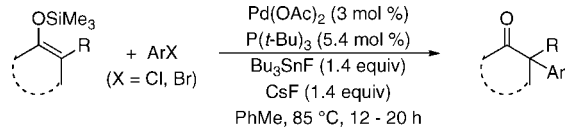
of cycloalkanones with electron-poor and electron-rich aryl iodides, bromides, and chlorides can be regioselectively accomplished by the use of a $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system in the presence of Bu_3SnF.[108] The synthesis of [3.3.1]bicyclic compound **52** by intramolecular arylation of silyl enol ether **51** according to this protocol is illustrated in Scheme 25.[108]

These authors envisaged a plausible mechanism for the intermolecular arylation reactions in which the required α-arylated cycloalkanones are obtained by treatment of trimethylsilylenol ethers of cycloalkanones with Bu_3SnF, transmetalation between the resulting tributylstannyl enolates and arylpalladium(II) species, followed by a reductive elimination reaction (Scheme 26).[108]

In 2007, a protocol similar to that developed by Iwama and Rawal[108] was applied by Guo, Twamley, and Shreeve for the preparation of α,α-difluoroketones **54** and α-fluoroketones **56** from silyl enol ethers **53** and **55**, respectively (Table 25).[109]

One year before this report, Verkade, Hartwig et al. had found that the coupling of silyl enol ethers of ketones with aryl bromides and chlorides is synergically promoted by the combination of two metal fluorides, and in light of this important finding, they developed two protocols for this

Table 26. $Pd(OAc)_2/P(t\text{-}Bu)_3$-Catalyzed Arylation of Silyl Enol Ethers with Aryl Halides Using a Combination of Bu_3SnF and CsF as Additives



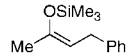
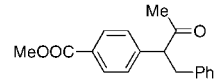
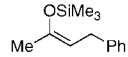
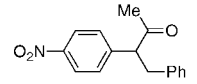
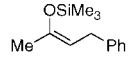
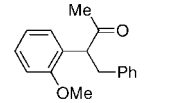
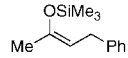
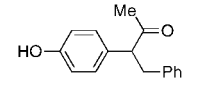
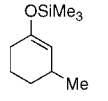
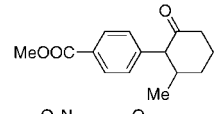
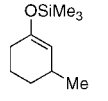
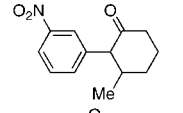
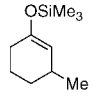
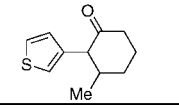
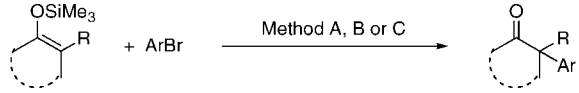
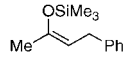
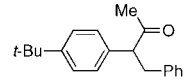
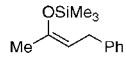
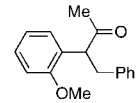
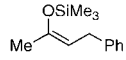
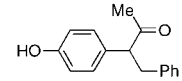
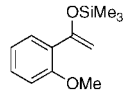
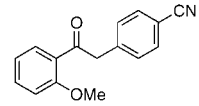
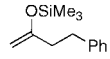
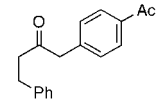
Entry	Silyl Enol Ether	Ar	X	Product	Yield (%)
1		4-$MeOOCC_6H_4$	Cl		89
2		4-$O_2NC_6H_4$	Br		84
3		2-$MeOC_6H_4$	Br		97
4		4-HOC_6H_4	Br		55
5		4-$MeOOCC_6H_4$	Cl		80
6		3-$O_2NC_6H_4$	Cl		77
7		3-thienyl	Br		78

Table 27. Pd-Catalyzed Arylation of Silyl Enol Ethers with Aryl Bromides in the Presence of ZnF_2 and CsF or MnF_2 as Additives



Method A: silylether/ArBr = 1.4:1, $Pd(dba)_2$ (3 mol %), $P(t\text{-}Bu)_3$ (5.4 mol %), CsF (0.4 equiv), ZnF_2 (1.4 equiv), DMF, 85 °C
Method B: silylether/ArBr = 1.5:1, $Pd(dba)_2$ (2 mol %), $P(t\text{-}Bu)_3$ (4 mol %), MnF_2 (0.4 equiv), ZnF_2 (1.0 equiv), DMF, 70 °C
Method C: silylether/ArBr = 5:1, $Pd(dba)_2$ (3 mol %), $P(t\text{-}Bu)_3$ (5.4 mol %), MnF_2 (1.4 equiv), ZnF_2 (1.4 equiv), DMF, 70 °C

Entry	Silyl Enol Ether	Ar	Method	Product	Yield (%)
1		4-*t*-BuC_6H_4	A		89
2		2-$MeOC_6H_4$	A		87
3		4-HOC_6H_4	A		53
4		4-NCC_6H_4	B		78
5		4-AcC_6H_4	B		71
6		Ph	C		68

arylation reaction.[110] In the first of these, silyl enol ethers, formed by the addition of Grignard reagents to α,β-unsaturated ketones in the presence of $CuBr \cdot Me_2S$, Me_3SiCl, and HMPT,[111] were reacted with aryl bromides or chlorides in toluene with a combination of Bu_3SnF and CsF as additives in the presence of catalytic amounts of $Pd(OAc)_2$ and $P(t\text{-}Bu)_3$ to give the required α-arylated ketones in moderate-to-excellent yields (Table 26).[110]

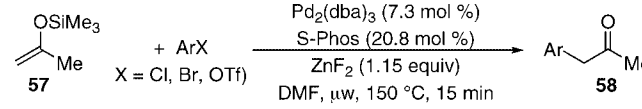
In the second protocol, the $Pd(OAc)_2/P(t\text{-}Bu)_3$-catalyzed reaction of silyl enol ethers of ketones with aryl bromides is carried out in DMF solution under tin-free conditions, but in the presence of a combination of stoichiometric amounts of ZnF_2 and either CsF or MnF_2 as additives.[110] Representative results obtained by using this protocol are reported in Table 27.

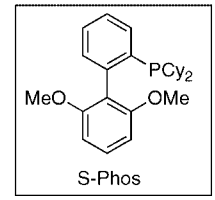
Recently, tin-free reaction conditions have also been employed by Chobanian et al. in an expedient method for the (hetero)arylation of 2-trimethylsilyloxypropene **57** with (hetero)aryl chlorides, bromides, and triflates that implies the synthesis of ketones **58** in modest-to-high yields by treatment of **57** with (hetero)aryl chlorides, bromides, or triflates under microwave irradiation in the presence of ZnF_2 as the additive and catalytic quantities of $Pd_2(dba)_3$ or $Pd(OAc)_2$ and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos) as the supporting ligand (Table 28).[112]

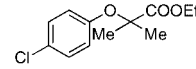
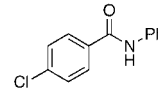
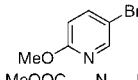
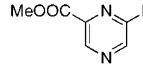
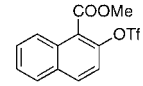
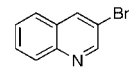
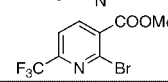
It has been postulated that this palladium-catalyzed reaction involves the in situ generation of a zinc enolate via reaction of 2-trimethylsilyloxypropene (**57**) with ZnF_2 (Scheme 27).[112]

Recently, Doucet, Santelli et al. have instead used the $[PdCl(\eta^3\text{-}C_3H_5)]_2$/*cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinylmethyl)cyclopentane (Tedicyp) (2:1) complex as the catalyst for the high-yielding synthesis of 2-aryl-1-phenylethanones **60** from 1-phenyl-1-(trimethylsilyloxy)ethylene **59** and aryl bromides in dimethylformamide (DMF) at 130 °C in the presence of K_2CO_3 (Table 29).[113]

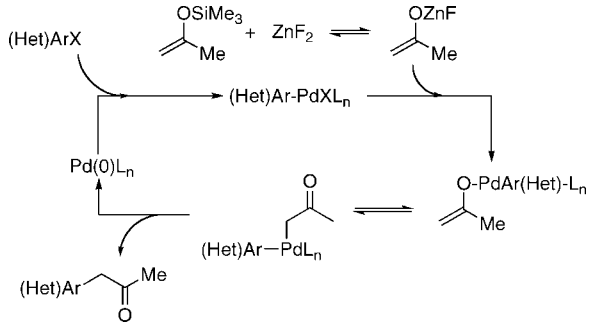
Table 28. Microwave-Assisted $Pd_2(dba)_3$/S-Phos-Catalyzed Arylation of 2-Trimethylsilyloxypropene in the Presence of ZnF_2





Entry	ArX	Yield (%)
1		82
2		88
3		63
4		25
5		48
6		70
7		32
8		55

Scheme 27. Plausible Mechanism for the $Pd_2(dba)_3$/S-Phos-Catalyzed Arylation of 2-Trimethylsilyloxypropene in the Presence of ZnF_2



4. Synthesis of α-Aryl-Substituted Ketones by Coupling of Enol Esters of Ketones with Aryl Halides or Pseudohalides

Enol esters, including enol acetates, of ketones have been used for the selective formation of enolates and have proven to be useful reagents for carbon−carbon bond formation.[114] A wide variety of methods have been developed to prepare these masked carbonyl compounds[115] and, because of their higher stability compared to the corresponding silyl enol ethers, significant attention has been deserved for their use for the synthesis of α-aryl substituted ketones.

In 1968, Heck synthesized α-arylated ketones by reaction of enol esters of ketones with arylpalladium(II) compounds, in situ generated from arylmercury derivatives and palladium salts.[116] In 1973, the Heck reaction of 4-chromanone enol acetates **61** with stoichiometric amounts of arylpalladium(II) compounds, in situ generated from the corresponding aryl-

Scheme 28. Arylation of 4-Chromanone Enol Acetates

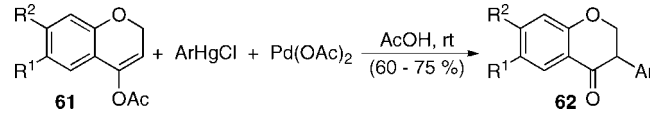
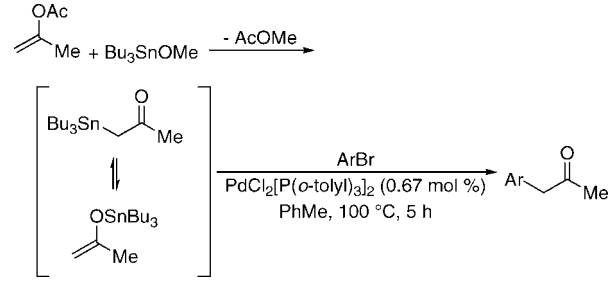
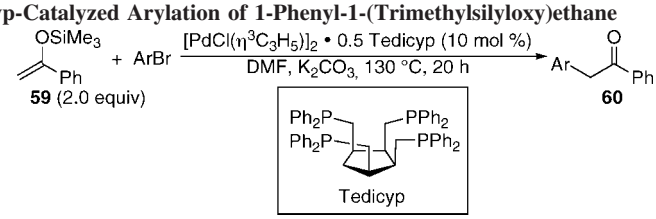


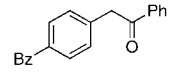
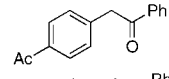
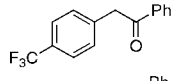
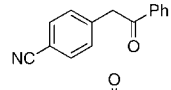
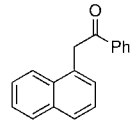
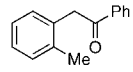
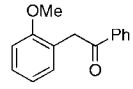
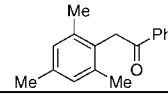
Table 30. $PdCl_2[P(o\text{-tolyl})_3]_2$-Catalyzed Acetonylation of Aryl Bromides via Acetonyltributyltin



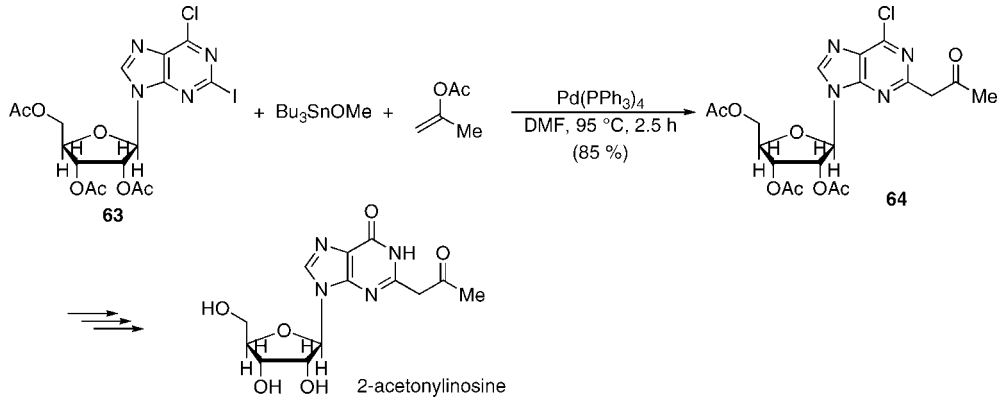
entry	Ar	yield (%)
1	Ph	78
2	2-MeC_6H_4	91
3	3-MeC_6H_4	88
4	4-MeC_6H_4	80
5	4-$MeOC_6H_4$	51
6	2-ClC_6H_4	80
7	4-ClC_6H_4	73
8	4-$Me_2NC_6H_4$	71
9	2,4,6-$(Me)_3C_6H_2$	94
10	2-AcC_6H_4	0
11	4-AcC_6H_4	64
12	4-$O_2NC_6H_4$	0

Table 29. $[PdCl(\eta^3\text{-}C_3H_5)]_2$/Tedicyp-Catalyzed Arylation of 1-Phenyl-1-(Trimethylsilyloxy)ethane

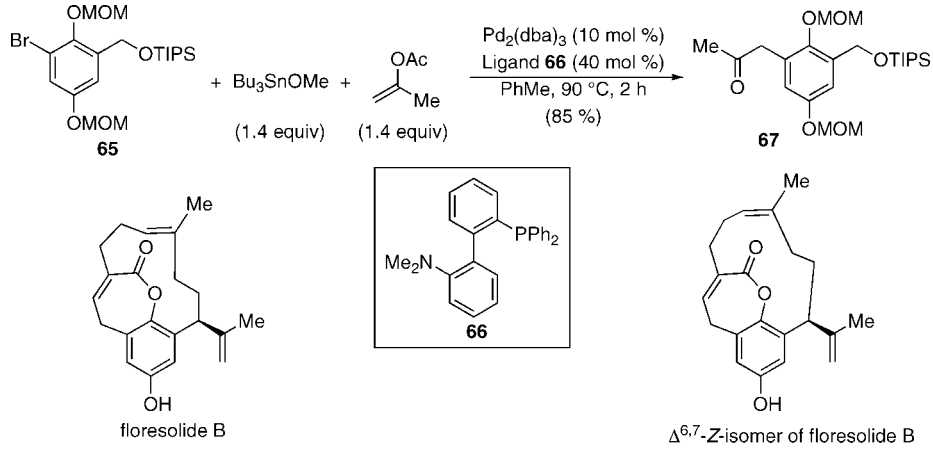


Entry	Substrate / Catalyst mole ratio	Ar	Product	Yield (%)
1	100	4-BzC_6H_4		83
2	100	4-AcC_6H_4		78
3	50	4-$CF_3C_6H_4$		82
4	50	4-NCC_6H_4		80
5	50	1-naphthyl		88
6	50	2-MeC_6H_4		65
7	50	2-$MeOC_6H_4$		81
8	50	2,4,6-$(Me)_3C_6H_2$		80

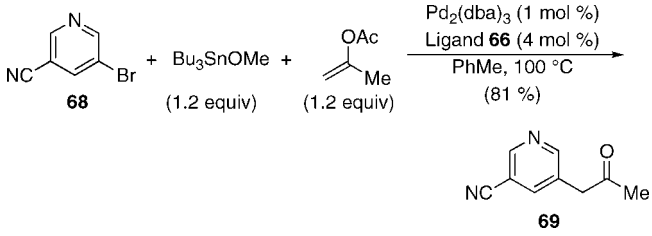
Scheme 29. Pd-Catalyzed Synthesis of the Acetonylpurine 64



Scheme 30. Pd-Catalyzed Synthesis of Benzyl Methyl Ketone 67



Scheme 31. Pd-Catalyzed Synthesis of Methyl Ketone 69



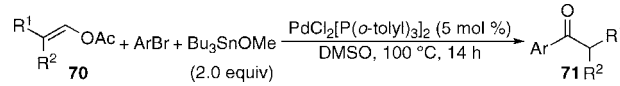
mercury chlorides and $Pd(OAc)_2$, was used by Kasahara et al. to prepare isoflavanones **62** in high yields (Scheme 28).[117]

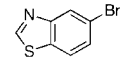
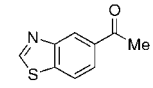
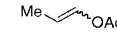
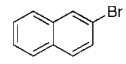
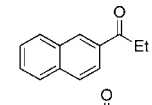
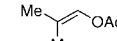
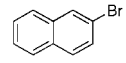
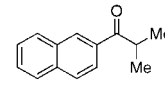
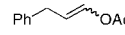
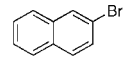
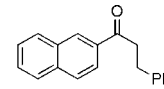
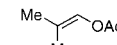
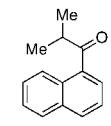
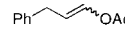
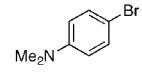
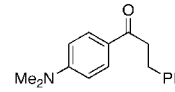
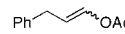
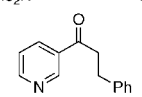
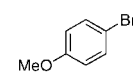
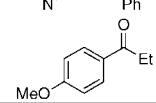
A significant development in the area concerning the arylation of enol acetates of ketones was subsequently reported by Migita et al., who pioneered the palladium-catalyzed coupling of aryl bromides with tributylstannyl enolates, in situ prepared from Bu_3SnOMe and enol acetates of ketones.[118−120] Table 30 illustrates the results of the $PdCl_2[P(o\text{-tolyl})_3]_2$-catalyzed acetonylation of aryl bromides via acetonyltributyltin.[120]

In 2005, Gupta and Nair similarly synthesized acetonylpurine **64** by $Pd(PPh_3)_4$-catalyzed reaction of 6-chloro-2-iodopurine ribonucleoside **63**, Bu_3SnOMe, and isopropenyl acetate (Scheme 29)[121] in a key step of the synthesis of 2-acetonylinosine, a potent antiviral compound.

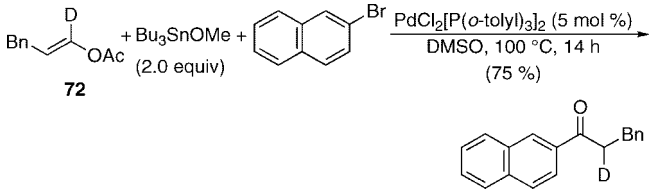
More recently, in the context of the total synthesis of the cytotoxin marin natural product floresolide B and its $\Delta^{6,7}$-*Z*-isomer, a high loading of the catalyst system composed of $Pd_2(dba)_3$ and 2-diphenylphosphino-2′-dimethylaminobinaphthyl **66** has been used by Nicolau and Xu in the synthesis of benzyl methyl ketone **67** from aryl bromide **65**, isopropenyl acetate, and Bu_3SnOMe (Scheme 30).[122]

Table 31. Synthesis of Aryl Ketones 71 by Pd-Catalyzed Coupling of Vinylic Acetates 70 with Aryl Bromides

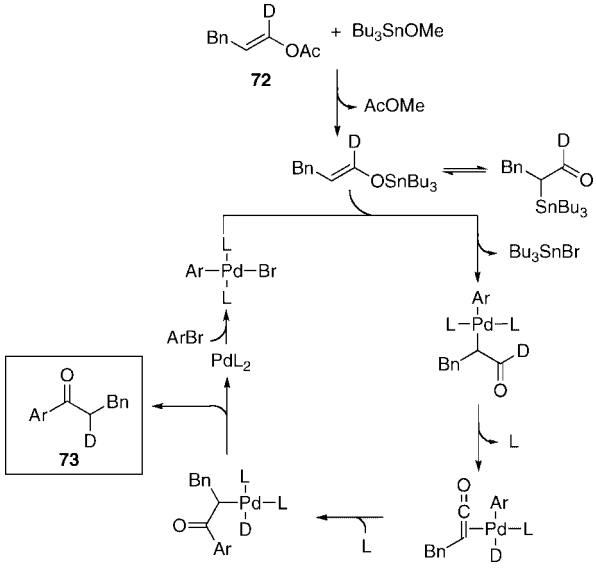


Entry	Vinylic Acetate	Aryl Bromide	Product	Yield (%)
1				49
2				49
3				75
4				72
5				76
6				69
7				28
8				47

Scheme 32. Pd-Catalyzed Synthesis of Deuterated Ketone 73



Scheme 33. Proposed Catalytic Cycle for the Pd-Catalyzed Synthesis of Deuterated Ketone 73



A significantly lower loading of the $Pd_2(dba)_3$/**66** catalyst system had previously been employed to perform the heteroarylation of isopropenyl acetate with a wide array of electronically and structurally diverse heteroaromatic chlorides, bromides, and triflates in good yields.[123] It is also worth mentioning that the protocol developed by Migita et al.[118−120] failed when it was applied to the preparation of methyl ketone **69** from heteroaryl bromide **68**. However, the use of the $Pd_2(dba)_3$/**66** catalyst system allowed for the access to **69** from **68**, isopropenyl acetate, and Bu_3SnOMe in 81% yield (Scheme 31).[123]

Surprisingly, formation of aryl ketones **71** has been recently observed when a protocol very similar to that disclosed by Migita et al.[118−120] was used for the palladium-catalyzed reaction of vinylic acetates **70** with aryl bromides (Table 31).[124]

Analogously, the $PdCl_2[P(o\text{-tolyl})_3]_2$-catalyzed reaction of 2-bromonaphthalene and vinylic acetate **72** produced the deuterated aryl ketone **73** in 75% yield (Scheme 32).[124] Preliminary mechanistic studies indicated that the unexpected formation of **73** proceeds by insertion of a ketene in the coordination sphere of palladium into the aryl−Pd bond followed by reductive elimination (Scheme 33).[124]

A similar coordination and insertion of a ketene into an aryl−Pd bond had previously been proposed by Watanabe et al. for the catalytic cycle of the palladium-catalyzed arylation of ketenes with aroyl chlorides.[125]

5. Synthesis of α-Aryl-Substituted Ketones via α-Arylation of Ketimines with Aryl Halides

Even though ketimines bearing a C−H bond in the α-position are known to easily undergo rapid isomerization to the corresponding enamines under basic conditions, in 2007, Barluenga et al. succeeded in performing the selective direct intermolecular palladium-catalyzed α-arylation of a ketimine bearing a C−H bond in the α-position with aryl halides in the presence of a base.[126] The bulky and electron-

Scheme 34. Pd-Catalyzed α-Arylation of Ketimine 74

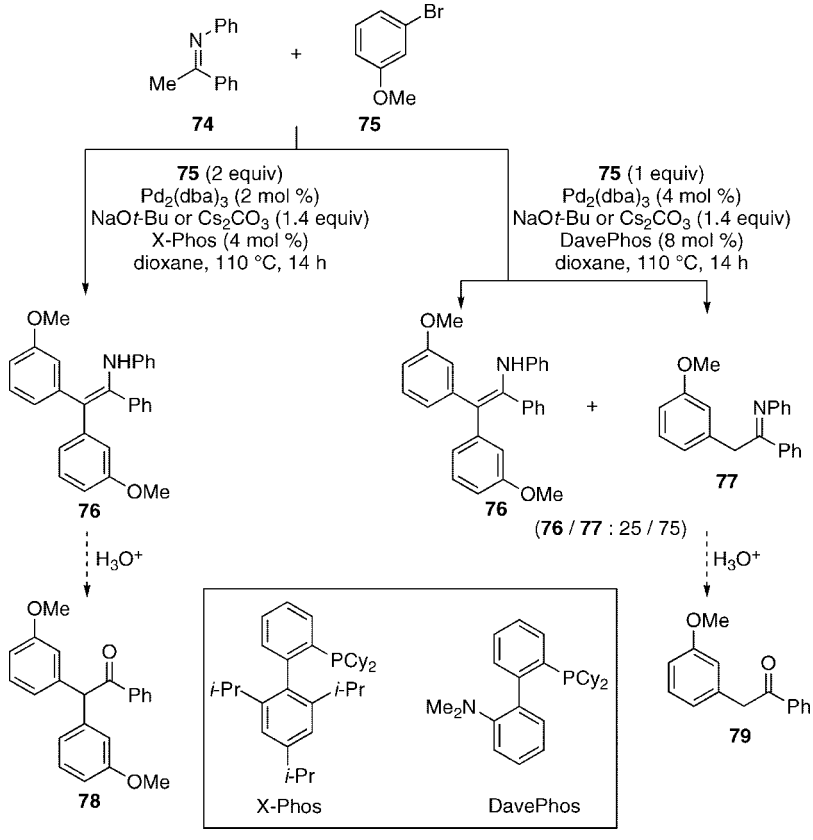
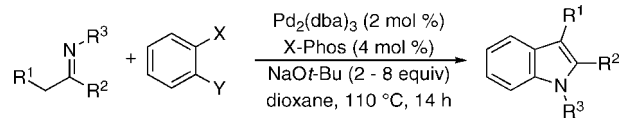
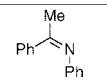
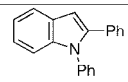
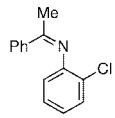
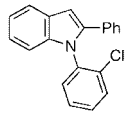
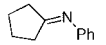
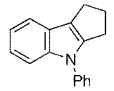
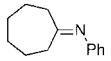
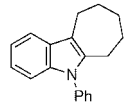
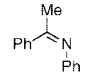
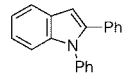
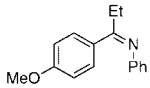
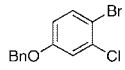
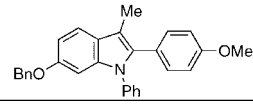


Table 32. Synthesis of Indoles from Ketimines and *o*-Dihalobenzenes



Entry	Imine	Dihalide	Indole	Yield (%)
1				86
2				77
3				86
4				80
5				80
6				70

rich biarylphosphines X-Phos and DavePhos [2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl] were found to be the best ligands to achieve the palladium-catalyzed α-arylation of ketimine **74** with 3-bromoanisole **75**. Specifically, α,α-diarylated ketimine **76** was efficiently prepared from equimolar amounts of **74** and **75** using catalytic quantities of $Pd_2(dba)_3$ and X-Phos as the supporting ligand and either NaO*t*-Bu or Cs_2CO_3 as the base (Scheme 34).

Remarkably, the selective monoarylation of **74** proved to be more elusive and a 25:75 mixture of **76** and the monoarylated imine **77**, respectively, was obtained when DavePhos was employed as the supporting ligand (Scheme 34).[126] Although compounds **76** and **77** might be easily converted to the corresponding α,α-diarylated and α-monoarylated ketones **78** and **79**, respectively, by acidic hydrolysis, this deprotection reaction was not reported by Barluenga et al.[126]

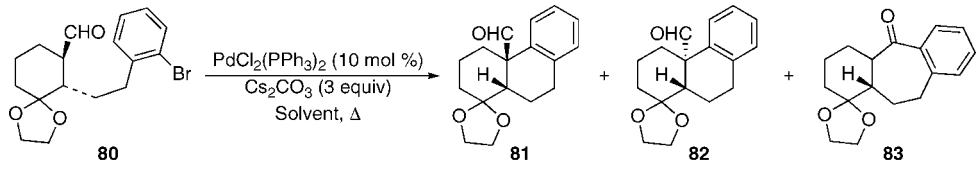
On the other hand, a sequence of palladium-catalyzed α-arylation and intramolecular *N*-arylation reactions involving ketimines and *o*-dihalobenzenes, which were performed using X-Phos as the supporting ligand and NaO*t*-Bu as the base, was employed by these authors to synthesize a wide variety of indoles in good yields (Table 32).[126] The required imines were made in situ by the coupling of amines with bromoalkenes.

6. Synthesis of α-Aryl-Substituted Aldehydes by α-Arylation of Aldehydes Bearing a Primary, Secondary, or Tertiary C−H Bond in the α-Position

Until the late 1990s, the direct formation of a Csp^3-Csp^2 bond by transition metal-catalyzed α-arylation of aldehydes bearing a primary, secondary, or tertiary C−H bond in the α-position remained unexplored, and α-aryl substituted aldehydes were synthesized by arylation of α-chloroaldimines at the α-position under Friedel−Crafts conditions via intermediacy of α-imidocarbenium ions.[127] However, starting from 1999, Muratake et al. extensively investigated the scope and generality of the intramolecular α-arylation of aldehydes bearing a tertiary C−H bond in the α-position and the synthetic applications of this reaction.[45b,128−131]

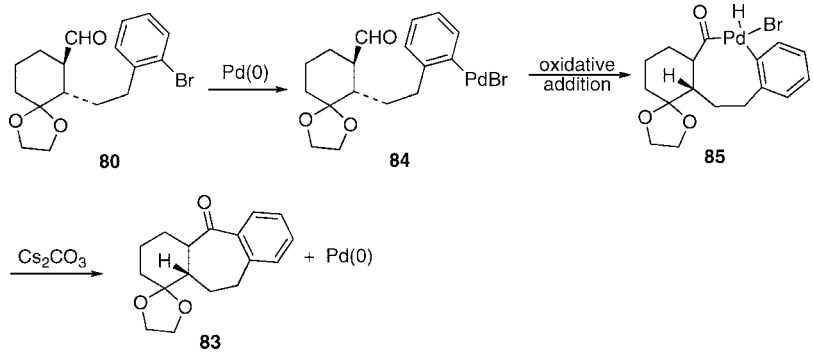
In a first study, it was found that, when the intramolecular arylation of properly designed substrates bearing a formyl group is achieved employing $PdCl_2(PPh_3)_2$ as the catalyst precursor and Cs_2CO_3 as the base, the arylation reaction occurs at the α-position of the formyl group (*α-arylation*) or at the carbonyl group (*carbonyl arylation*) depending on the solvent of the reaction and the structure of the substrate.[128] In fact, in the case of compound **80**, the α-arylation tended to increase

Scheme 35. Intramolecular Pd-Catalyzed Cyclization of Aldehyde 80



Solvent	Reaction Temp. (°C)	Yield (%) 81	82	83
PhMe	110	49	4	22
THF	100 (sealed tube)	52	9	-

Scheme 36. Plausible Mechanism for the Formation of Ketone 83 from Aldehyde 80



Scheme 37. Intramolecular Pd-Catalyzed Arylation of Bromoaldehyde 86

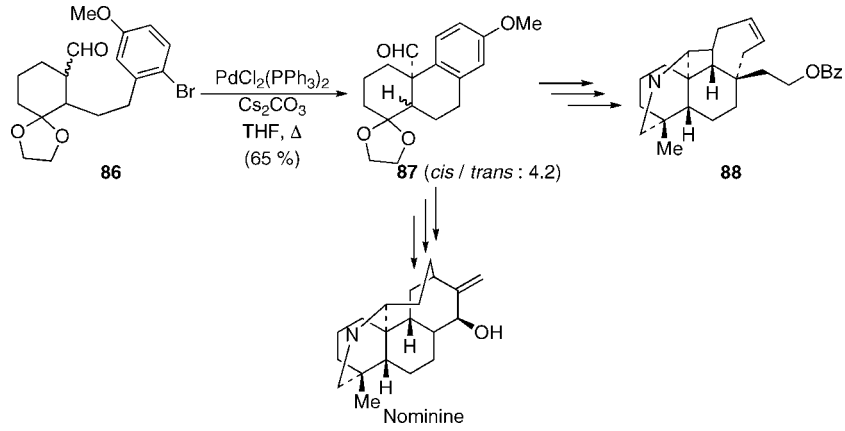
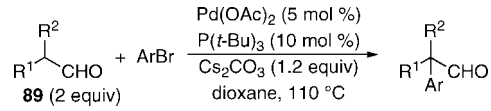


Table 33. Intermolecular Pd-Catalyzed α-Arylation of Aldehydes with Aryl Halides



entry	R^1	R^2	Ar	reaction time (h)	isolated yield (%)
1	H	n-C_6H_{13}	4-MeC_6H_4	2	67
2	H	n-C_6H_{13}	4-$MeOC_6H_4$	2	61
3	H	n-C_6H_{13}	4-PhC_6H_4	3	59
4	H	n-C_6H_{13}	1-naphthyl	3	69
5	H	n-Pr	4-PhC_6H_4	4	54
6	H	Bn	4-PhC_6H_4	3	45
7	H	Ph	Ph	2	56
8	Me	Ph	4-PhC_6H_4	3	43
9	Me	Me	4-PhC_6H_4	3	36

when the cyclization reaction was performed in THF, but the carbonyl addition increased in toluene (Scheme 35).

Moreover, as demonstrated by the fact that aldehydes **81** and **82** were formed preferentially from **80**, a six-membered ring was formed in preference to a five- and seven-membered ring. Formation of ketone **83**, which was noticed when the cyclization was run in toluene, was interpreted supposing that, in this solvent, the enolization of aldehyde **80** is so slow that the carbonyl arylation product **83** is formed through the Pd(II) and Pd(IV) intermediates **84** and **85**, respectively (Scheme 36).[128] In this regard, it should be noted that the oxidative addition of a σ-arylpalladium(II) complex to the formyl C−H bond, similar to that postulated to convert **84** to complex **85**, had previously been reported.[132]

In 2002, Muratake and Natsume prepared a stereoisomeric mixture of aldehyde **87** by palladium-catalyzed intramolecular arylation of compound **86** and used this stereoisomeric mixture as a precursor to the hexacyclic compound **88** having the essential structural unit of the hetisine-type aconite alkaloids (Scheme 37).[129] Some years later, a similarly prepared stereoisomeric mixture of aldehyde **87** was employed as an intermediate in a 40-step total synthesis of racemic nominine, a heptacyclic hetisine-type alkaloid (Scheme 37).[130,131]

In 2002, Miura et al. successfully tackled the challenge of the intermolecular α-arylation of aliphatic linear and α-branched aldehydes with aryl halides[133] and developed an effective protocol for the synthesis of α-arylated aldehydes that involves treatment of aldehydes **89** with aryl bromides in dioxane at 110 °C in the presence of Cs_2CO_3 and a catalyst system composed of a combination of $Pd(OAc)_2$ and P(t-Bu)$_3$ (Table 33). Remarkably, the protocol illustrated in this

Scheme 38. Pd-Catalyzed α-Arylation of Isobutanal with 2-Chlorotoluene

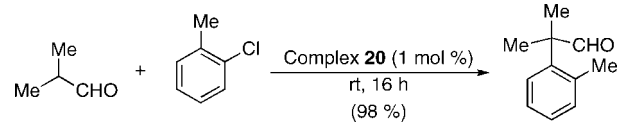
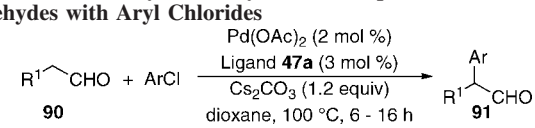
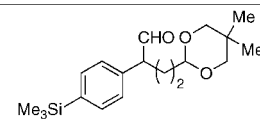
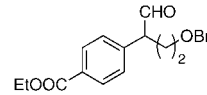
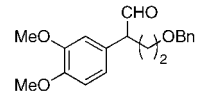
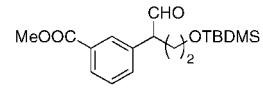
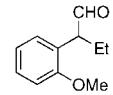
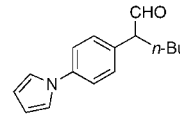
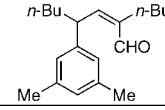


table was also effective in providing aldehydes having a quaternary carbon at the α-position. On the other hand, the use of PPh_3 or PCy_3 as the catalyst supporting ligand and DMF as the solvent resulted in side-reactions occurring by aldol condensation and the use of PPh_3 or PCy_3 in dioxane did not give the required α-arylated aldehydes.[133]

Despite its importance, the synthesis of α-arylated aldehydes from compounds **89** and aryl bromides suffers,

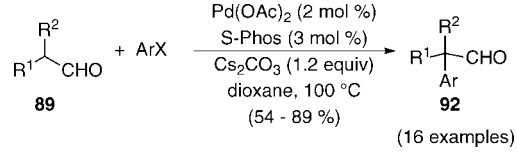
Table 34. Pd-Catalyzed α-Arylation of Aliphatic Linear Aldehydes with Aryl Chlorides



Entry	Product	Yield (%)
1		83
2		73
3		75
4		78
5		64
6		84
7		83[a]

[a] This reaction was run using 2 equiv of aldehyde and 2.4 equiv of Cs_2CO_3 in DMF as the solvent.

Scheme 39. Pd-Catalyzed α-Arylation of α-Branched Aldehydes with Aryl Halides

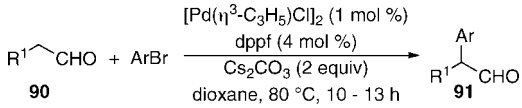


however, from the following limitations: (i) Two equiv of aldehydes **89** are required. (ii) The process involves the use of a high catalyst loading and a high reaction temperature. (iii) The substrate scope is low in both coupling partners.

A substantial improvement of the protocol for performing this reaction was reported by Bertrand at al. in 2005,[79] who described that isobutanal is able to undergo α-arylation with 2-chlorotoluene in the presence of 1 mol % of Pd complex **20** to give 2-methyl-2-(*o*-tolyl)propanal in 98% yield (Scheme 38). Unfortunately, experimental details including the molar ratio between the coupling partners and the nature of the solvent and the base used in the reaction were not described.

In 2007, Martin and Buchwald extensively studied this reaction[134] and identified an efficient and general protocol

Table 35. [Pd(η^3-C_3H_5)Cl]$_2$/dppf-Catalyzed α-Arylation of Linear Aldehydes with Aryl Bromides



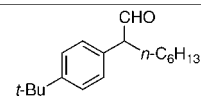
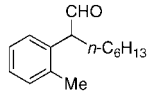
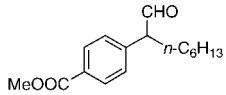
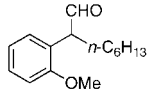
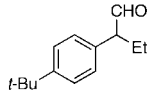
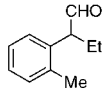
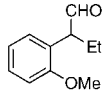
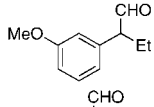
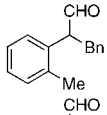
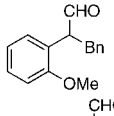
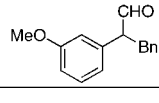
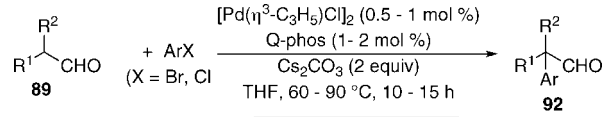
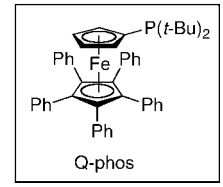
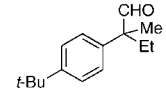
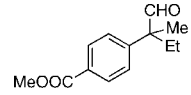
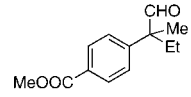
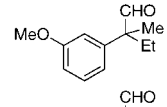
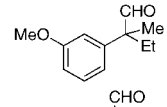
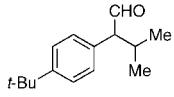
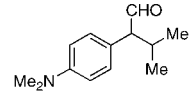
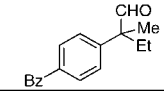
Entry	R^1	Product	Yield (%)
1	*n*-C_6H_{13}		83
2	*n*-C_6H_{13}		93
3	*n*-C_6H_{13}		67
4	*n*-C_6H_{13}		77
5	Et		67
6	Et		75
7	Et		70
8	Et		70
9	Bn		67
10	Bn		76
11	Bn		61

Table 36. [Pd(η^3-C_3H_5)Cl]$_2$/Q-Phos-Catalyzed α-Arylation of Branches Aldehydes with Aryl Halides





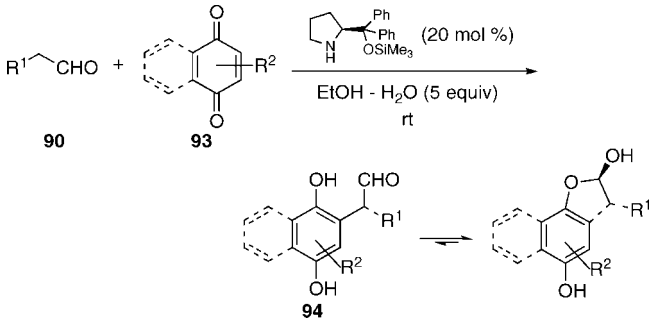
Entry	X	Product	Yield (%)
1	Br		91
2	Br		81
3	Cl		77
4	Br		83
5	Cl		76
6	Br		80
7	Br		67
8	Br		79

for the direct intermolecular α-arylation of a wide variety of linear and α-branched aldehydes with aryl chlorides and bromides. Specifically, the efficient arylation of linear aldehydes **90** (1.2 equiv) with aryl bromides was performed in dioxane at 80 °C in the presence of Cs_2CO_3 (1.2 equiv), 2 mol % of $Pd(OAc)_2$, and 3 mol % of *rac*-BINAP. Alternatively, α-arylated aldehydes **91** could be synthesized in high yields by treatment of aldehydes **90** (1.2 equiv) with less reactive aryl chlorides in dioxane at 100 °C in the presence of Cs_2CO_3, 2 mol % of $Pd(OAc)_2$, and 3 mol % of the dialkylphosphinobinaphthyl ligand **47a** (Table 34).[134]

Reaction conditions essentially identical to those described in Table 34 were then employed for the α-arylation of α-branched aldehydes with aryl bromides and chlorides, but the use of S-Phos as the supporting ligand was found to provide superior results when using aryl bromides. As with aliphatic linear aldehydes, the process, which could entail the use of electron-poor, electron-neutral, and electron-rich aryl halides, showed a high degree of functional compatibility and provided the required α-arylated aldehydes **92** in good yields (Scheme 39).[134]

More recently, Vo and Hartwig have used a catalyst system composed of [Pd(η^3-C_3H_5)Cl]$_2$ and dppf [1,1′-bis(diphenylphosphino)ferrocene] for the α-arylation of linear aldehydes **90** with electron-rich, electron-poor, and electron-

Scheme 40. Asymmetric Organocatalytic α-Arylation of Aldehydes



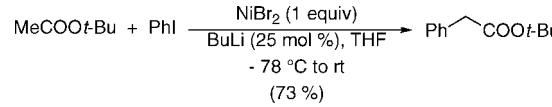
neutral aryl bromides in dioxane at 80 °C in the presence of Cs_2CO_3 as the base (Table 35).[135]

The α-arylation reactions of branched aldehydes **89** in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and dppf were found to occur in yields lower than those obtained by arylation of linear aldehydes, but good results were obtained when compounds **89** were reacted with 0.5 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 1 mol % Q-Phos [1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)-ferrocene].[135,136] Remarkably, aryl chlorides were also able to react with aldehydes **89** under these conditions, but a higher catalyst loading {1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 2 mol % Q-Phos} was necessary.[135] Representative examples of these arylation reactions of aldehydes **89** with aryl bromides and chlorides are reported in Table 36.

In concluding this section, we think it right also to mention that, until late June 2008, the enantioselective transition metal-catalyzed α-arylation of aldehydes had not been reported in the literature.

However, Jørgensen et al. recently developed an organocatalytic enantioselective version of this intermolecular reaction that involves treatment of aldehydes **90** with quinones **93** in the presence of catalytic amounts of (*S*)-2-[bis(3,5-trifluorophenyl-)trimethylsilanyloxymethyl]pyrrolidine (Scheme 40).[137] Optically active α-arylated aldehydes **94** were so obtained in high yields and with excellent enantioselectivities.

Scheme 41. Ni-Mediated α-Arylation of *tert*-Butyl Acetate with Iodobenzene



7. Direct Arylation of Carboxylic Acid Esters, Azlactones, Lactones, and Silyl Ketene Acetals with Aryl Halides or Pseudohalides

7.1. α-Arylation of Carboxylic Acid Esters and Azlactones

There has been considerable interest in the synthesis of α-aryl substituted carboxylic acid esters over the past three decades. In fact, their structural motif is found at the core of a number of analgesic and nonsteroidal anti-inflammatory drugs,[138] such as Flurbiprofen, Naproxen, Diclofenac, Indomethacin, Ibuprofen, Ketoprofen, Sulindac, and Zomepirac, as well as of natural products including lucuminic acid, a compound isolated from the seed of *Calocarpum sapota*,[139] and polymastiamide A, an antimicrobial metabolite from *Polymastia bolatiformis*[140] (Figure 5).

The catalytic processes used to prepare arylacetic and 2-arylpropionic acids esters include electrochemical reduction of mixtures of aryl halides and α-chloroesters in DMF in the presence of catalytic amounts of $NiBr_2$(2,2′-bipyridine),[141,142] a coupling reaction of α-chloroesters with aryl halides in DMF in the presence of Mn metal and a catalytic quantity of $NiBr_2$(2,2′-bipyridine),[143] a Pd-catalyzed coupling reaction of arylboronic acids or esters with ethyl α-bromoacetate,[2f] and a Ni-catalyzed reaction of arylboronic acids with alkyl bromoacetates or 2-bromopropionates.[30b] Other methods include the transition metal-catalyzed arylations of acetoacetate esters or diethyl malonate with aryl halides, which will be described and discussed in section 9.

It is also worth mentioning that, in 1977, it was described that *tert*-butyl phenylacetate can be prepared in 73% yield by

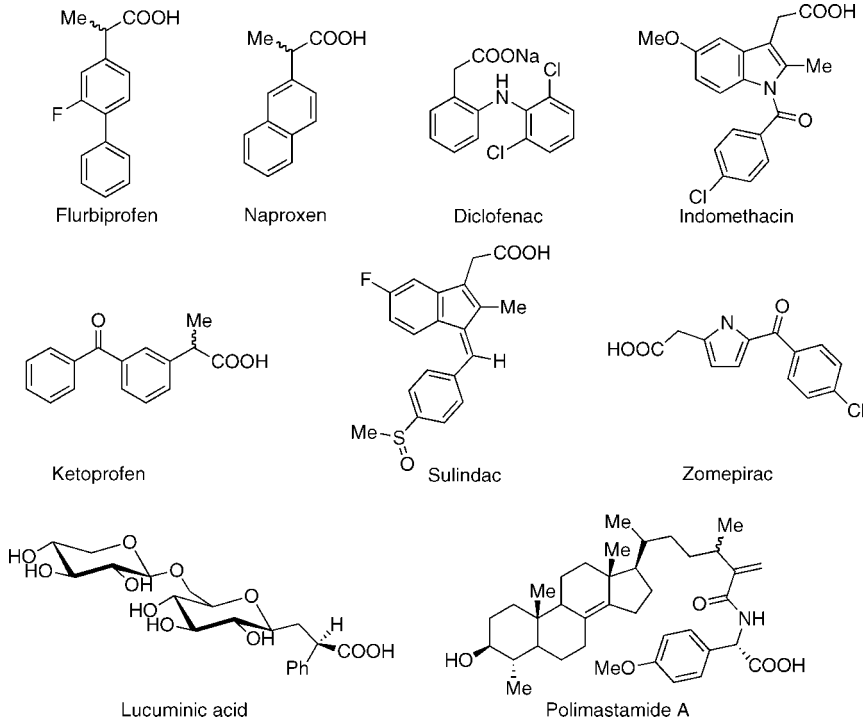
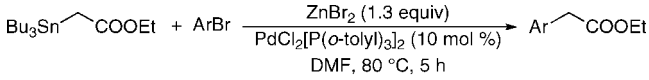


Figure 5. Chemical structures of some anti-inflammatory drugs, lucuminic acid, and polymastiamide A.

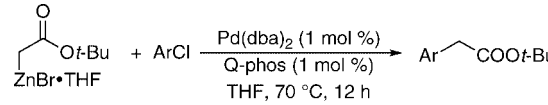
Scheme 42. Pd-Catalyzed Coupling of Ethyl Tributylstannylacetate with Aryl Bromides in the Presence of $ZnBr_2$



Ar	Yield (%)
4-$O_2NC_6H_4$	34
4-NCC_6H_4	67
4-MeC_6H_4	93
2-MeC_6H_4	71
4-ClC_6H_4	89
2-ClC_6H_4	66
2-$MeOC_6H_4$	82
4-$MeOC_6H_4$	47
3-MeC_6H_4	60

reaction of iodobenzene with *tert*-butyl acetate in the presence of a stoichiometric amount of $NiBr_2$ and 25 mol % of BuLi (Scheme 41).[144] This report suggested that a transition metal-catalyzed protocol might be developed for the α-arylation of ester enolates. In fact, starting from 1979, a number of examples of nickel-[145] and palladium-catalyzed[146−150] reactions of Reformatsky reagents with aryl halides were described.

Scheme 43. α-Arylation of the Isolated Reformatsky Reagent of *tert*-Butyl Acetate with Aryl Chlorides

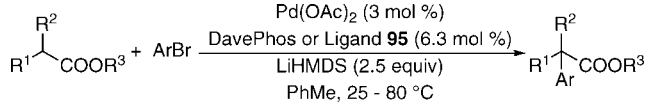


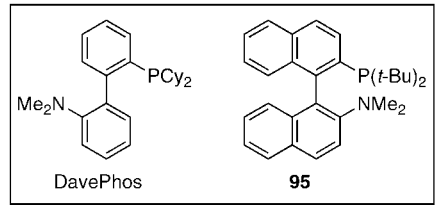
Ar	Yield (%)
C_6H_5	95
4-NCC_6H_4	86
4-$MeOOCC_6H_4$	85
4-$O_2NC_6H_4$	83

Moreover, in 1985, Migita et al. discovered that ethyl tributylstannylacetate, the tin analogue of an ethyl halozincioacetate, is able to undergo cross-coupling reaction with aryl bromides in the presence of $ZnBr_2$ and catalytic quantities of $PdCl_2[P(o\text{-tolyl})_3]_2$ to give ethyl arylacetates in low-to-excellent yields (Scheme 42).[151]

In 2008, Hama and Hartwig reported that reaction of the isolated Reformatsky reagent of *tert*-butyl acetate with chlorobenzene and electron-poor aryl chlorides occurs in high yields in the presence of 1 mol % of the catalyst system composed of $Pd(dba)_2$ and Q-Phos as the supporting ligand (Scheme 43).[152]

Table 37. $Pd(OAc)_2$/DavePhos or Ligand 95-Catalyzed α-Arylation of Carboxylic Acid Esters with Aryl Bromides





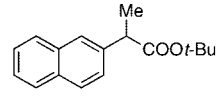
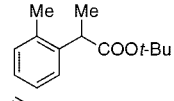
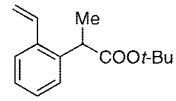
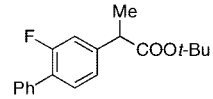
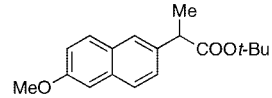
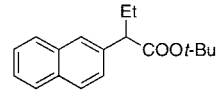
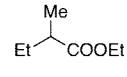
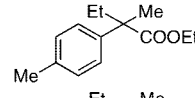
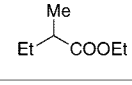
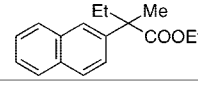
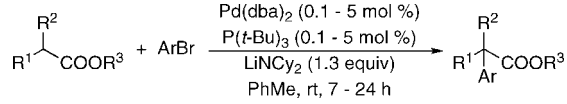
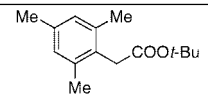
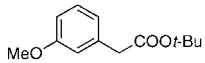
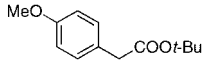
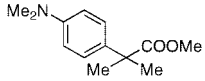
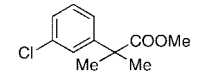
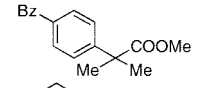
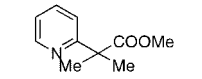
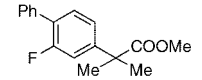
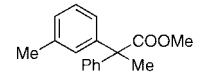
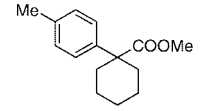
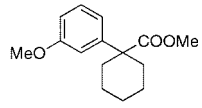
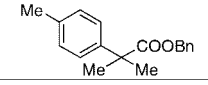
Entry	Ester	Ar	Ligand	Product	Reaction conditions (°C / h)	Yield (%)
1	EtCOO*t*-Bu	2-naphthyl	DavePhos		80 / 0.25	92
2	EtCOO*t*-Bu	2-MeC_6H_4	DavePhos		80 / 2	82
3	EtCOO*t*-Bu	2-$(CH_2{=}CH)C_6H_4$	DavePhos		80 / 2	77
4	EtCOO*t*-Bu	3-F,4-PhC_6H_3	DavePhos		80 / 0.3	86
5	EtCOO*t*-Bu	6-MeO-2-naphthyl	DavePhos		25 / 15	79
6	*n*-PrCOO*t*-Bu	2-naphthyl	DavePhos		80 / 2	81
7		4-MeC_6H_4	**95**		80 / 0.5	48
8		2-naphthyl	**95**		40 / 17	52

Table 38. Pd(dba)$_2$/P(*t*-Bu)$_3$-Catalyzed α-Arylation of Carboxylic Acid Esters with Aryl Bromides

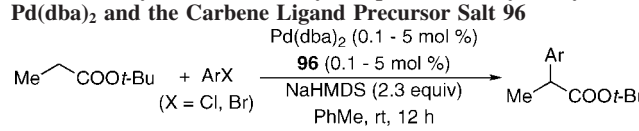


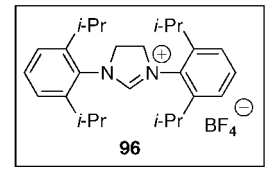
Entry	Product	Catalyst loading	Reaction time (h)	Yield (%)
1		0.2	10	97
2		0.5	24	94
3		0.5	24	95
4		0.05	18	88
5		0.1	12	71
6		3	16	73
7		5	7	94
8		0.1	10	83
9		0.5	8	89
10		0.2	24	95
11		0.1	20	94
12		1	12	90

Interestingly, all of the above-mentioned palladium-catalyzed reactions of ethyl tributylstannylacetate and *tert*-butyl bromozincioacetate occurred under neutral conditions and thus allowed for the use of aryl halides bearing nitro, cyano, and ester groups, which are able to react with strong bases and nucleophiles. However, the scope of these cross-couplings was narrow. In fact, the procedures involve the separate preparation of the tin and zinc derivatives and the yields of the reaction proved to be variable. Moreover, the palladium-catalyzed reaction of *tert*-butyl bromozincioacetate with electron-poor aryl chlorides was found to occur in less than 50% yields.[152]

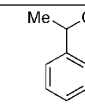
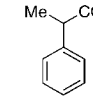
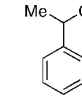
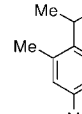
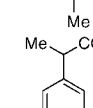
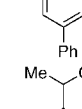
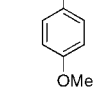
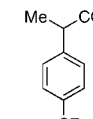
In order to overcome these limitations, at the beginning of this century, Buchwald's and Hartwig's groups turned their attention to the development of more direct and efficient protocols for the synthesis of α-arylated carboxylic acid esters, and, independently, discovered novel and experimentally simple one-pot procedures for the palladium-catalyzed intermolecular α-arylation of carboxylic acid esters with aryl halides. The protocols involve generation of the requisite metal enolates by α-deprotonation of carboxylic acid esters and the use of properly designed palladium-catalyst systems for reaction of these metal enolates with aryl halides.[148,153,154] In the protocol developed by Moradi and Buchwald,[153] a catalyst system consisting of a combination of Pd(OAc)$_2$ and

Table 39. Arylation of *tert*-Butyl Propionate Catalyzed by Pd(dba)$_2$ and the Carbene Ligand Precursor Salt 96



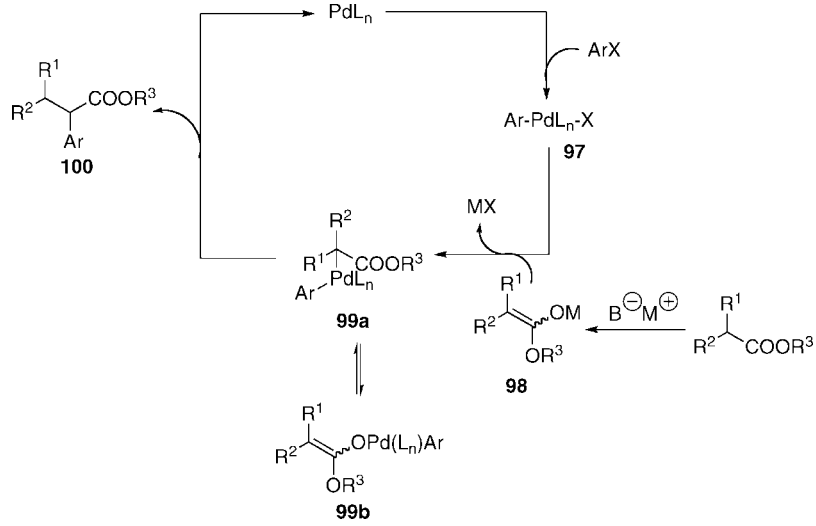


96

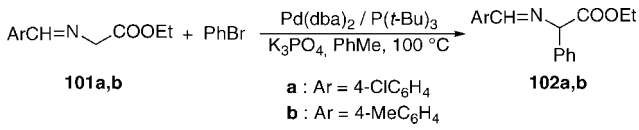
Entry	ArX	Product	Catalyst loading (mol %)	Yield (%)
1	PhBr		0.5	75
2	PhCl		1.0	71
3	2-MeC$_6$H$_4$Br		0.5	88
4	2,4,6-(Me)$_3$C$_6$H$_2$Br		1.0	74
5	3-F,4-PhC$_6$H$_3$Br		2.0	66
6	4-MeOC$_6$H$_4$Br		1.0	82
7	4-CF$_3$C$_6$H$_4$Br		5.0	74
8	2-Br-6-MeO-naphthalene		1.0	83

DavePhos is treated with a large excess of LiHMDS, followed by addition of toluene and a carboxylic acid ester at −10 °C. After formation of the required enolate, an aryl bromide or chloride is added at −10 °C and the reaction mixture is allowed to warm to room temperature. In same cases, the temperature is increased to 80 °C. As shown in Table 37, where some representative results are summarized, this procedure enabled the highly selective preparation of a variety of α-arylated esters in very good yields. Table 37 also shows that, when 2-di-*tert*-butylphosphino-2′-(*N*,*N*-dimethylamino)-1,1′-binaphthyl **95** was used as the supporting ligand, it was possible to prepare carboxylic acid esters bearing a quaternary center in the α-position by α-arylation of alkyl α,α-dialkyl-substituted acetates with aryl bromides (entries 7 and 8). However, no examples of arylation reactions with aryl halides that could form benzyne inter-

Scheme 44. Proposed Catalytic Cycle for the Pd-Catalyzed Buchwald−Hartwig α-Arylation of Ester Enolates



Scheme 45. Pd-Catalyzed α-Arylation of Ethyl *N*-Benzylideneglycinates 101 with Bromobenzene



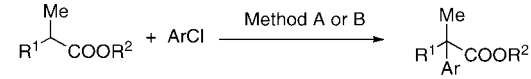
mediates under basic conditions or contain functional groups able to interfere with the coupling process were reported.

On the other hand, Hartwig et al. performed the selective monoarylation of a variety of carboxylic acid esters, including *tert*-butyl acetate, *tert*-butyl propionate, ethyl 3-methylbutyrate, methyl cyclohexylacetate, ethyl *N*,*N*-dimethylglycinate, ethyl *N*-(diphenylmethylene)glycinate, and ethyl *N*-benzylideneglycinate, with aryl bromides at room temperature using LiHMDS or NaHMDS as the base and a catalyst system consisting of a 1:1 mixture of Pd(dba)$_2$ and P(*t*-Bu)$_3$ (Table 38) or Pd(dba)$_2$ and salt **96** as a heterocyclic carbene ligand precursor (Table 39).[148,154]

The use of LiHMDS as the base allowed for the efficient α-arylation of *tert*-butyl acetate, while the use of NaHMDS led to high yields for reactions of *tert*-butyl propionate.[154] Hence, *tert*-butyl α-arylpropionates, such as the *tert*-butyl esters of Flurbiprofen and Naproxen, were prepared in high yields by reaction of *tert*-butyl propionate and the required aryl bromides in toluene at room temperature in the presence of NaHMDS and catalytic quantities of Pd(dba)$_2$ and the hindered saturated heterocyclic carbene ligand precursor **96** (Table 39).[148] On the other hand, the selective monoarylation of *tert*-butyl acetate and the efficient α-arylation of α,α-disubstituted esters were performed by the use of LiNCy$_2$ as the base and a catalyst system composed of Pd(dba)$_2$ and P(*t*-Bu)$_3$ as the ligand (Table 38).[148] It should be noted that *tert*-butyl esters were in preference employed in these protocols to suppress nucleophilic attack at the carbonyl carbon atom in an undesired reaction of esters with enolates resulting in Claisen products, *β*-ketoesters. It is also worth noting that hydrodehalogenation of the aryl halides was the major competing reaction when supporting ligands different from the carbene derived from salt **96** were used in the Pd-catalyzed α-arylation of *tert*-butylpropionate.[155]

Scheme 44 illustrates the proposed catalytic cycle for the palladium-catalyzed Hartwig and Buchwald α-arylation of carboxylic acid ester enolates.[22] In this mechanism, the Pd-enolate intermediates **99**, generated by metathesis of the

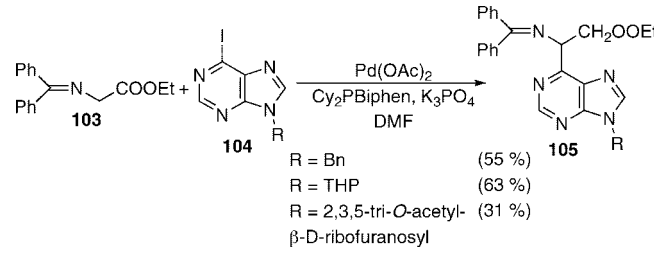
Table 40. Pd-Catalyzed α-Arylation of *tert*-Butyl Propionate and Methyl Isobutyrate with Aryl Chlorides



Method A: NaHMDS (1.2 equiv), {PdBr[P(t-Bu)$_3$]}$_2$ (0.1–0.4 mol %), PhMe, rt–100 °C, 4 h
Method B: NaHMDS (1.2 equiv), Pd(dba)$_2$ (0.2–1 mol %), P(t-Bu)$_3$ (0.2–1 mol %), PhMe, rt–100 °C, 4h

entry	ester	Ar	method	mol % of Pd	reaction temp (°C)	yield (%)
1	EtCOO*t*-Bu	Ph	A	0.2	rt	94
2	EtCOO*t*-Bu	Ph	B	0.4	rt	91
3	EtCOO*t*-Bu	4-MeOOCC$_6$H$_4$	B	1	rt	69
4	EtCOO*t*-Bu	4-MeOOCC$_6$H$_4$	A	0.4	rt	88
5	EtCOO*t*-Bu	2,6-(Me)$_2$C$_6$H$_3$	A	0.2	60	81
6	EtCOO*t*-Bu	2,6-(Me)$_2$C$_6$H$_3$	B	0.4	60	42
7	EtCOO*t*-Bu	4-BrC$_6$H$_4$	B	0.3	60	84
8	*i*-PrCOOMe	Ph	B	0.1	100	92
9	*i*-PrCOOMe	Ph	A	0.2	100	89
10	*i*-PrCOOMe	4-FC$_6$H$_4$	B	0.4	100	90
11	*i*-PrCOOMe	3-CF$_3$C$_6$H$_4$	A	0.2	100	71
12	*i*-PrCOOMe	2-pyridyl	A	0.2	100	71

Scheme 46. Pd-Catalyzed Synthesis of Protected (Purin-6-yl)glycines

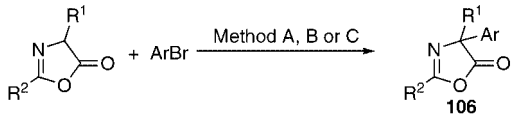


enolates **98** with the arylpalladium(II) complexes **97**, undergo reductive elimination to form the required α-arylated esters **100** and to regenerate the catalytically active Pd(0) species.

Hartwig et al. also found that high yields of the protected α-aminoacid derivatives **102** could be obtained by α-arylation of ethyl *N*-benzylideneglycinates **101** with bromobenzene using K$_3$PO$_4$ as the base and a catalyst system composed of Pd(dba)$_2$ and P(*t*-Bu)$_3$ (Scheme 45).[154]

More recently, Hama and Hartwig have shown that the sodium enolates of *tert*-butyl propionate and methyl isobutyrate are able to undergo high yielding reaction with aryl chlorides in the presence of NaHMDS as the base and 0.2−1.0 mol %

Table 41. Pd-Catalyzed α-Arylation of Azlactones with Aryl Bromides



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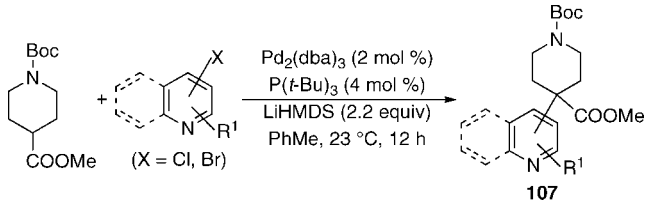
Method A: azlactone (1.5 equiv), $Pd(OAc)_2$ (5 mol%), Q-phos (5 mol %), K_2CO_3 (3.0 equiv), PhMe, 80 °C, 14 h
Method B: azlactone (2.0 equiv), $Pd(OAc)_2$ (5 mol%), $(1\text{-Ad})_2P(t\text{-Bu})$ (10 mol %), K_2CO_3 (3.0 equiv), PhMe, 100 °C, 14 h
Method C: azlactone (1.5 equiv), $Pd(OAc)_2$ (5 mol%), $(1\text{-Ad})_2P(t\text{-Bu})$ (5 mol %), K_3PO_4 (3.3 equiv), PhMe, 80 °C, 14 h

entry	R^1	R^2	Ar	method	yield (%)
1	Ph	Ph	Ph	A	94
2	Ph	Ph	Ph	B	55
3	Ph	Ph	$3\text{-}CF_3C_6H_4$	A	92
4	Ph	Ph	$3\text{-}CF_3C_6H_4$	B	55
5	Bn	Ph	$4\text{-}MeOC_6H_4$	A	75
6	Bn	Ph	$4\text{-}MeOC_6H_4$	B	30
7	Bn	Ph	Ph	C	78
8	Bn	Ph	Ph	B	65
9	Bn	Ph	$3\text{-}CF_3C_6H_4$	C	74
10	*i*-Bu	Ph	Ph	C	47
11	*i*-Pr	Ph	Ph	C	29
12	*i*-Bu	*t*-Bu	$4\text{-}t\text{-}BuC_6H_4$	C	82
13	*i*-Pr	*t*-Bu	Ph	C	63

Scheme 47. Pd-Catalyzed Synthesis of 4-Heteroaryl-4-carboxypyridines 107



107

of $\{PdBr[P(t\text{-}Bu)_3]\}_2$ (method A) or a combination of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ in a 1:1 molar ratio (method B) (Table 40).[152]

Complex $\{PdBr[P(t\text{-}Bu)_3]\}_2$ has also been recently used by Bercot, Caille et al. as the catalyst precursor for a diastereoselective α-arylation of 4-substituted cyclohexyl esters.[156] The reaction was found to proceed at room temperature, providing products in 37:1 dr.[156]

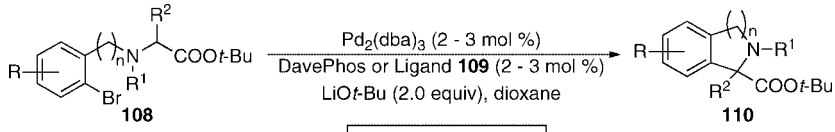
In 2004, a straightforward synthesis of protected (purin-6-yl)glycines **105**, potential buiding blocks of stable covalent peptide−nucleic acid conjugates, was achieved by Hocek in acceptable yields by direct α-arylation of ethyl *N*-(diphenylmethylidene)glycinate **103** with 6-iodopurines **104** (Scheme 46) according to an optimized procedure involving the use of a $Pd(OAc)_2$/2-(dicyclohexylphosphino)biphenyl catalyst system and K_3PO_4 as the base in DMF at 100 °C.[157a] More recently, Larhed and co-workers have been able to smoothly synthesize a diverse array of simple phenylglycine derivatives in useful yields by $Pd[P(t\text{-}Bu)_3]_2$-catalyzed microwave-enhanced α-arylation of **103** with aryl bromides in neat water under air in the presence of K_3PO_4 as the base.[157b]

Three different protocols (methods A−C) were developed by Liu and Hartwig to prepare α-alkyl aminoacid derivatives in good yields by Pd-catalyzed α-arylation of azlactone derivatives with aryl bromides (Table 41).[158]

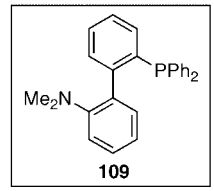
Arylations of azlactones derived from alanine, valine, phenylalanine, phenylglycine, and leucine all provided good yields of arylated products. Method B, involving the use of K_2CO_3 as the base and $Pd(dba)_2$ and di-1-adamantyl-*tert*-butylphosphine as the supporting ligand, was preferred for reactions involving azlactones from alkyl- and benzyl-substituted α-aminoacids. On the other hand, the reactions of azlactones derived from phenylglycine were best conducted using method A, which involves the use of $Pd(OAc)_2$ and Q-Phos as the supporting ligand and K_2CO_3 as the base. However, method C, which represents a modification of method B involving the use of K_3PO_4 in place of K_2CO_3 as the base, allowed for the α-arylation of the alanine-derived azlactone with bromobenzene, 3-bromobenzotrifluoride, and 4-bromoanisole in yields higher than those obtained using method B.[158] Interestingly, α-arylated azlactones **106** could be hydrolyzed easily to generate the corresponding α-alkyl-α-aryl amino acids.[159] Mechanistic studies of the arylation reaction revealed that a stable complex containing a ligand formed by reaction of dba with the azlactone accounts for a new inhibiting effect of dba when the reactions are initiated with $Pd(dba)_2$.[158]

A catalyst system composed of $Pd_2(dba)_3$ and $P(t\text{-}Bu)_3$ was used by Wang and Nair for the α-arylation of *N*-Boc-4-methoxycarbonylpiperidine with chloro- and bromopyridines and 3-bromoquinolines in toluene at room temperature in the presence of LiHMDS as the base (Scheme 47).[160] 4-Carboxy-4-heteroarylpiperidines **107** were so generally

Table 42. Pd-Catalyzed Synthesis of Dihydroisoindole and Tetrahydroisoquinoline Carboxylic Acids Esters



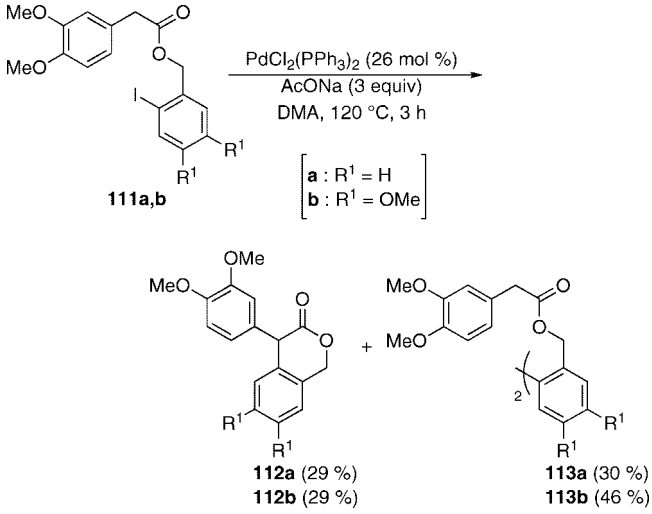
108 110



109

entry	R	R^1	R^2	*n*	ligand	reaction conditions (°C/h)	yield (%)
1	H	Ph	H	1	DavePhos	85/1	79
2	$3,4\text{-}(MeO)_2$	Ph	H	1	DavePhos	85/24	89
3	H	Me	*i*-Pr	1	**109**	110/48	51
4	H	Me	Ph	1	**109**	90/2	99
5	H	Ph	H	2	**109**	85/8	79
6	$3,4\text{-}(MeO)_2$	Me	H	2	**109**	85/3	75
7	H	Ph	Me	2	**109**	85/24	62
8	H	Ph	Me	2	DavePhos	85/24	27
9	$3,4\text{-}(MeO)_2$	Me	Me	2	**109**	100/45	66

Scheme 48. Intramolecular Pd-Catalyzed Arylation of 2-Iodobenzyl-3,4-Dimethoxybenzylacetates



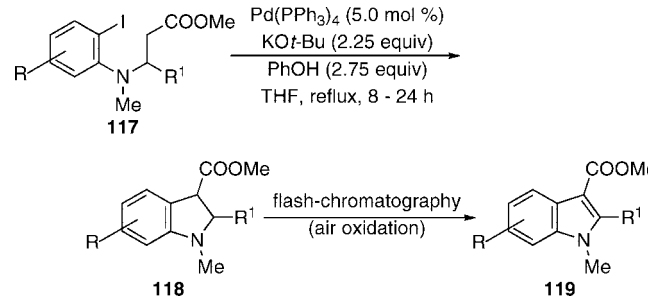
obtained in high yields, but for halides bearing cyano groups, no α-arylated product was obtained due to the nucleophilic attack on the cyano group to form amidines.[160]

Interestingly, the $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system had been formerly employed by Shetty and Moffett for the coupling of methyl isobutyrate with aryl bromides in toluene at room temperature in the presence of $LiNCy_2$ as the base.[161]

In the past few years, synthetically valuable intramolecular versions of the palladium-catalyzed α-arylation of carboxylic acid esters have also been developed. In 2002, Gaertzen and Buchwald reported that dihydroisoindole carboxylic acid esters **110** ($n = 1$) can efficiently be prepared by treatment of *N*-protected α-amino acid *tert*-butyl esters **108** ($n = 1$) with LiO*t*-Bu in dioxane in the presence of catalytic quantities of $Pd_2(dba)_3$ and DavePhos or phosphine **109** as the supporting ligand.

[162]Representative examples of these intramolecular reactions (entries 1−4), including the preparation of tetrahydroisoquinoline carboxylic acid esters **110** ($n = 2$) (entries 5−9), are summarized in Table 42.[162]

Scheme 50. Intramolecular Pd-Catalyzed α-Arylation of *β*-(2-Iodoanilino) Esters



In 2007, Taylor, Ung, and Pyne found that the palladium-catalyzed intramolecular arylation of 2-iodobenzyl 3,4-dimethoxyacetates **111** results in the formation of benzo[*c*-]chromen-6-ones **112** and unexpected biphenyls **113** (Scheme 48).[163]

On the other hand, the palladium-catalyzed intramolecular arylation of 3,4-dimethoxybenzyl 2-iodophenylacetate **114a** unexpectedly gave a separable mixture of succinate **115** (as a 1.8:1 mixture of diastereomers) and biphenyl **116**, while compound **114b** gave benzo[*c*]chromen-6-one **112b** (Scheme 49).[163]

Finally, in 2008, Solé and Serrano synthesized a variety of indoline 3-carboxylic acid ester derivatives **118** by intramolecular α-arylation of *β*-(2-iodoanilino) esters **117** in refluxing THF in the presence of phenol, KO*t*-Bu, and catalytic quantities of $Pd(PPh_3)_4$, but, after column chromatography, compounds **117** were partly converted to the corresponding indole derivatives **118** by air oxidation (Scheme 50).[164] Interestingly, indolines **118** could also be prepared in satisfactory yields by treatment of compounds **117** with 10 mol % $Pd(PPh_3)_4$, 3 equiv of K_3PO_4, and 0.3 equiv of phenol in DMF at 90 °C in a sealed tube. Longer reaction times were required, however, when this protocol was used.[164]

Scheme 49. Palladium-Catalyzed Reaction of 3,4-Dimethoxybenzyl-2-iodophenylacetates

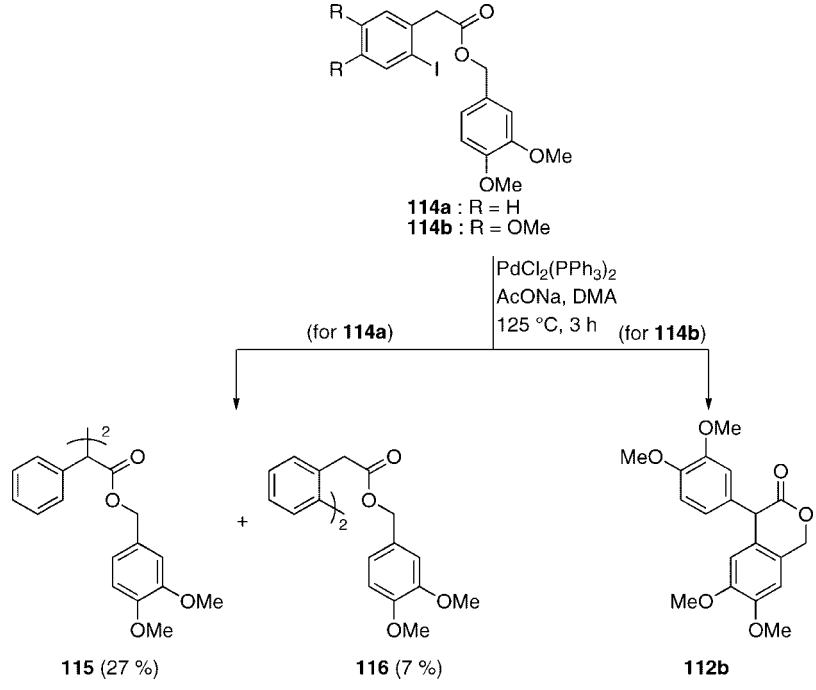
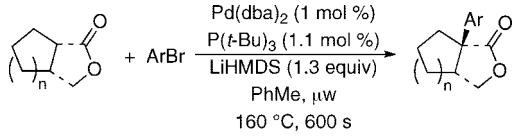
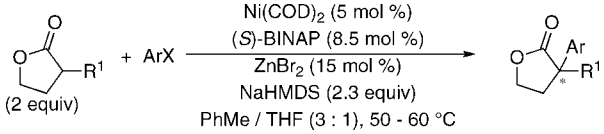


Table 43. Pd-Catalyzed α-Arylation of Bicyclic Lactones with Aryl Bromides



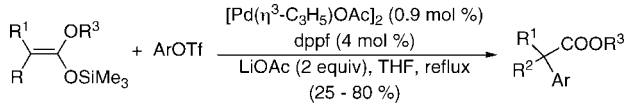
entry	*n*	Ar	yield (%)
1	1	Ph	49
2	1	4-$MeOC_6H_4$	62
3	1	3-$MeOC_6H_4$	59
4	1	2-$MeOC_6H_4$	25
5	2	Ph	51
6	2	4-$MeOC_6H_4$	41
7	2	3-$MeOC_6H_4$	15
8	2	2-$MeOC_6H_4$	8

Table 44. $Ni(COD)_2$/(*S*)-BINAP-Catalyzed Enantioselective α-Arylation of α-Substituted γ-Butyrolactones



entry	R^1	ArX	yield (%)	ee (%)
1	Me	2-NaphthylBr	33	98
2	Me	2-NaphthylCl	95	94
3	Me	3-$MeOC_6H_4Br$	29	99
4	Me	3-$MeOC_6H_4Cl$	86	96
5	Me	3-$Me_2NC_6H_4Cl$	81	>97
6	Me	3-*t*-$BuOOCC_6H_4Br$	58	93
7	Bn	2-NaphthylCl	91	96
8	allyl	3-$MeOC_6H_4Cl$	56	95
9	*n*-Pr	PhCl	84	98

Scheme 51. Pd-Catalyzed Arylation of Silyl Ketene Acetals with Aryl Triflates



7.2. α-Arylation of Lactones

In stark contrast to the palladium-catalyzed α-arylation of carboxylic acid esters, to date, little attention has been devoted to the transition metal-catalyzed α-arylation of lactones with aryl halides. In 2005, Malcom, Shao et al.[165] reported that easily accessible bicyclic lactones are able to undergo efficient and scalable α-arylation with aryl bromides under slightly modified Hartwig−Buchwald's conditions to form quaternary centers with complete *cis*-selectivity. A significant rate acceleration was observed when the $Pd(dba)_2$/$P(t\text{-}Bu)_3$-catalyzed reaction was carried out under microwave irradiation (Table 43).[165]

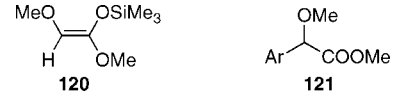


Figure 6. Chemical structures of compounds **120** and **121** .

Three years before, a small series of optically active α-aryl substituted γ-butyrolactones had been prepared by Spielvogel and Buchwald[166] in moderate-to-excellent yields and excellent enantioselectivities by treatment of α-alkyl- or α-benzyl-γ-butyrolactones with aryl chlorides or bromides in a mixture of toluene and THF in the presence of NaHMDS as the base, $ZnBr_2$, and a catalyst system composed of $Ni(COD)_2$ and (*S*)-BINAP. The use of $ZnBr_2$ was due to the fact that this salt caused an accelerating effect in the reactions since its Lewis acid character probably facilitates halide abstraction from the intermediate (BINAP)NiArX complexes to form cationic $[(BINAP)NiAr]^+$ species, which subsequently undergo transmetalation more rapidly.[166] As shown in Table 44, where some representative examples of these highly enantioselective reactions are reported, the yields were sometimes higher when aryl chlorides were used as the arylating reagents. It was also observed that, unfortunately, *ortho*-substituted aryl halides give none of the desired product. Remarkably, palladium-catalyzed reactions, analogous to those reported in Table 44, proved to proceed with moderate yields and enantioselectivities.[166]

7.3. Arylation of Silyl Ketene Acetals

Another well-established methodology for the synthesis of α-aryl substituted carboxylic acid esters is the palladium-catalyzed reaction of *O*-silyl ketene acetals with aryl halides or triflates.[149,167−172] Remarkably, the use of these important carboxylic acid ester derivatives[173] allows one to avoid the basic conditions present in the alkali metal enolate methodology developed by Hartwig and Buchwald that limit its use because functional groups like cyano and nitro are reactive toward bases.

In 1991, Musco, Santi et al.[167] reported that a combination of $[Pd(\eta^3\text{-}C_3H_5)OAc]_2$ and dppf, in the presence of LiOAc, effectively catalyzes the reaction of ketene silyl acetals with aryl triflates to yield alkyl 2-arylalkanoates (Scheme 51).[167] Interestingly, aryl halides could be used in place of aryl triflates in these reactions, provided that a stoichiometric amount of TlOAc was employed.[167]

Musco, Santi et al. also found that, when (*E*)-1-methoxy-1-trimethylsilyloxypropene was reacted with aryl bromides in the presence of TlOAc and a catalyst system consisting of a combination of $[Pd(\eta^3\text{-}C_4H_7)OAc]_2$ and (+)-DIOP {2,2-dimethyl-4,5-[(diphenylphosphino)dimethyl]dioxolane}, (*R*)-BINAP [(*R*)-2,2′-bis(diphenylphosphino)1,1′-dinaphthyl], (*R*)-

Scheme 52. Enantioselective Synthesis of Methyl 2-Arylpropionates

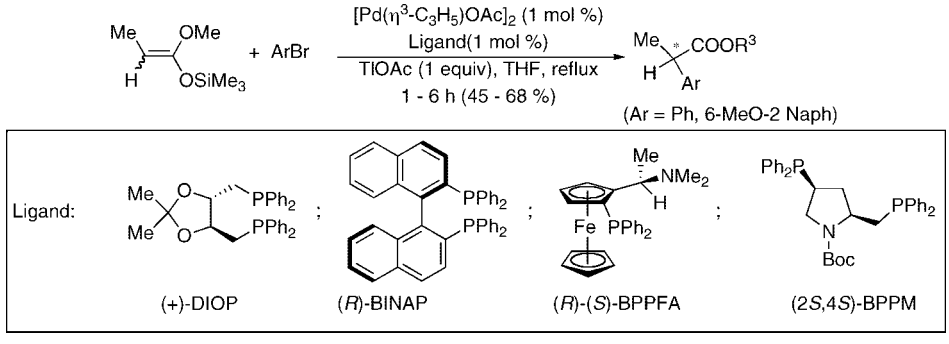
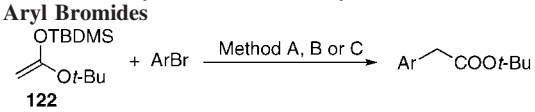


Table 45. Pd-Catalyzed Reaction of Silyl Ketene Acetal 122 with Aryl Bromides



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Method A: Bu_3SnF (2.0 equiv), $PdCl_2[P(o\text{-tolyl})_3]_2$ (2-5 mol %), PhH, reflux
Method B: CuF_2 (2.0 equiv), $PdCl_2[P(o\text{-tolyl})_3]_2$ (2-5 mol %), PhH, reflux
Method C: CuF_2 (2.0 equiv), $PdCl_2[P(o\text{-tolyl})_3]_2$ (2-5 mol %), THF, reflux

entry	Ar	method	reaction time (h)	yield (%)
1	4-AcC_6H_4	A	6	80
2	4-AcC_6H_4	B	6	80
3	4-AcC_6H_4	C	9	76
4	4-$MeOOCC_6H_4$	A	22	82
5	4-$MeOOCC_6H_4$	C	22	73
6	2-$MeOC_6H_4$	A	20	42
7	2-$MeOC_6H_4$	C	22	81
8	4-$MeOC_6H_4$	A	22	51
9	4-$MeOC_6H_4$	C	28	95
10	2-naphthyl	C	16	75

Scheme 53. Pd-Catalyzed Synthesis of Ester 125

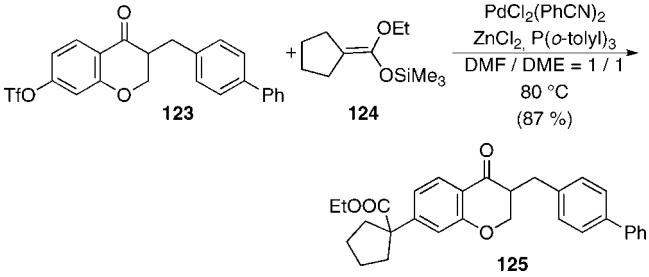
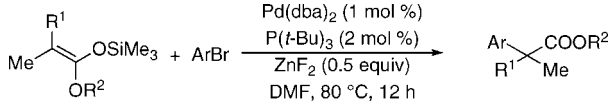


Table 46. $Pd(dba)_2/P(t\text{-}Bu)_3$-Catalyzed Arylation of Silyl Ketene Acetals with Aryl Bromides in the Presence of $ZnBr_2$



entry	R^1	R^2	Ar	yield (%)
1	Me	Me	Ph	91
2	Me	Me	4-$O_2NC_6H_4$	98
3	H	*t*-Bu	4-$O_2NC_6H_4$	76
4	Me	Me	4-$MeOOCC_6H_4$	94
5	H	*t*-Bu	4-$MeOOCC_6H_4$	80
6	H	*t*-Bu	2-NCC_6H_4	75
7	H	*t*-Bu	3-NCC_6H_4	67
8	Me	Me	4-BzC_6H_4	99
9	Me	Me	4-AcC_6H_4	78
10	H	*t*-Bu	4-AcC_6H_4	68
11	Me	Me	4-$MeOC_6H_4$	88

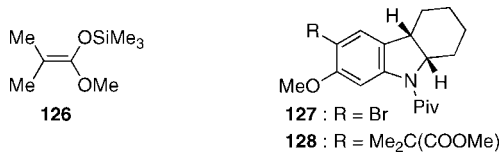


Figure 7. Chemical structures of compounds **126**−**128** .

(*S*)-BPPFA {(*R*)-(*S*)-*N*,*N*-dimethyl-1-[2,1′-bis(diphenylphosphino)ferrocenylethylamine], or (2*S*,4*S*)-BPPM [(2*S*,4*S*)-(−)-1-Boc-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine] as the ligand, methyl-2-arylpropionates were obtained in modest enantioselectivities (37−54%) (Scheme 52).[168]

Subsequently, Sakamoto et al.[169] reported that, in contrast to Musco's report, PPh_3 seems to be somewhat better than dppf as ligand of the $Pd(PPh_3)_4$-catalyzed reaction of (*Z*)-1,2-dimethoxy-1-trimethylsilyloxyethene **120** (Figure 6) with aryl iodides in THF in the presence of TlOAc. This reaction provided methyl α-methoxyarylacetates **121** (Figure 6) in 13−83% yield.[169]

In 1998, a wide variety of *tert*-butyl arylacetates were synthesized in modest-to-good yields by $PdCl_2[P(o\text{-tolyl})_3]_2$-catalyzed cross-coupling reaction of aryl bromides with a large molar excess of 1-*tert*-butoxy-1-*tert*-butyldimethylsilyloxyethene **122** in refluxing benzene or THF in the presence of suprastoichiometric amounts of CuF_2 or Bu_3SnF (Table 45).[171] The most practical set of conditions to effect the cross-coupling reactions consisted of using 2 equiv of CuF_2 as an additive and $PdCl_2[P(o\text{-tolyl})_3]_2$ as the catalyst precursor in THF (method C, Table 45). Unfortunately, *tert*-butyl 2-naphthylacetate proved to be inseparable from tin byproduct when, according to method A, Bu_3SnF was used as the additive in its preparation. However, this ester was easily purified by chromatography when CuF_2 was used as the activating agent (entry 10, Table 45).[171]

On the other hand, a catalyst system consisting of a combination of $Pd(PhCN)_2Cl_2$, $ZnCl_2$, and $P(o\text{-tolyl})_3$ was used by Koch et al.[172] for the preparation of ester **125** in 87% yield from aryl trifluoromethanesulfonate **123** and silyl ketene acetal **124** in a 1:1 mixture of DMF and 1,2-dimethoxyethane (DME) at 80 °C (Scheme 53). Unfortunately, the experimental details of this reaction were not reported.

A synthetically very interesting general protocol for the palladium-catalyzed arylation of silyl ketene acetals with aryl bromides that does not entail the use of suprastoichiometric quantities of toxic Bu_3SnF or CuF_2 was published by Hartwig et al. in 2002.[149] Specifically, these authors used ZnF_2 (1.05 equiv) as cocatalyst in a high-yielding synthesis of α-arylated esters involving treatment of silyl ketene acetals of *tert*-butyl propionate and methyl isobutyrate with aryl bromides in DMF at 80 °C in the presence of catalytic quantities of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$.

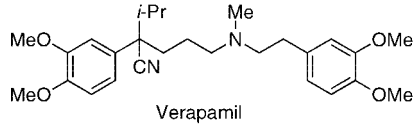
One year later, Liu and Hartwig described the full details of this new protocol that allowed for the use of aryl bromides bearing a variety of functional groups not tolerated by the coupling of alkali metal enolates (Table 46).[170]

More recently, Rawal et al. have used this protocol to prepare compound **128** from silyl ketene acetal **126** and aryl bromide **127** (Figure 7).[174]

8. α-Arylation of Nitriles, Carboxyamides, Lactams, and Trimethylsilyl Enolates of Imides

8.1. Synthesis of α-Arylated Nitriles

α-Aryl substituted nitriles not only constitute versatile building blocks for the synthesis of heterocycles, such as imidazoles, triazoles, tetrazoles, thiazoles, and oxazolines,[175]



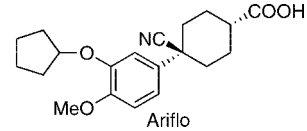
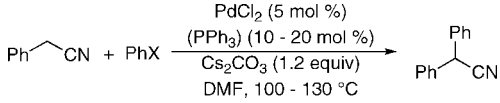


Figure 8. Chemical structures of Verapamil and Ariflo.

Table 47. Pd-Catalyzed Phenylation of Phenylacetonitrile



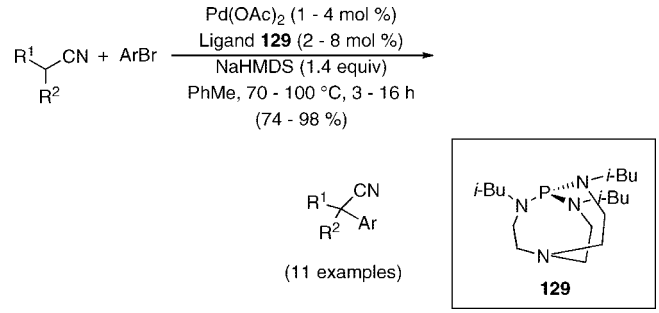
entry	X	equiv of PPh_3	reaction conditions (°C/h)	GLC yield (%)
1	I		100/2	18
2	Br	0.1−0.2	100/6	47
3	Br	0.1−0.2	130/2	68 (44)[(a)]

[(a)] Value in parentheses indicates isolated yield.

but also include pharmacologically active compounds such as the L-type calcium channel blocker Verapamil[176] and Ariflo[177] (Figure 8), which are used in the clinic for treatment of hypertension and chronic obstructive pulmonary disease, respectively.

Consequently, in the past few years, a variety of methods have been developed to prepare α-aryl substituted nitriles[178] with direct nucleophilic aromatic substitution being one of the most powerful strategies employed to achieve the synthesis of this important class of organic derivatives.[179] Nevertheless, in the past decade, the palladium-catalyzed direct α-arylation of nitriles bearing a C−H bond in the α-position with aryl halides has emerged as a major advancement.[180−184] An early example of this approach was reported in 1998 by Miura et al., who found that the $PdCl_2$-catalyzed reaction of phenylacetonitrile with iodo- or bromobenzene in DMF at 100 °C in the presence of Cs_2CO_3 produces diphenylacetonitrile in modest-to-low yield (Table 47).[180]

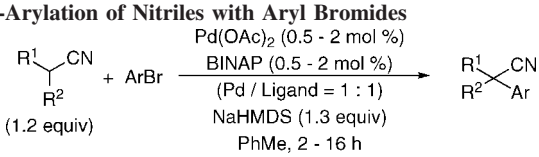
Scheme 54. $Pd(OAc)_2$/Ligand 129-Catalyzed α-Arylation of Nitriles with Aryl Bromides



In 2002, a more efficient palladium-catalyzed α-arylation of nitriles with aryl bromides was developed by Culkin and Hartwig by exploring the structure and reactivity of arylpalladium cyanoalkyl complexes.[181] High yields and short reaction times were found to characterize the α-arylation of primary benzylic and secondary nitriles performed in toluene at 70−100 °C using NaHMDS as the base and a catalyst system composed of $Pd(OAc)_2$ and BINAP (Table 48).[181]

Shortly after, α-aryl substituted nitriles were synthesized in excellent yields by You and Verkade by reaction of primary and secondary nitriles with aryl bromides possessing electron-poor, electron-rich, electron-neutral, and sterically hindered groups in the presence of NaHMDS as the base and a catalyst system composed of $Pd(OAc)_2$ and bicyclic triaminophosphine **129** as bulky electron-rich supporting ligand (Scheme 54).[182]

Table 48. $Pd(OAc)_2$/BINAP-Catalyzed α-Arylation of Nitriles with Aryl Bromides



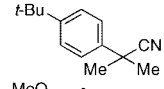
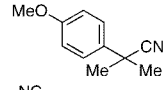
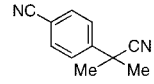
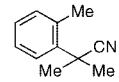
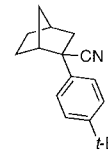
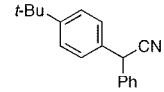
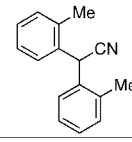
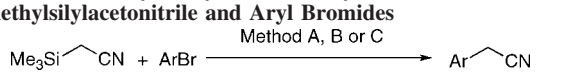
Entry	R^1	R^2	$Pd(OAc)_2$ / BINAP mol %	Reaction conditions (°C / h)	Product	Yield (%)
1	Me	Me	1	100 / 2		87
2	Me	Me	1	100 / 8		83
3	Me	Me	0.5	100 / 1		99
4	Me	Me	1	100 / 6		70
5			2	100 / 4		69
6	H	H	1	100 / 16		62
7	Ph	H	2	100 / 2		95
8	H	H	5	100 / 16		60

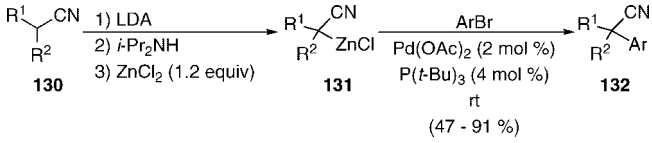
Table 49. Pd-Catalyzed Synthesis of Arylacetonitriles from Trimethylsilylacetonitrile and Aryl Bromides



entry	Ar	method[a]	reaction time (h)	yield (%)
1	4-*t*-BuC_6H_4	A	18	87
2	4-$MeOC_6H_4$	A	15	64
3	4-$Me_2NC_6H_4$	C	18	83
4	3,5-$(Me)_2C_6H_3$	A	18	74
5	3-(1,3-dioxolan-2-yl)C_6H_4	A	18	78
6	4-MeO-2-naphthyl	A	18	87
7	4-FC_6H_4	A	18	78
8	4-$O_2NC_6H_4$	A	8	68
9	4-$CF_3C_6H_4$	A	8	78
10	4-BzC_6H_4	A	8	92
11	4-$EtOOCC_6H_4$	A	8	84
12	4-AcC_6H_4	A	8	78
13	4-NCC_6H_4	A	8	81
14	2-MeC_6H_4	A	24	83
15	2,4-$(Me)_2C_6H_3$	B	24	78
16	2-*i*-PrC_6H_4	B	24	69
17	2-CyC_6H_4	B	24	71
18	2,6-$(Me)_2C_6H_3$	B	24	84

[a] Method A: $Pd_2(dba)_3$ (2 mol %), XantPhos (2 mol %), ZnF_2 (0.5 equiv), DMF, 90 °C. Method B: $Pd_2(dba)_3$ (2 mol %), P(*t*-Bu)$_3$ (4 mol %), ZnF_2 (0.5 equiv) DMF, 90 °C. Method C: $Pd_2(dba)_3$ (2 mol %), PhP(*t*-Bu)$_2$ (4 mol %), ZnF_2 (0.5 equiv), DMF, 90 °C.

Scheme 55. Preparation and Cross-Coupling Reactions of the Zinc Cyanoalkyl Reagents 131



Two new palladium-catalyzed procedures for the α-arylation of nitriles under less basic conditions than those previously reported were disclosed by Wu and Hartwig in 2005.[184] In the first of these, which was compatible with a variety of functional groups including cyano, keto, nitro, and ester groups, the selective monoarylation of acetonitrile and primary nitriles was achieved by treatment of α-silylnitriles with aryl bromides in DMF in the presence of ZnF_2 and catalytic amounts of $Pd_2(dba)_3$ and XantPhos (method A), $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ (method B), or $Pd_2(dba)_3$ and PhP(*t*-Bu)$_2$ (method C).

Table 49 illustrates the scope of the coupling reactions of aryl bromides with trimethylsilylacetonitrile according to methods A−C.

Interestingly, the conditions for the coupling of aryl bromides with trimethylsilylacetonitrile according to methods A and B were found to be applicable for the synthesis of α-arylpropionitriles from aryl bromides and 2-trimethylsilylpropionitrile, but they could not be extended to the coupling of aryl bromides with hindered α-silylnitriles such as α-trimethylsilylcyclohexanecarbonitrile.[184]

The second procedure developed by Wu and Hartwig proved to be very useful for the α-arylation of secondary nitriles in satisfactory-to-good yields (Scheme 55). It entails the use of the zinc cyanoalkyl reagents **131**, which were prepared in situ by treatment of nitriles **130** with LDA and removal of diisopropylamine generated from the deprotonation, followed by reaction with $ZnCl_2$.[184] Reaction of the organozinc reagents **131** with aryl bromides in THF at room temperature in the presence of catalytic quantities of $Pd(OAc)_2$ and P(*t*-Bu)$_3$ then produced the required α-arylated nitriles **132** in 47−91% yield.[184]

The utility of this procedure was demonstrated in a high-yielding synthesis of tertiary nitrile **132a**, which was used as the direct precursor to Verapamil (Scheme 56).[184]

8.2. Synthesis of α-Arylated Carboxyamides and Lactams

Even though carboxylic acid amide derivatives include compounds of pharmacological interest,[185] exhibit a wide range of industrial applications,[186] and represent versatile building blocks in synthetic organic chemistry,[187] prior to 1988 a limited number of methodologies for the synthesis of α-aryl substituted carboxyamides and lactams were reported in the literature. They involve Friedel−Crafts or photoinitiated addition of haloamides to arenes,[188] coupling of aryl halides with *N*-methylpyrrolidinone in the presence of an excess of a strong base,[189] or coupling of aryl halides and amide enolates via an $S_{RN}1$ mechanism initiated photochemically.[190] However, these methods gave variable yields and poor regioselectivity[188,189] or required very high enolate to aryl halide molar ratios to achieve a significant selectivity.[190]

In view of these literature data, in 1998, Hartwig et al. explored the extension of the Pd-catalyzed direct α-arylation of ketones with aryl halides to the α-arylation of carboxyamides and lactams[191] and found that the intermolecular arylation of *N*,*N*-dimethylacetamide (DMA) with unfunctionalized or electron-rich aryl bromides can be performed in dioxane at 100 °C using KHMDS as the base and catalyst formed in situ from $Pd(dba)_2$ and BINAP to give *N*,*N*-dimethyl arylacetamides in modest selectivity and satisfactory yields (Table 50). Unfortunately, this protocol was less effective with homologous carboxyamides, but a similar procedure in which NaO*t*-Bu was employed in place of KHMDS as the base was shown to allow for the efficient synthesis of oxindoles **134** by intramolecular Pd-catalyzed arylation of 2-bromoanilides **133** (Scheme 57).[191]

Scheme 56. Synthesis of Verapamil

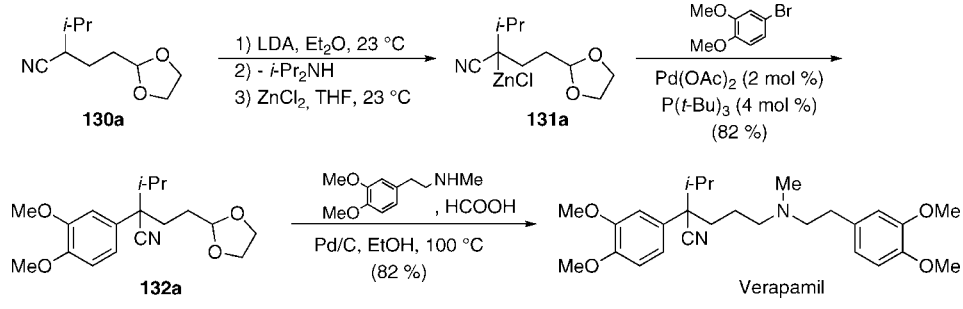
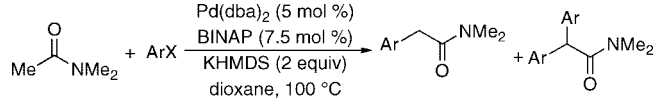
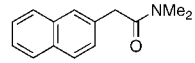
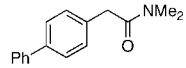
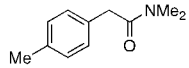
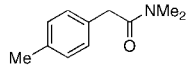
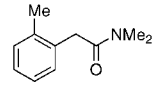
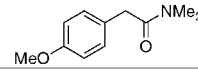


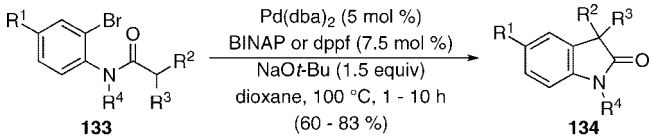
Table 50. Pd-Catalyzed Arylation of DMA with Aryl Halides



Entry	ArX	Reaction time (h)	Major Product	Yield of monoarylated derivative	Yield of diarylated derivative[a]
1	2-NaphthylBr	2		70	9
2	4-PhC_6H_4	2		66	13
3	4-MeC_6H_4Br	1.5		72	10
4	4-MeC_6H_4I	1		70	(4)
5	2-MeC_6H_4Br	1.5		72	(4)
6	4-$MeOC_6H_4Br$	4		48	18

[a] Values in parentheses refer to GLC yield.

Scheme 57. Synthesis of Oxindoles 134 from 2-Bromoanilides 133



133 134 (8 examples)

R^1 = H; OMe, CN
R^4 = Me; Bn
R^2 = R^3 = H; Me
R^2 = H, R^3 = Ph; Me
R^2; R^3 = $(CH_2)_3$-CH

Interestingly, this intramolecular reaction was significantly more tolerant of both steric and electronic modifications of the substrate than was the intermolecular reaction.[191]

In 2000, Freund and Mederski[192] synthesized 1,2-dihydrospiro[3*H*-indole-3,4′-piperidin]-2-ones **136** in modest-to-satisfactory yields by intramolecular cyclization of *tert*-butyl-4-[(benzyl)(2-bromo-4-arylamino)carbonyl]piperidin-1-carboxylates **135** (Figure 9) according to the experimental conditions developed by Hartwig et al.[191] In 2004, these experimental conditions were also used by Gallagher et al. for the intramolecular α-arylation of compound **137**.[193] Thus-prepared adduct **138** (Figure 9) was then employed as a

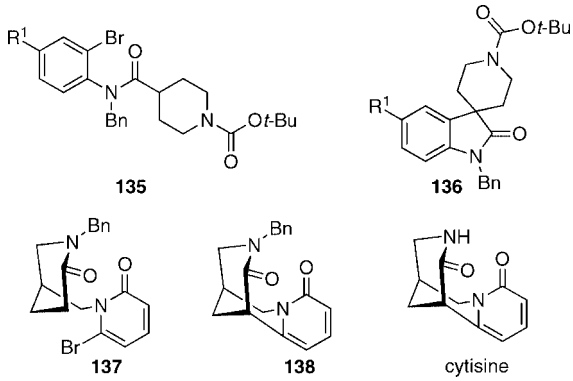
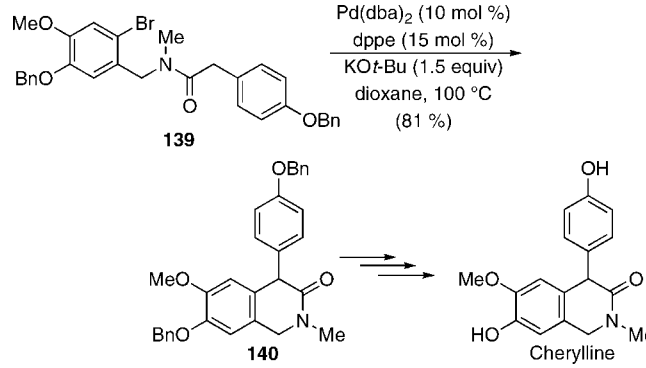
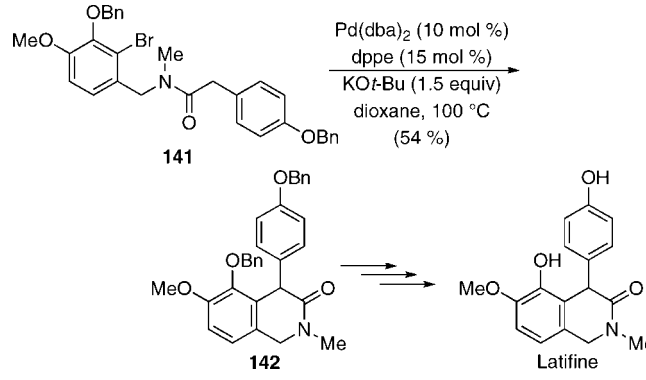


Figure 9. Chemical structures of compounds **135**−**138** and cytisine.

Scheme 58. Intramolecular Arylation of Amide 139



Scheme 59. Intramolecular Arylation of Compound 141

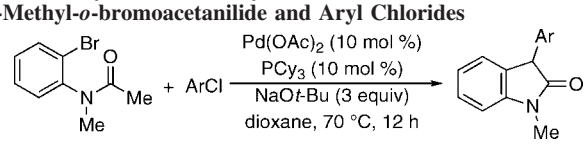


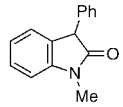
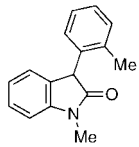
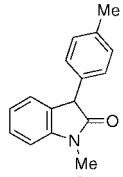
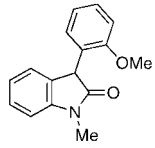
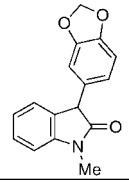
precursor to racemic cytisine,[193] a representative member of the lupin class of alkaloids.

In 2001, the six-membered lactam **140**, which is a precursor to the 1,2,3,4-tetrahydroisoquinoline alkaloid cherylline, was synthesized in 81% yield by Honda et al. via intramolecular coupling of amide **139** in the presence of KO*t*-Bu as the base and a catalyst system composed of Pd/$(dba)_2$ and 1,2-bis(diphenylphosphino)ethane (dppe) (Scheme 58).[194]

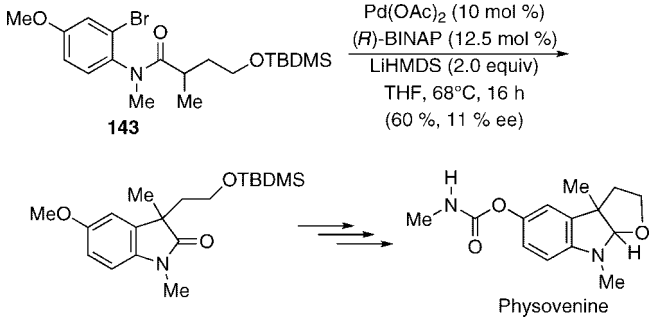
Analogous reaction conditions were then used by these authors to convert carboxyamide **141** into lactam **142**, which was used as a precursor to alkaloid latifine (Scheme 59).[194]

Table 51. Synthesis of 3-Aryloxindoles from *N*-Methyl-*o*-bromoacetanilide and Aryl Chlorides



Entry	Product	Yield (%)
1		61
2		56
3		55
4		60
5		56

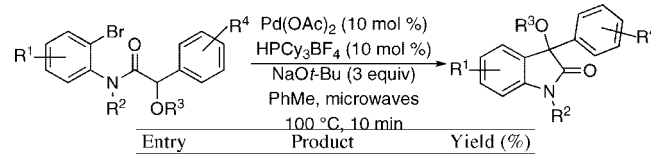
Scheme 60. Pd-Catalyzed Intramolecular Arylation of *o*-Bromoanilide 143

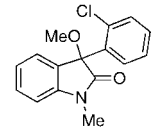
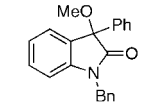
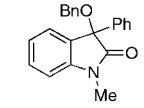
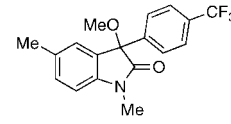
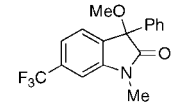
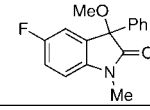


In 2001, it was also shown by Lee and Hartwig that a catalyst system composed of a 1:1 mixture of $Pd(OAc)_2$ and PCy_3 or a sterically hindered *N*-heterocyclic carbene ligand provides fast rates for the synthesis of oxindoles **134** by α-arylation of *o*-bromoanilides **133** or the corresponding *o*-chloro derivatives at 50−70 °C in the presence of NaO*t*-Bu as the base.[195] Most important, the reactions occurred in high yields to form the quaternary carbon in α,α-disubstituted oxindoles. Surprisingly, catalysts containing *tert*-butylphosphine ligands, which had been shown to be most reactive for ketone arylation, were less active than those containing PCy_3.[195]

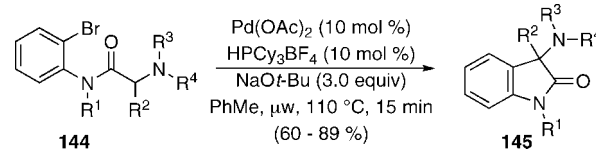
Studies directed at clarifying the mechanism of the cyclization reactions showed that these reactions involve rate-limiting oxidative addition of the aryl halide and that the base-induced formation of and reductive elimination from arylpalladium enolate intermediates are both faster than

Table 52. Pd-Catalyzed Synthesis of 3-Alkoxy-3-aryloxindoles

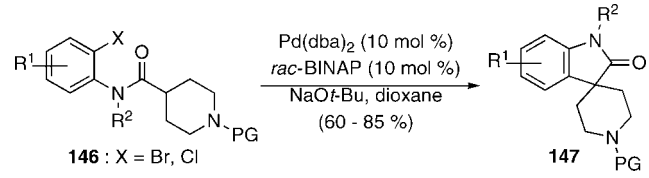


Entry	Product	Yield (%)
1		76
2		86
3		73
4		75
5		81
6		79

Scheme 61. Pd-Catalyzed Synthesis of Quaternary 3-Aminooxindoles 145



Scheme 62. Synthesis of 3-Spirocyclic Indolin-2-ones 147



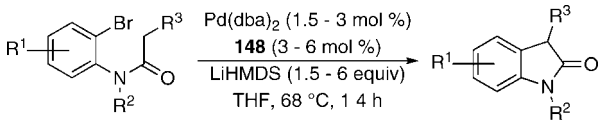
oxidative addition. Deprotonation of the tethered amides appeared to be faster than reductive elimination of the resulting palladium enolates to form the oxindole products.[195]

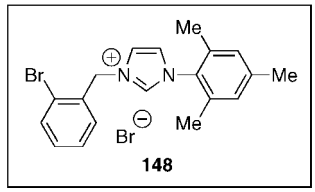
Lee and Hartwig also demonstrated that the $Pd(OAc)_2$/PCy_3 catalyst system can afford the combined inter- and intramolecular arylation reaction of *N*-methyl-*o*-bromoacetanilide to form 3-aryloxindoles in good yields (Table 51).[195]

In 2002 was published an expedient formal total synthesis of the calabar alkaloid physovenine in which the intramolecular arylation of *o*-bromoanilide **143** in the presence of LiHMDS as the base and catalytic amounts of $Pd(OAc)_2$ and (*R*)-BINAP was a key step (Scheme 60).[196]

Very recently, the palladium-catalyzed intramolecular arylation of *o*-haloanilides, first disclosed by Lee and Hartwig,[195] has been extended to a novel synthesis of medicinally important 3-alkoxy-3-aryloxindoles.[197] Specifically, these compounds have been prepared by the rapid microwave-promoted intramolecular arylation of mandelate-

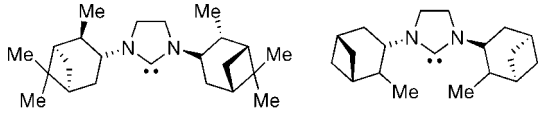
Table 53. $Pd_2(dba)_3$/NHC-Catalyzed Synthesis of *N*-Substituted Oxindoles





148

entry	R^1	R^2	R^3	yield (%)
1	4-Me	Me	Me	80
2	4-Me	Bn	Me	83
3	H	Bn	Me	90
4	4-F	Bn	Me	40
5	4-MeO	Me	Me	67
6	4-Me	Bn	$Bn(CH_2)_2$	47
7	4-Me	Bn	Et	62
8	H	Me	$MeO(CH_2)_2$	82



149 150

Figure 10. Chemical structures of optically active carbenes **149** and **150** .

derivatives in the presence of NaO*t*-Bu as the base and a catalyst system composed of $Pd(OAc)_2$ and $HPCy_3BF_4$.[197] Representative examples of the results obtained using this reaction are reported in Table 52.

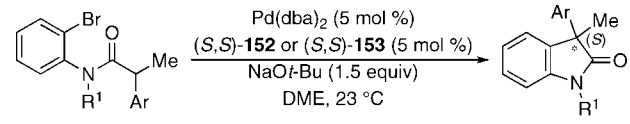
Similar reaction conditions have also been used by Marsden et al. to prepare quaternary 3-aminooxindoles **145** from *N*-(2-bromophenyl)-*N*-methyl-2-dialylaminoacylamides **144** in high yields (Scheme 61).[198]

In 2005, the reaction conditions originally developed by Hartwig for the synthesis of oxindoles from 2-bromoanilides,[191] which involve the use of *rac*-BINAP as the supporting ligand, were employed by Bignan et al. to prepare 3-spirocyclic indolin-2-ones **147** from the corresponding *o*-haloanilides **146** (Scheme 62).[199]

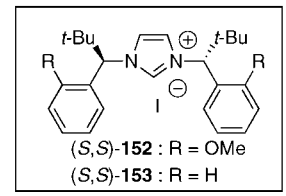
It is worth noting that the palladium-catalyzed synthesis of oxindole derivatives has also been accomplished using *N*-heterocyclic carbenes as ancillary ligands. In fact, in 2002, a catalyst system consisting of a combination of $Pd_2(dba)_3$ and the carbene ligand, obtained by dehydrohalogenation of imidazolium bromide **148**, was employed for the synthesis of racemic *N*-substituted oxindoles via intramolecular arylation of the corresponding *o*-bromoanilides (Table 53).[200]

Moreover, catalyst systems composed of $Pd(OAc)_2$ and optically active carbene ligands **149** and **150** (Figure 10), which were obtained by treatment of optically active *N*,*N*′-diisopinocampheylimidazolium tetrafluoroborate and *N*,*N*′-dibornylimidazolium tetrafluoroborate, respectively, with NaO*t*-Bu, were employed by Lee and Hartwig in 2001 in an asymmetric variant of the intramolecular arylation of 2-haloanilides.[195] Notably, these catalysts allowed for the asymmetric synthesis of α,α-disubstituted oxindoles in high yields and substantial enantioselectivities (37−71% ee). The highest ee values were obtained in reactions conducted below room temperature.

Table 54. Asymmetric Pd-Catalyzed Intramolecular Arylation of *N*-Substituted *o*-Bromoanilides 151



151



(*S*,*S*)-**152** : R = OMe
(*S*,*S*)-**153** : R = H

entry	ligand precursor	R^1	Ar	reaction time (h)	yield (%)	ee (%)
1	(*S*,*S*)-**152**	Me	Ph	24	98	87
2	(*S*,*S*)-**153**	Me	Ph	24	99	94
3	(*S*,*S*)-**153**	Me	4-MeC_6H_4	24	99	93
4	(*S*,*S*)-**153**	Me	4-$MeOC_6H_4$	14	98	93
5	(*S*,*S*)-**152**	Me	2-$MeOC_6H_4$	36	42	84
6	(*S*,*S*)-**152**	Bn	Ph	24	75	79
7	(*S*,*S*)-**153**	Bn	Ph	24	94	8
8	(*S*,*S*)-**152**	Me	1-naphthyl	24	98	84

A few years later, a catalyst precursor consisting of a 1:1 mixture of $Pd(dba)_2$ and one of the two bulky homochiral carbene ligands prepared from imidazolium salts (*S*,*S*)-**152** and (*S*,*S*)-**153** was used by Kündig et al. for the intramolecular enantioselective arylation of the *N*-substituted *o*-bromoanilides **151** (Table 54).[201]

(*S*)-3-Alkyl-3-aryloxindoles were so prepared in high yields and enantiomeric purities up to 94% ee. Table 54 illustrates some representative results of these intramolecular reactions.

In contrast, modest enantioselectivities had previously been obtained in asymmetric cyclizations of 2-haloanilides to oxindoles, which were performed using catalyst systems composed either of a Pd(0) or a Pd(II) source and an enantiomerically pure C_2-symmetrical tricyclic NHC such as **154**, **155**, or **156**,[202] (4*R*,5*R*)-4,5-diphenyl-1,3-dialkyl-4,6-dihydroimidazolidene **157**,[203,204] or [(*S*)-H_8−BINAP] **158**[205] (Figure 11) as the supporting ligand or constituted of chiral *N*-ferrocenyl-substituted (NHC)PdI_2−pyridine complexes.[206] Similarly, a low ee (11%) was observed in the Pd-catalyzed cyclization of a 1-bromoanilide when a chiral chelating di-*N*-heterocyclic carbene, prepared via base-induced 1,3-cycloaddition of tosylmethyl isocyanide to *trans*-1,2-diaminocyclohexane, was used as the ligand.[207]

In 2008, excellent results were instead obtained by Kündig et al., who reported that catalytic amounts of $Pd(dba)_2$ and the new chiral *N*-heterocyclic carbene precursor (*R*,*R*)-**159** (Figure 11) allow for the asymmetric α-arylation of amide enolates containing heteroatom substituents to give chiral 3-alkoxy- and 3-aminooxindoles in high yields and with enantioselectivities up to 97% ee.[201b] These asymmetric Pd/NHC-catalyzed reactions were performed in toluene at 50 °C in the presence of NaO*t*-Bu as the base.

In the same year, Durbin and Willis used X-Phos as the optimal ligand for the synthesis of racemic *N*-substituted 3-aryloxindoles via intramolecular palladium-catalyzed arylation of *N*-substituted oxindoles with aryl chlorides, bromides, or triflates in a mixture of toluene and THF at 70 °C in the presence of KHMDS as the base (Scheme 63).[208] Significant variation of the substitution pattern on both the oxindole and aryl halide was shown to be possible.

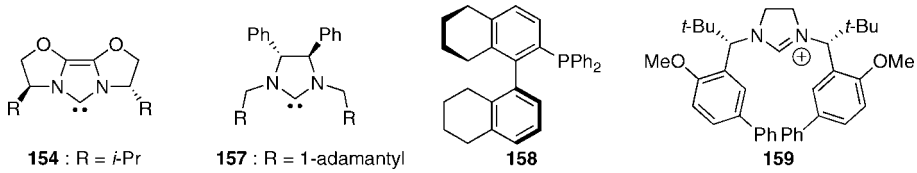


Figure 11. Chemical structures of ligands **154**−**158**, and the NHC−ligand precursor (*R*,*R*)-**159**.

Scheme 63. $Pd_2(dba)_3$/X-Phos-Catalyzed α-Arylation of *N*-Substituted Oxindoles

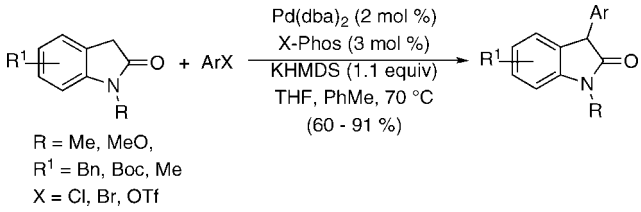
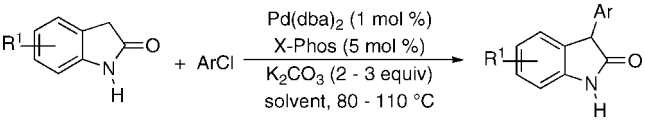


Table 55. Pd-Catalyzed C-3 Arylation of Free (NH)-Oxindoles with Aryl Chlorides



entry	R^1	Ar	solvent	reaction temp. (°C)	yield (%)
1	H	4-$MeOC_6H_4$	THF	80	92
2	H	3-$CF_3C_6H_4$	dioxane	100	81
3[a]	H	4-NCC_6H_4	THF	80	55
4	5-F	3-$Me_2NC_6H_4$	dioxane	100	80
5	H	3-$MeOOCC_6H_4$	THF	80	77
6	7-MeOOC	4-MeC_6H_4	THF	80	63
7[b]	H	4-*t*-BuC_6H_4	*t*-BuOH	110	67
8	H	4-HOC_6H_4	dioxane	100	89

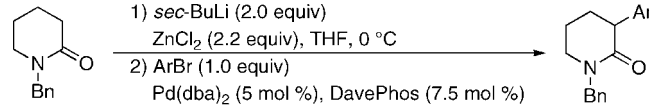
[a] The reaction was run in the presence of 4 Å molecular sieves. [b] The reaction was run using the required $ArSO_2Ph$.

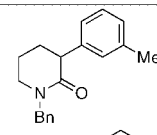
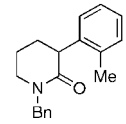
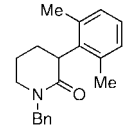
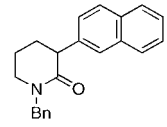
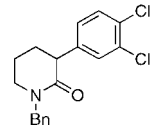
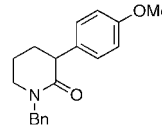
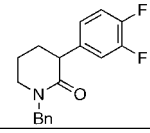
In 2008, the first examples of intramolecular palladium-catalyzed arylations of free (NH)-oxindoles with aryl halides have also been described.[209] It was found that, even though free (NH)-oxindoles possess protons at the C-3 and N-1 positions with identical acidities (pK_a = 18.5),[210] these lactams are able to undergo complete regioselective C-3 arylation by reaction with aryl chlorides in the presence of K_2CO_3 as the base and catalytic quantities of $Pd_2(dba)_3$ and X-Phos as the supporting ligand (Table 55).[209]

On the contrary, arylation proved to occur exclusively at the nitrogen using a Cu-diamine-based catalyst system.[209] In this study, Buchwald and co-workers also found that the use of bidentate or biarylmonophosphine ligands different from X-Phos provides low conversions of the starting materials and low yields of the products and that the $Pd_2(dba)_3$/X-Phos-catalyzed C-3 arylation of oxindoles with aryl chlorides is able to tolerate a variety of functional groups on the *para*- and *meta*-positions of the electrophiles but furnishes a low conversion of the reagents when *ortho*-substituted aryl chlorides are used as arylating species.[209]

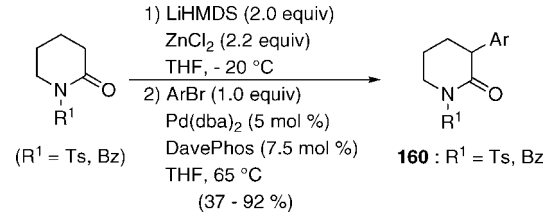
N-Protected 2-piperidinones represent another interesting class of lactams that has been used in intermolecular[211−213] and intramolecular Pd-catalyzed arylation reactions.[214] In a conclusive paper, Cossy et al. showed that the zinc enolates, generated by treatment of *N*-benzyl-2-piperidinones with *sec*-BuLi and $ZnCl_2$, can efficiently be arylated with aryl bromides using a $Pd(dba)_2$/DavePhos catalyst system (Table 56).[213b]

Table 56. $Pd(dba)_2$/DavePhos-Catalyzed α-Arylation of *N*-Benzyl-2-piperidinones with Aryl Bromides



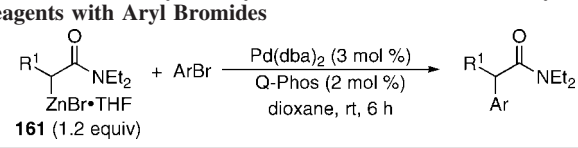
Entry	Product	Yield (%)
1		97
2		83
3		0
4		81
5		70
6		99
7		82

Scheme 64. α-Arylation of *N*-Tosyl- and *N*-Benzoyl-2-piperidinone with Aryl Bromides



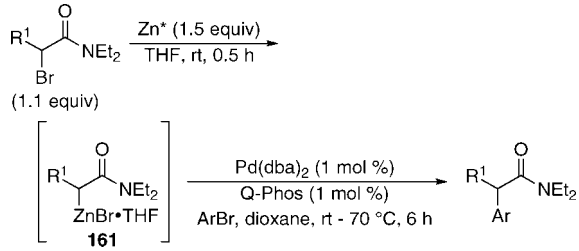
As shown in this table, the aryl bromides employed in the arylation reactions contained electron-donor or electron-withdrawing substituents but lacked potentially reactive protic

Table 57. Pd-Catalyzed Arylation of Isolated Reformatsky Reagents with Aryl Bromides



entry	R^1	Ar	yield (%)
1	H	4-*t*-BuC_6H_4	92
2	Me	4-*t*-BuC_6H_4	88
3	H	4-$EtOOCC_6H_4$	94
4	Me	4-$EtOOCC_6H_4$	95
5	Me	4-$O_2NCC_6H_4$	97
6	H	4-$NCCC_6H_4$	86
7	H	4-$MeOCC_6H_4$	81
8	Me	3-$MeOCC_6H_4$	88
9	Me	4-$CF_3C_6H_4$	88
10	H	4-$CF_3C_6H_4$	91

Table 58. Pd-Catalyzed Arylation of *N*,*N*-Diethylacetamide and *N*,*N*-Diethylpropionamide Reformatsky Reagents Generated in situ from the Corresponding α-Bromoamides and Activated Zinc Metal



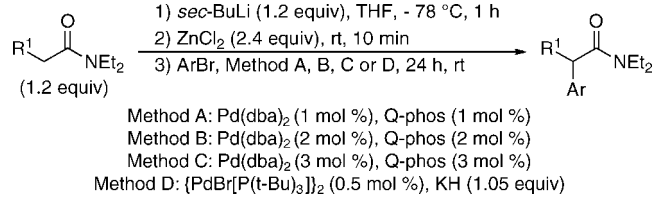
entry	R^1	Ar	reaction temp. (°C)	yield (%)
1	H	4-*t*-BuC_6H_4	rt	90
2	H	4-$MeOOCC_6H_4$	rt	89
3	H	4-NCC_6H_4	rt	87
4	H	4-$O_2NCC_6H_4$	rt	81
5	H	2,4,6-$(Me)_3C_6H_2$	rt	91
6	H	2-FC_6H_4	rt	91
7	Me	4-$Me_2NC_6H_4$	70	89
8	Me	4-$MeOOCC_6H_4$	rt	87

or functional groups such as hydroxyl, amino, keto, nitro, and ester groups. Cossy et al. also investigated the arylation of *N*-tosyl- and *N*-benzoyl-2-piperidinone with different aryl bromides and observed that the enolates generated by treatment of these substrates with LiHMDS and $ZnCl_2$ were efficiently arylated with aryl bromides in the presence of $Pd(dba)_2$ and DavePhos to give the required α-arylated derivatives **160** in good-to-excellent yields (Scheme 64).[213b] Again, the presence and nature of the phosphine ligand on the palladium center proved to be crucial to the outcome of the arylation reaction.

On the other hand, Maier has very recently described a novel strategy to 1,5-methano-3-benzazocines in which a key step is the intramolecular arylation of *N*-benzylpiperidones that carry a 2-bromobenzyl substituent in the 5-position.[214] The reaction, which was carried out in THF in the presence of NaHMDS as the base and catalytic amounts of $Pd(dba)_2$ and P(*t*-Bu)$_3$, was found to require the use of $ZnCl_2$ as an additive and produced the required pharmaceutically interesting tricyclic compounds in moderate yields.[214]

Before closing this paragraph, we think it right also to mention that, in the past few years, a few limited examples of syntheses of α-monoarylated carboxyamides that involve palladium-catalyzed cross-coupling reactions of zinc enolates of carboxyamides with aryl bromides have been reported.[149,150]

Table 59. Pd-Catalyzed Arylation of Zinc Enolates of *N*,*N*-Diethylacetamide and *N*,*N*-Diethylpropionamide Generated via the Corresponding Lithium Amide Enolates



entry	R^1	Ar	method	yield (%)
1	H	4-*t*-BuC_6H_4	A	93
2	H	4-ClC_6H_4	A	94
3	H	4-$MeSC_6H_4$	A	91
4	H	4-$MeOC_6H_4$	A	93
5	H	4-$MeOOCC_6H_4$	A	97
6	H	4-NCC_6H_4	A	96
7	H	4-$O_2NCC_6H_4$	A	90
8	H	4-BzC_6H_4	A	92
9	H	4-AcC_6H_4	B	92
10	H	4-$Me_2NC_6H_4$	C	90
11	H	2-FC_6H_4	C	92
12	H	2,4,6-$(Me)_3C_6H_2$	A	96
13	H	4-HOC_6H_4	D	80
14	H	4-$H_2NC_6H_4$	D	80
15	Me	4-$CF_3C_6H_4$	A	90
16	Me	2-$MeOC_6H_4$	C	88
17	Me	4-HOC_6H_4	D	95
18	Me	4-$H_2NC_6H_4$	D	90
19	Me	4-$MeSC_6H_4$	A	94
20	Me	4-$O_2NCC_6H_4$	C	87

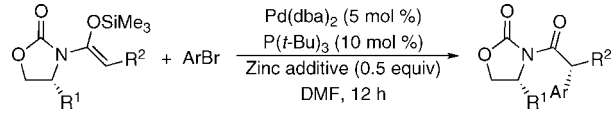
The reactions were limited to zinc enolates of *N*,*N*-disubstituted acetamides and propionamides and were conducted with isolated zinc amides formed from the corresponding α-haloamides.

In 2006, Hartwig et al. presented a full account of the scope and limitations of the α-arylation of carboxyamides by palladium-catalyzed coupling of aryl bromides with zinc enolates of amides (Table 57)[215] and reported that the reaction takes place in high yields with isolated Reformatsky reagents **161** generated from α-bromoamides, with Reformatsky reagents generated in situ from α-bromoamides (Table 58), and with zinc enolates generated by quenching lithium enolates of amides with $ZnCl_2$ (Table 59).[215]

As shown in Table 57, the arylation of isolated Reformatsky reagents **161** was found to occur at room temperature with electron-neutral, electron-rich, and electron-poor aryl bromides in the presence of the Pd-catalyst generated from $Pd(dba)_2$ and Q-Phos as the ligand. Interestingly, the reaction also occurred in high yields with aryl bromides containing ester, nitro, and cyano groups.[215] The palladium catalyst generated from $Pd(dba)_2$ and Q-Phos was also used for high yielding reactions of reagents **161**, generated in situ from α-bromoacetamide and α-bromopropionamide and activated Zn metal, with aryl bromides containing electron-donating or electron-withdrawing substituents (Table 58).

On the other hand, Table 59 shows that most of the arylation reactions of the zinc enolates of *N*,*N*-diethylacetamide and *N*,*N*-diethylpropionamide, generated from the corresponding lithium amide enolates, furnished yields exceeding 90% and that the reactions also occurred with aryl bromides containing the hydroxyl or amino group provided that 1.05 equiv of KH were added to deprotonate these groups prior to addition of the zinc enolates. The reactions with these aryl bromides occurred in high yields when [P(*t*-Bu)$_3$PdBr]$_2$ was used as the catalyst precursor.[215] However, a catalyst system composed of $Pd(dba)_2$ and ligand Q-Phos

Table 60. Diastereoselective Arylation of Silyl Keteneimides Bearing the Evans Auxiliary with Aryl Bromides



			product				
entry	zinc additive	reaction temp. (°C)	R^1	R^2	Ar	yield (%)	d.r.
1	ZnF_2	80	*i*-Pr	Me	Ph	67	87:13
2	$Zn(O\text{-}t\text{-}Bu)_2$	rt	*i*-Pr	Me	Ph	70	91:9
3	ZnF_2	80	*t*-Bu	Me	Ph	58	92:8
4	$Zn(O\text{-}t\text{-}Bu)_2$	rt	*t*-Bu	Me	Ph	61	95:5
5	ZnF_2	80	*i*-Pr	Et	3-AcC_6H_4	75	84:16
6	ZnF_2	80	*i*-Pr	Et	4-*t*-BuC_6H_4	57	83:17
7	ZnF_2	80	*i*-Pr	Et	4-NCC_6H_4	65	77:13
8	ZnF_2	80	*i*-Pr	*t*-$BuCH_2$	Ph	35	89:11

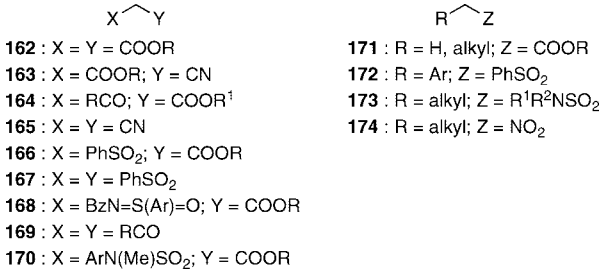
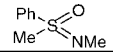


Figure 12. Chemical structures of compounds **162**−**174**.

Table 61. Equilibrium Acidities in DMSO at 23 °C[218]

Compound	pKa
2,2-Dimethyl-1,3-dione-4,6-dione (Meldrum's acid)	7.3
$PhCOCH_2CN$	10.2
1,3-Cyclohexanedione	10.3
$CH_2(CN)_2$	11.0
$PhSO_2CH_2COPh$	11.4
$PhSO_2CH_2CN$	12.0
$PhCH_2NO_2$	12.3
$MeCOCH_2COMe$	13.3
$MeCOCH_2COOEt$	14.2
Nitrocyclopentane	16.0
$CH_2(COOEt)_2$	16.4
$PhCH_2COOEt$	22.6
PhCOMe	24.7
γ-Valerolactone	25.2
2-Piperidinone	26.4
Cyclohexanone	26.4
MeCN	31.3
	33.0

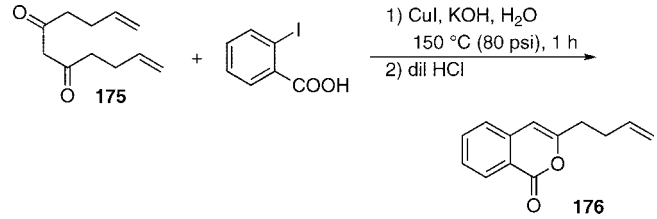
was preferred for arylation reactions of the zinc enolates of morpholine acetamide and propionamide,[215] the products of which are able to undergo functional group interconversions similar to those of Weinreb amides.[216]

8.3. Arylation of Silyl Keteneimides

In 2004, Liu and Hartwig[170] investigated the palladium-catalyzed arylation of trimethylsilyl keteneimides and found that the $Pd(dba)_2/P(t\text{-}Bu)_3$-catalyzed reaction of aryl bromides with silyl keteneimides bearing the Evans auxiliary[217] in the presence of ZnF_2 or $Zn(O\text{-}t\text{-}Bu)_2$ as an additive proceeds in satisfactory yields and diastereoselectivities up to 90% diastereomeric excess (de) (Table 60).

Interestingly, the reactions conducted with $Zn(O\text{-}t\text{-}Bu)_2$ as an additive occurred at room temperature in modest-to-satisfactory yields and gave enhanced diastereoselectivities.[170]

Scheme 65. CuI-Mediated Synthesis of 3-But-3-enylisochromen-1-one 17



9. α-Arylation of β-Dicarbonyl Compounds, Ethyl Cyanoacetate, Malononitrile, Ethyl Phenylsulfonylacetate, Methanesulfonamides, N-Sulfoximines, and Nitroalkanes

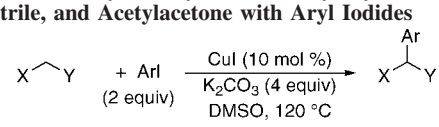
Since the 1980s, the α-arylation of substrates **162**−**170** bearing two electron-withdrawing moieties linked at a methylene group and of compounds **171**−**174**, where only one electron-withdrawing group is linked at a methylene group (Figure 12), has attracted much attention.

The significance of the products of these arylation reactions is due to the fact that these substances are useful synthetic intermediates and some of them, including dialkyl arylmalonates and alkyl 2-arylacetoacetates, represent important precursors to nonsteroidal anti-inflammatory drugs.

Table 61 illustrates that many of the substrates reported in Figure 12 possess values for C−H acidity significantly higher than those of simple ketones, carboxylic acid esters, nitriles, lactones, and lactams containing a sp^3-hybridized C−H bond in the α-position. On the other hand, the values for C−H acidity of these substrates have represented an important parameter to be considered in the choice of the experimental conditions, including the nature of the base, for their direct palladium-, nickel-, or copper-catalyzed arylation reactions with aryl halides or pseudohalides.

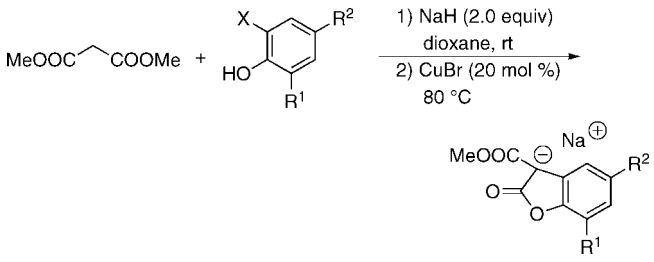
In this section, the discussion and comments of the literature data on the transition metal-catalyzed reactions of the substrates reported in Figure 12 has been subdivided in two subsections. The former is concerned with the results of copper-catalyzed arylations of β-diketones, β-ketoesters, ethyl cyanoacetate, diethyl malonate, and malononitrile, and the second subsection regards the literature data on the palladium-catalyzed α-arylation reactions of diethyl malonate, malononitrile, β-ketoesters, β-diketones, sulfonyl C−H acids, ethyl cyanoacetate, and nitro compounds with aryl halides as well as the results obtained in the nickel-catalyzed monoarylation of malononitrile with aryl halides.

Table 62. CuI-Catalyzed Arylation of Ethyl Cyanoacetate, Malononitrile, and Acetylacetone with Aryl Iodides

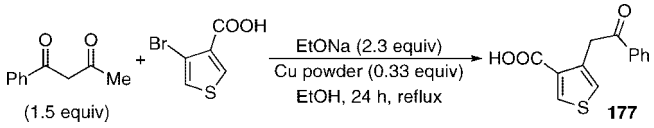


entry	X	Y	Ar	reaction time (h)	yield (%)
1	CN	COOEt	Ph	20	78
2	CN	COOEt	4-MeC_6H_4	20	75
3	CN	COOEt	4-ClC_6H_4	18	81
4	CN	COOEt	1-naphthyl	9	47
5	CN	COOEt	2-naphthyl	4	70
6	CN	CN	Ph	16	55
7	CN	CN	2-naphthyl	20	73
8	Ac	Ac	Ph	4	65

Scheme 66. Synthesis of the Sodium Salts of 3-Methoxycarbonylbenzofuran-2(3*H*)-ones



Scheme 67. Cu-Mediated Synthesis of Ketoacid 177



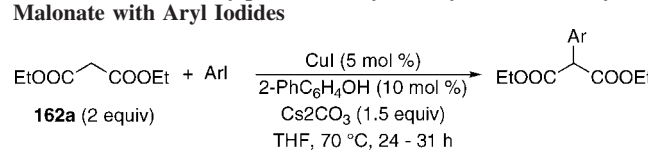
9.1. Copper-Catalyzed α-Arylations

In the 1970s, McKillop et al. established that C−H acids, such as ethyl acetoacetate, acetylacetone, 1-phenylbutane-1,3-dione, and diethyl malonate, can be C-arylated in good-to-excellent yields by reaction with a variety of 2-bromobenzoic acids and other haloaromatic carboxylic acids in the presence of NaH and a catalytic amount of CuBr.[219] Nevertheless, in the 1980s and in the early 1990s, many arylations of activated methylene compounds with aryl halides were performed using stoichiometric or even supra-stoichiometric amounts of copper salts.[220−225] These non-catalytic reactions, which date back to the development of the Hurtley reaction,[226,227] were found to give good yields only with aryl halides bearing electron-withdrawing groups or *ortho*-substituents capable of coordinating to copper and when they were performed at high temperature in polar solvents such as dimethyl sulfoxide (DMSO), pyridine, or hexamethylphosphoramide (HMPA); unfortunately, under these experimental conditions, the reaction products easily decomposed.

More recently, a stoichiometric amount of CuI has been used for the synthesis of 3-but-3-enylisochroman-1-one **176** by arylation of dione **175** with *o*-iodobenzoic acid in near critical water at 150 °C in a synthetic microwave pressure reactor (Scheme 65).[228]

In 1993, Miura et al. described a synthetically interesting procedure for the α-arylation of active methylene compounds, including acetylacetone, ethyl cyanoacetate, and malononitrile, with aryl iodides, in which a catalytic amount of air-stable CuI was employed and the use of a large molar excess of the arylating reagents was involved (Table 62).[229]

Table 63. CuI/2-Phenylphenol-Catalyzed Arylation of Diethyl Malonate with Aryl Iodides



entry	Ar	yield (%)
1	Ph	91
2	3,5-$(Me)_2C_6H_3$	95
3	1-naphthyl	96
4	2-*i*-PrC_6H_4	84
5	4-ClC_6H_4	94
6	3-pyridyl	73
7	3-$CF_3C_6H_4$	89
8	2,4-$(Me)_2C_6H_3$	87
9	3-FC_6H_4	84
10	4-AcC_6H_4	86
11	3-$EtOOCC_6H_4$	86
12	4-HOC_6H_4	80
13	3-NCC_6H_4	61
14	4-$AcNHC_6H_4$	75
15	4-$NH_2C_6H_4$	79
16	3-$NO_2C_6H_4$	84

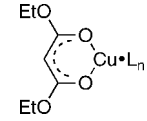


Figure 13. Required bidentate binding of copper diethyl malonate enolate.

In 1999, Konopelski et al. developed a copper-catalyzed arylation of dimethyl malonate,[230] but the substrate scope was limited. In fact, only *ortho*-halophenols and *ortho*-haloanisoles were used as electrophiles and the copper catalyst was CuBr, which is an air-sensitive compound. As shown in Scheme 66, the reaction, which was carried out in the presence of NaH as the base, produced the sodium salts of 3-methoxycarbonylbenzofuran-2(3*H*)-ones.[230]

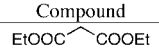
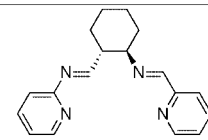
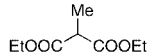
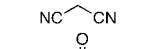
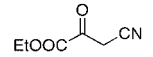
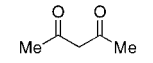
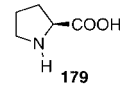
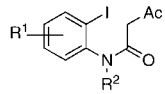
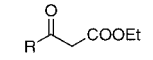
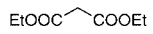
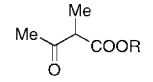
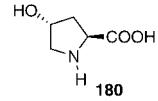
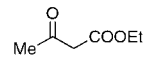
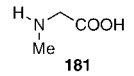
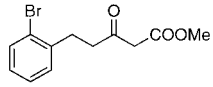
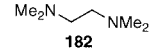
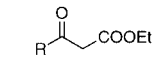
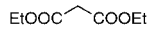
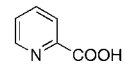
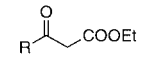
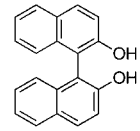
In the same year, the original EtONa/Cu powder/EtOH conditions of the Hurtley reaction[226] were used to effect the coupling of 1-phenylbutane-1,3-dione with 4-bromothiophene-3-carboxylic acid combined with a retro-Claisen reaction to provide compound **177** in 22% yield (Scheme 67).[231]

Remarkably, the yield of **177** could be raised to 40% by addition of NaH (2.4 equiv) to 4- bromothiophene-3-carboxylic acid (1 equiv), 1-phenylbutane-1,3-dione (5 equiv), and a catalytic amount of CuBr in toluene, followed by heating the reaction mixture under reflux for 2 days.[231]

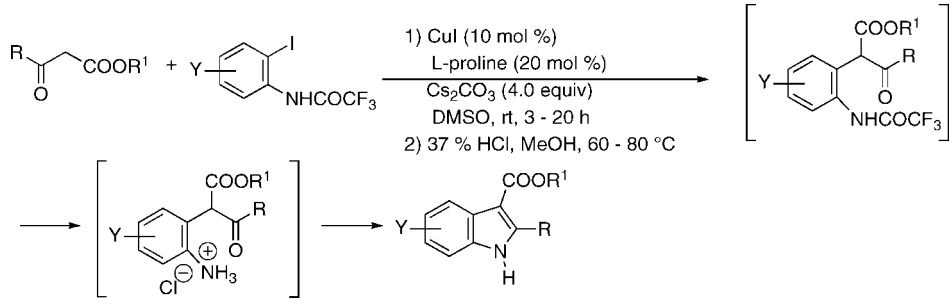
A mild, general method for accessing a variety of diethyl arylmalonates from diethyl malonate **162a** and aryl iodides in good-to-excellent yields was described by Hennessy and Buchwald in 2002.[232] It involves treatment of a molar excess of **162a** with aryl iodides in THF in the presence of Cs_2CO_3 and catalytic amounts of CuI and 2-phenylphenol as a supporting ligand (Table 63).[232,233]

It is worth noting that the functional groups expected to be problematic in the corresponding Pd-catalyzed arylation reactions (e.g., NO_2, OH, NH_2) were in general well-tolerated using this Cu-based catalyst system. However, when the reaction conditions of Table 63 were applied to the attempted arylation of Meldrum's acid, 1,3-cyclopentadienone, and 1,3-cyclohexadienone, no desired products were observed. This suggested that a bidentate binding of the diethyl malonate enolate through the oxygen atoms to copper is required for

Table 64. Types of Ligands Used for the CuI-Catalyzed Inter- and Intramolecular C-arylation of Activated Methylene or Methine Compounds with Aryl Halides

Activated Methylene or Methine Compound	Aryl Halide	Ligand	Ref.
	ArI	 Chxn-Py-Al **178**	234
	ArI	**178**	234
	ArI	**178**	234
	ArI	**178**	234
	ArI	 **179**	235
	–	**179**	242
 (R = Me, Ph, *i*-Pr)	ArX (X = Br, I)	**179**	236a,b
	ArX (X = Br, I)	**179**	236
	ArI	 **180**	237
	ArI	 **181**	238
	–	 **182**	239
 (R = Me, *i*-Pr, CH_2OBn, Ph, CH_2=CH-$(CH_2)_2$)	ArX (X = Br, I)	**176**	240a,b
	ArX (X = Br, I)	 **183**	241
	2-$H_2NC_6H_4I$	 BINOL **184**	240b

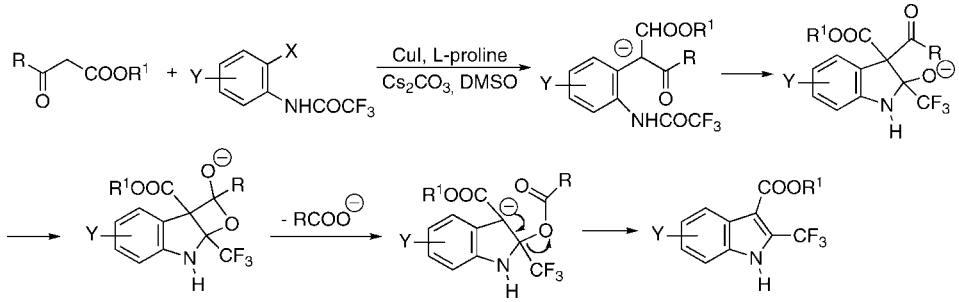
Scheme 68. Synthesis of 2,3-Disubstituted Indoles via a Cascade α-Arylation−Condensation Process



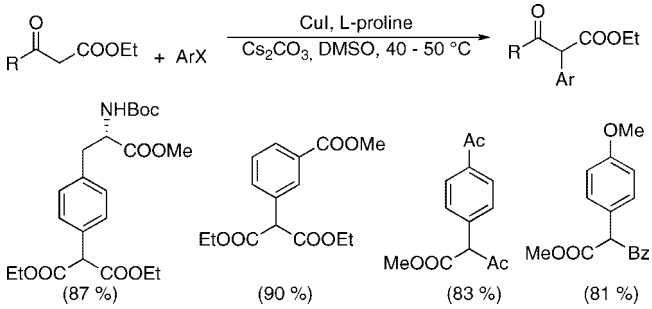
a successful arylation reaction (Figure 13).[232] The role played by 2-phenylphenol in the reaction was not elucidated, but it was observed that, in the absence of this additive, the arylation reactions proceed to only 80% conversion.[232]

The importance of a supporting ligand in the CuI-catalyzed arylation of activated methylene compounds, which was displayed for the first time in the above-mentioned investigation, was subsequently proved in several studies.[234−242]

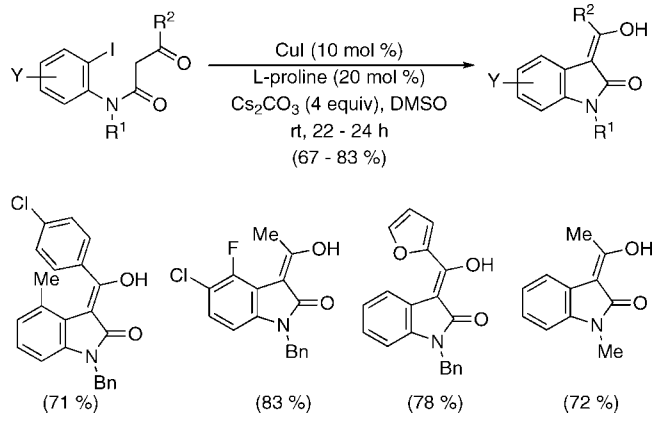
Scheme 69. Possible Reaction Mechanism for the Synthesis of 3-Alkoxycarbonyl-2-(trifluoromethyl)-1*H*-indoles



Scheme 70. CuI/L-Proline-Catalyzed Intermolecular Arylation of Activated Methylene Compounds



Scheme 71. Synthesis of 3-Acyl Oxindoles via Intramolecular Arylation of *β*-Keto-2-iodoanilides



Several different ligand types used for CuI-catalyzed inter- and intramolecular arylation reactions of activated methylene and methine compounds with aryl iodides and bromides are reported in Table 64. Remarkably, as far as we are aware, aryl chlorides have never been used as arylating reagents in CuI-catalyzed arylations of activated methylene and methine compounds.

Cristeau, Taillefer et al. found that chelating Schiff base Chxn-Py-Al **178** generates a remarkable general copper catalyst for the C-arylation of diethyl malonate, diethyl

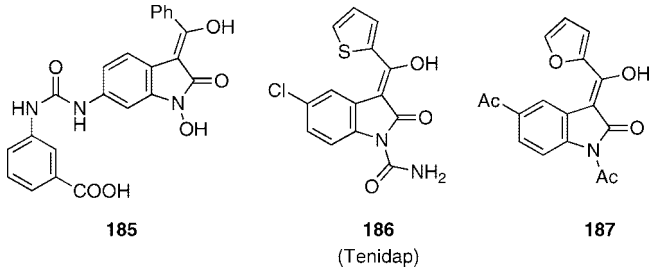
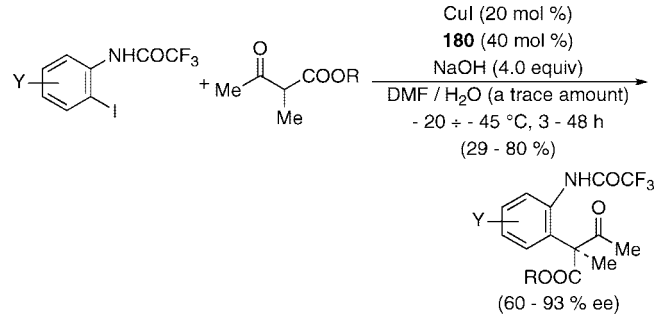


Figure 14. Chemical structures of compounds **185**−**187**.

Scheme 72. CuI/(2*S*,4*R*)-4-Hydroxyproline-Catalyzed Enantioselective Arylation of Alkyl 2-Methylacetoacetates



methylmalonate, and ethyl cyanoacetate with aryl iodides under mild conditions.[234]

In 2005, Jiang et al. showed that the coupling reaction of acetylacetone and alkyl cyanoacetates with aryl halides under catalysis of CuI/L-proline works at relatively mild conditions to provide 3-aryl-2,4-pentanediones and α-aryl cyanoacetates, respectively, in moderate-to-good yields.[235]

Subsequently, L-proline was also employed by Ma et al. as a ligand in the CuI-catalyzed coupling of *β*-ketoesters with 2-iodotrifluoroacetanilides.[240a] In situ acidic induced hydrolysis of the resulting C-arylated compounds furnished 2,3-disubstituted indole derivatives with high regioselectivity (Scheme 68).[240a]

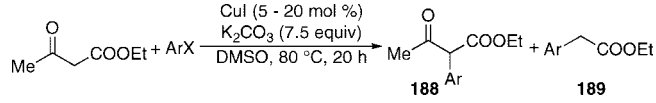
In the same year, Tanimori et al. synthesized these heterocycles by a one-step process involving the coupling of *β*-ketoesters with *o*-iodoaniline in DMSO in the presence of K_2CO_3 or Cs_2CO_3 as the base and catalytic quantities of CuI and ligand **179**, **181**, **182**, or 1,1′-bi-2-naphthol (BINOL) **184**.[240b]

More recently, 3-alkoxycarbonyl-2-(trifluoromethyl)-1*H*-indoles have been synthesized in good-to-excellent yields via a cascade coupling/condensation/deacylation process, which occurs when 2-halotrifluoroacetanilides are reacted with *β*-ketoesters in anhydrous DMSO under the action of Cs_2CO_3 at 40−80 °C in the presence of catalytic amounts of CuI and L-proline.[236b] A possible reaction mechanism for this cascade process is reported in Scheme 69.

In 2007, Yip et al. employed 2-picolinic acid as an ancillary ligand in the copper-catalyzed α-arylation of malonates.[241] In the presence of catalytic amounts of this ligand and CuI, the coupling of diethyl malonate with aryl iodides was found to proceed smoothly even at room temperature and proved to offer a high level of functional compatibility.

L-Proline has also been used as an ancillary ligand for the CuI-catalyzed arylation of diethyl malonate, ethyl benzoyl acetate, and ethyl acetoacetate with aryl bromides and iodides (Scheme 70), and it has been found that the coupling

Table 65. CuI-Catalyzed Arylation of Ethyl Acetoacetate under Ligandless Conditions



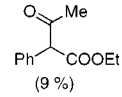
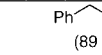
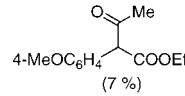
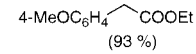
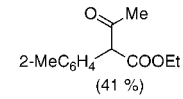
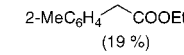
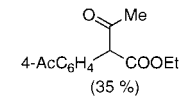
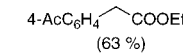
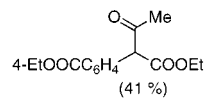
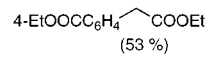
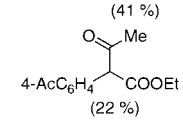
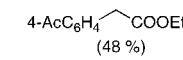
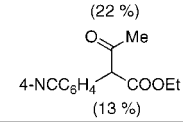
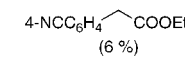
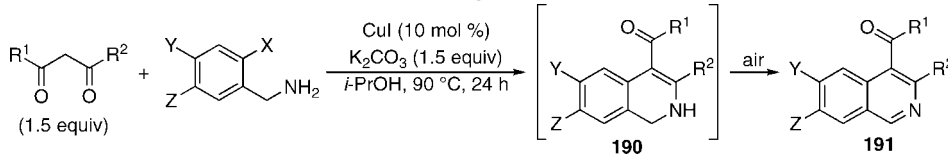
Entry	ArX	Conversion of acetoacetate	Products	
			188 (yield %)	**189** (yield %)
1	PhI	77	 (9 %)	 (89 %)
2	4-$MeOC_6H_4I$	78	 (7 %)	 (93 %)
3	2-MeC_6H_4I	90	 (41 %)	 (19 %)
4	4-AcC_6H_4I	76	 (35 %)	 (63 %)
5	4-$EtOOCC_6H_4I$	80	 (41 %)	 (53 %)
6	4-AcC_6H_4Br	80	 (22 %)	 (48 %)
7	4-NCC_6H_4Br	94	 (13 %)	 (6 %)

Table 66. Synthesis of Isoquinolines via CuI-Catalyzed Reaction of β-Dicarbonyl Compounds with 2-Halobenzylamines



entry	X	Y	Z	R^1	R^2	yield (%) of **191**
1	Br	H	H	OMe	Et	90
2	Br	H	H	OMe	*i*-Pr	53
3	Br	H	H	OEt	but-3-enyl	80
4	Br	H	H	OMe	Bn	59
5	Br	H	H	OEt	4-$O_2NC_6H_4$	53
6	Br	H	H	OMe	4-ClC_6H_4	51
7	Br	H	OMe	OEt	Me	73
8	I	Cl	H	OEt	Me	76
9	Br	H	H	Me	Me	23
10	Br	H	H	$(CH_2)_3$	61	
11	Br	O−CH_2−O	OMe	Me	76	
12	Br	O−CH_2−O	OMe	4-$MeOC_6H_4$	72	
13	Br	H	H	OMe	4-(EtCONH)C_6H_4	79
14	Br	H	H	CH_2−$C(Me)_2$-CH_2	51	

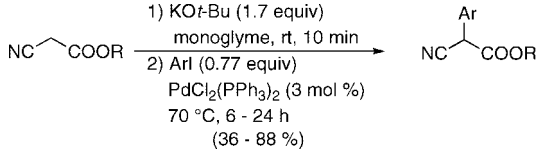
reactions involving aryl iodides generally occur at 40 °C while those concerning aryl bromides occur at 50 °C in DMSO.[236a,243]

The reactions provide the required 2-aryl-1,3-dicarbonyl compounds in good yields but must be carried out in an argon atmosphere using a high loading of CuI (20 mol %) and L-proline (40 mol %).[236a]

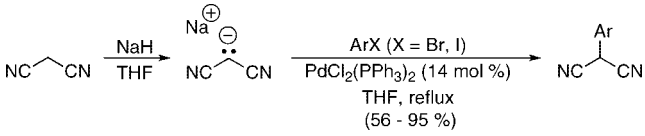
The CuI/L-proline catalyst system was also used by Lu and Ma in 2006 for the high-yielding synthesis of 3-acyloxindoles via intramolecular coupling of β-keto-2-iodoanilides in DMSO at room temperature in the presence of Cs_2CO_3 as the base (Scheme 71).[242] The starting materials were prepared from aryl chlorides, Meldrum's acid, and *N*-protected 2-iodoanilines in a one-pot procedure

It should be noted that 3-acyloxindoles, which represent a common structural motif in a number of pharmaceutically important compounds, including influenza endonuclease inhibitor **185**,[243a] Tenidap **186**,[243b] which is a potent inhibitor of cyclooxygenase, and GSK3 kinase inhibitor **187**[243c] (Figure 14), are usually prepared by acylation of the corresponding oxindoles with acyl chlorides or by condensation of the oxindoles with esters.[244,245] However, these methods are hampered by the poor solubility of the substrates.

Scheme 73. $PdCl_2(PPh_3)_2$-Catalyzed Arylation of Alkyl Cyanoacetates with Aryl Iodides



Scheme 74. $PdCl_2(PPh_3)_2$-Catalyzed Synthesis of Arylmalononitriles



(2*S*,4*R*)-4-Hydroxyproline **180** was used by Ma et al. in 2006 as a homochiral ancillary ligand in the highly enantioselective CuI-catalyzed arylation of alkyl 2-methylacetoacetates with 2-iodotrifluoroacetanilides (Scheme 72).[237] Remarkably, the reaction could be performed at −45 °C when a trace amount of water was added to DMF, the reaction solvent. However, the reason for this action of water was not elucidated.

Ma et al. also observed that increasing the size of the ester moiety of 2-methylacetoacetates significantly improved the enantioselectivity.[237] In fact, several α-arylations of *tert*-butyl 2-methylacetoacetate were found to occur with enantioselectivity values up to 93% ee.[237]

One year later, Parkinson demonstrated that ethyl acetoacetate can undergo CuI-catalyzed coupling reaction with aryl iodides as well as electron-deficient aryl bromides in DMSO at 80 °C in the absence of additional ligands to yield mixtures of ethyl 2-arylacetoacetates **188** and ethyl arylacetates **189** (Table 65).[246] Prolonged heating was found to shift the product distribution toward compounds **189**.[246]

More recently, Ma et al. have developed a CuI-catalyzed cascade process for the assembly of substituted isoquinolines from β-ketoesters or β-diketones and *o*-halobenzylamines in isopropanol under the action of K_2CO_3 (Table 66).[247] Remarkably, 1,2-dihydroisoquinolines **190**, which are the coupling/cyclocondensation products, were found to undergo smooth dehydrogenation under air atmosphere to produce isoquinolines **191**.[247] It is also worth noting that the reaction conditions allowed for the presence of a number of functional groups in both the β-dicarbonyl compound and the halobenzylamine moieties.

9.2. Pd- and Ni-Catalyzed Arylations

Examples of palladium-catalyzed arylations of substrates containing activated methylene groups, such as β-dicarbonyl compounds, ethyl cyanoacetate, and malononitrile, with aryl halides date back to the 1980s, but these reactions, which sometimes represent useful alternatives to the corresponding copper-catalyzed reactions, have undergone significant development especially over recent years and have been extended to the α-arylation of sulfonyl C−H acids and nitroalkanes.

In 1984, Takahashi et al. synthesized a variety of alkyl arylcyanoacetates in modest-to-good yields by treatment of alkyl cyanoacetates with KO*t*-Bu in monoglyme, followed by addition of aryl iodides and a catalytic amount of $PdCl_2(PPh_3)_2$ (Scheme 73).[248]

Similar reaction conditions were subsequently employed for the arylation of ethyl cyanoacetate with dihaloarenes.[249]

Scheme 75. Pd-Catalyzed Intramolecular Arylation of β-Diketones 192 and 194

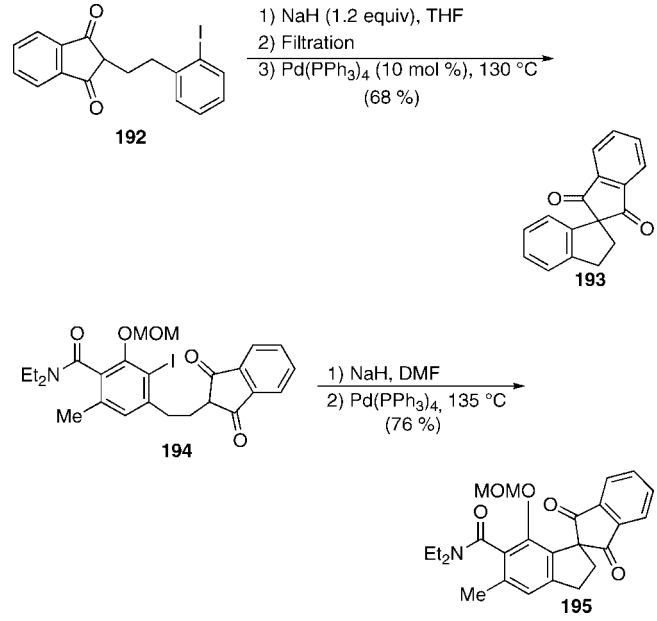
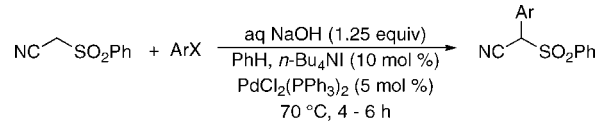
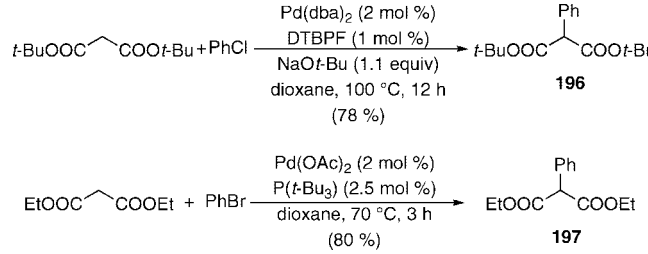


Table 67. Pd-Catalyzed Arylation of Phenylsulfonylacetonitrile under Phase-Transfer Conditions



entry	Ar	X	yield (%)
1	Ph	Br	72
2	Ph	I	90
3	4-MeC_6H_4	Br	70
4	4-MeC_6H_4	I	91
5	4-BrC_6H_4	Br	68
6	4-BrC_6H_4	I	87
7	2-naphthyl	Br	72
8	1-naphthyl	Br	69

Scheme 76. Pd-Catalyzed Synthesis of Dialkyl Phenyl Malonates 196 and 197

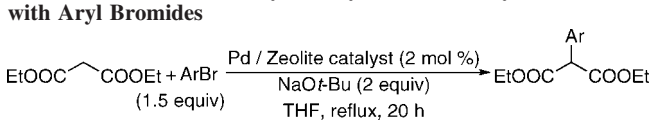


On the other hand, catalytic amounts of $PdCl_2(PPh_3)_2$ were also used to prepare arylmalonitriles in moderate-to-excellent yields by treatment of the sodium salt of malononitrile with aryl iodides in THF (Scheme 74).[250]

In 1987, Ciufolini and Browne synthesized the spyrocyclic derivative **193** by $Pd(PPh_3)_4$-catalyzed intramolecular arylation of β-diketone **192**,[251] and shortly afterward, compound **195** was similarly prepared in 76% yield from diketone **194**[252] (Scheme 75).

In 1993, α-aryl-α-cyanosulfones were prepared under mild conditions with good yields by $PdCl_2(PPh_3)_2$-catalyzed coupling reactions between α-cyanosulfones and aryl halides in benzene in the presence of aqueous NaOH and a phase-transfer catalyst (Table 67).[253]

Table 68. Pd/Zeolite-Catalyzed Arylation of Diethyl Malonate with Aryl Bromides



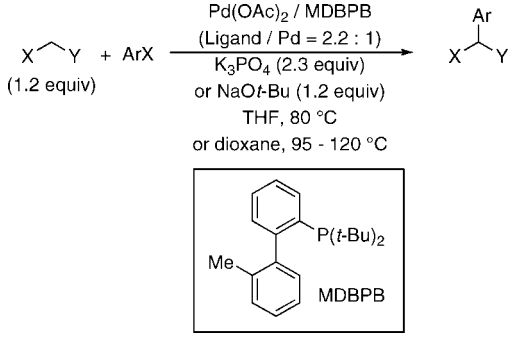
entry	catalyst	Ar	Yield (%)
1	$Pd(OAc)_2$−NaY	4-MeC_6H_4	29
2	$Pd(NH_3)_4$−NaY	4-MeC_6H_4	38
3	$Pd(NH_3)_4$−NaY	4-$MeOC_6H_4$	45
4	$Pd(NH_3)_4$−NaY	Ph	41
5	$Pd(NH_3)_4$−NaY	4-AcC_6H_4	60
6	$Pd(NH_3)_4$−NaY	4-FC_6H_4	50
7	$Pd(NH_3)_4$−NaY	4-$O_2NC_6H_4$	84

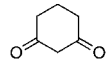
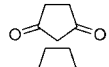
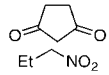
Since the late 1990s, much attention has particularly been turned to the development of efficient methods to prepare dialkyl arylmalonates. In 1999, Kawatsura and Hartwig reported that the use of either DTBPF or P(*t*-Bu)$_3$ in combination with $Pd(dba)_2$ and $Pd(OAc)_2$, respectively, allows mild arylation of dialkylmalonates.[51] Thus, reaction of chlorobenzene with di-*tert*-butyl malonate in dioxane in the presence of NaO*t*-Bu and a combination of DTBPF and $Pd(dba)_2$ as the catalyst precursor gave the required arylmalonate **196** in a high yield (Scheme 76).

However, the efficient synthesis of diethyl phenylmalonate **197** from diethyl malonate and bromobenzene was found to require the use of a combination of P(*t*-Bu)$_3$ and $Pd(OAc)_2$ as the catalyst precursor (Scheme 76).[51]

Catalytic quantities of {[$Pd(NH_3)_4$-NaY} or [$Pd(OAc)_2$-NaY] were used by Djakovitch and Köhler in 2000 for the highly selective monoarylation of diethyl malonate with different *para*-substituted aryl bromides (Table 68).[254] These heterogeneous catalysts could easily be separated from the reaction products and reused without a real loss in activity.[254,255]

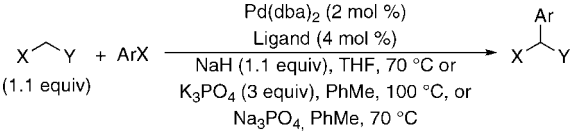
Table 69. $Pd(OAc)_2$/MDBPB-Catalyzed Arylation of Diethyl Malonate, 1,3-Diketones, and Nitroalkanes

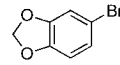
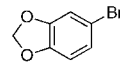


Entry	Activated Methylene Compound	ArX	Mol % Pd	Base	Solvent	Reaction time (h)	Yield (%)
1	EtOOC COOEt	4-*t*-BuC_6H_4Br	1.0	K_3PO_4	THF	10	92
2		3,5-$(Me)_2C_6H_3Br$	1.0	K_3PO_4	THF	15	84
3		3-$MeOOCC_6H_3Br$	1.0	K_3PO_4	dioxane	20	73
4		4-*t*-BuC_6H_4Br	1.0	K_3PO_4	THF	23	96
5	Et NO_2	4-MeC_6H_4Br	3.0	NaO*t*-Bu	dioxane	20	76
6[a]	Me NO_2	4-*t*-BuC_6H_4Br	3.0	NaO*t*-Bu	dioxane	22	80

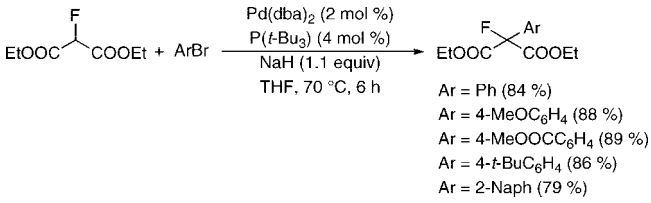
[a] 1.0 equiv of aryl halide, 2.0 equiv of nitroalkane, and 1.2 equiv of NaO*t*-Bu were used.

Table 70. Pd-Catalyzed Arylation Reactions of Malonates and Ethyl Cyanoacetate Involving the Use of P(*t*-Bu)$_3$, Q-Phos, or (1-Ad)P(*t*-Bu)$_2$ as the Supporting Ligand

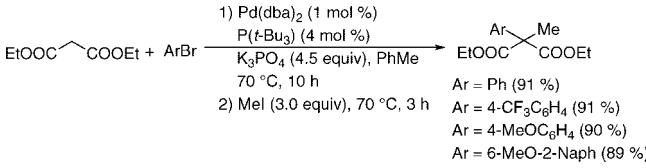


Entry	Activated Methylene Compound	ArX	Ligand	Base	Reaction time (h)	Yield (%)
1	EtOOC COOEt	PhBr	P(*t*-Bu)$_3$	NaH	1	89
2	EtOOC COOEt	2-$MeOC_6H_4Br$	P(*t*-Bu)$_3$	NaH	8	89
3	EtOOC COOEt	4-$MeOOCC_6H_4Br$	P(*t*-Bu)$_3$	NaH	3	91
4	EtOOC COOEt		Q-Phos		21	85
5	*t*-BuOOC COO*t*-Bu	4-$F_3CC_6H_4Br$	P(*t*-Bu)$_3$	K_3PO_4	6	88
6	*t*-BuOOC COO*t*-Bu		P(*t*-Bu)$_3$	NaH	6	87
7	*t*-BuOOC COO*t*-Bu	2-$MeOC_6H_4Br$	P(*t*-Bu)$_3$	NaH	12	86
8	EtOOC CN	2-$MeOC_6H_4Br$	P(*t*-Bu)$_3$	NaH	6	85
9	EtOOC CN	4-$PhOC_6H_4Br$	P(*t*-Bu)$_3$	Na_3PO_4	6	90
10	EtOOC CN	2-$MeOC_6H_4Cl$	Q-Phos	Na_3PO_4	6	81
11	EtOOC CN	4-$F_3CC_6H_4Cl$	(1-Ad)P(*t*-Bu)$_2$	K_3PO_4	81	86

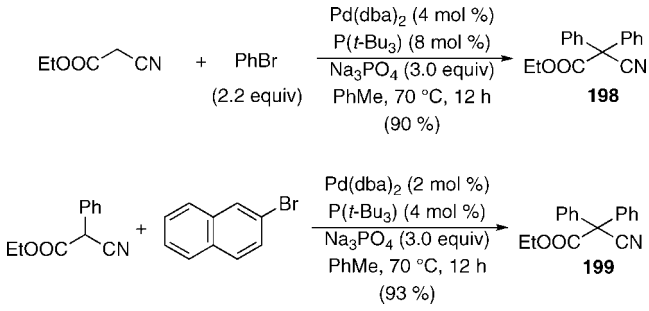
Scheme 77. Pd(dba)$_2$/P(*t*-Bu)$_3$-Catalyzed Arylation of Diethyl Fluoromalonate with Aryl Bromides



Scheme 78. One-Pot Synthesis of Diethyl 2-Aryl-2-methylmalonates



Scheme 79. Pd-Catalyzed Synthesis of Symmetrical and Unsymmetrical Ethyl Diarylcyanoacetates 198 and 199, Respectively



Nevertheless, they could not rival the best homogeneous catalysts developed by Hartwig[47,51,191] and Buchwald.[46,95]

On the contrary, a homogeneous catalyst system composed of a mixture of Pd(OAc)$_2$ and 2-methyl-2′-di-*tert*-butylphosphinobiphenyl (MDBPB) in a 2.2:1 molar ratio was employed by Buchwald et al. in 2000 to perform high-yielding arylation reactions of diethyl malonate, 1,3-diketones, and nitroalkanes with aryl bromides and chlorides in THF in the presence of K_3PO_4 as the base (Table 69).[54]

In 2002, the influence of various bases on yield and selectivity in the palladium-catalyzed α-arylation of diethyl malonate with chloro-, bromo-, and iodobenzene was investigated by Aremandia et al., and it was found that Ba(OH)$_2$ gives excellent results for reactions performed in DMA at 100 °C in the presence of 2 mol % Na_2PdCl_4.[256] The bases used were easily removed from the reaction medium by filtration.

In the same year, the α-monoarylation of diethyl malonate, di-*tert*-butyl malonate, and ethyl cyanoacetate with sterically hindered and unhindered aryl bromides and chlorides was performed in high yields by Beare and Hartwig using a catalyst system composed of Pd(dba)$_2$ and P(*t*-Bu)$_3$, Q-Phos, or (1-Ad)P(*t*-Bu)$_2$ as the supporting ligand.[257] Table 70 summarizes representative examples of these reactions.

Interestingly, the use of Q-Phos or (1-Ad)P(*t*-Bu)$_2$ allowed for the prevention of hydrodehalogenation of the aryl chlorides in the α-arylation of diethyl malonate. On the other hand, the catalyst system composed of Pd(dba)$_2$ and P(*t*-Bu)$_3$ exhibited a good activity toward the arylation of diethyl fluoromalonate with aryl bromides (Scheme 77).[257]

Unfortunately, the catalyst systems used in Table 69 did not enable the α-arylation of alkyl cyanoacetates with pyridyl

Scheme 80. Pd$_2$(dba)$_3$/Ligand 129-Catalyzed Arylation of Ethyl Cyanoacetate with Aryl Bromides[182] and Chlorides[184]

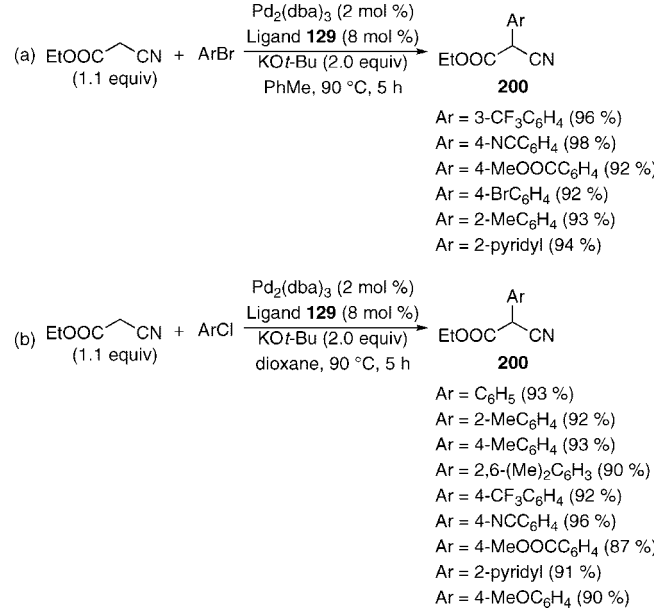
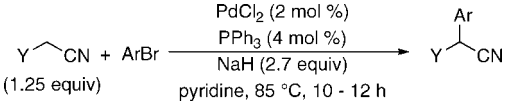


Table 71. PdCl$_2$/PPh$_3$-Catalyzed Coupling of Malononitrile and Ethyl Cyanoacetate with Aryl Bromides



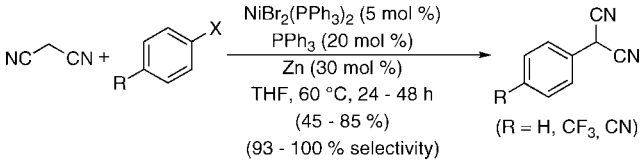
entry	Y	Ar	yield (%)
1	CN	Ph	88
2	COOEt	Ph	84
3	CN	2-MeC$_6$H$_4$	73
4	COOEt	2-MeC$_6$H$_4$	77
5	CN	4-MeOC$_6$H$_4$	72
6	COOEt	4-MeOC$_6$H$_4$	75
7	CN	4-FC$_6$H$_4$	73
8	COOEt	4-FC$_6$H$_4$	85
9	CN	1-naphthyl	82
10	COOEt	1-naphthyl	67
11	CN	2-MeOC$_6$H$_4$	75
12	COOEt	2-MeOC$_6$H$_4$	73

halides, halobenzonitriles, 4-haloacetophenones, 4-halobenzophenones, and methyl 4-halobenzoates as well as the coupling of aryl halides with dialkyl alkylmalonates and ethyl alkylcyanoacetates.[257] Nevertheless, Beare and Hartwig succeeded in performing a high-yielding one-pot preparation of diethyl 2-aryl-2-methylmalonates from diethyl malonate via sequential palladium-catalyzed arylation and alkylation reactions (Scheme 78).[257]

On the other hand, it was found that reaction of ethyl cyanoacetate with 2 equiv of aryl bromides in the presence of Na_3PO_4 as the base and catalytic quantities of Pd(dba)$_2$ and P(*t*-Bu)$_3$ furnishes symmetrical ethyl diarylcyanoacetates such as **198** in high yields (Scheme 79).[258]

Diarylation of ethyl cyanoacetate was also observed as a side-reaction in some palladium-catalyzed reactions with electron-poor aryl halides in which P(*t*-Bu)$_3$ or Q-Phos was used as the supporting ligand.[257] However, this side-reaction did not occur when the arylation of ethyl cyanoacetate was carried out using 0.9 equiv of alkyl bromides or chlorides, including electron-poor derivatives, in the presence of KO*t*-Bu as the base and a catalyst system composed of $Pd_2(dba)_3$ and bicyclic triaminophosphine **129** as the supporting

Scheme 81. Ni-Catalyzed Monoarylation of Malononitrile with Aryl Halides



Scheme 82. Pd/NHC-Catalyzed Arylation of Malononitrile with Aryl Chlorides and Bromides

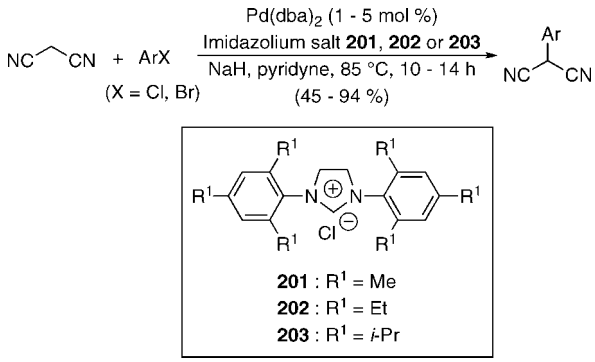
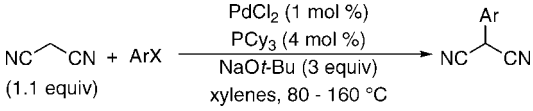


Table 72. $PdCl_2/PCy_3$-Catalyzed Coupling of Malononitrile with Aryl Halides



entry	ArX	reaction conditions (°C/h)	yield (%)
1	2,4,6-$(Et)_3C_6H_2Br$	160/20	92
2	2,4,6-$(Me)_3C_6H_2Br$	80/20	86
3	2,4,6-$(Et)_3C_6H_2Br$	8/20	58
4	3-$F_3CC_6H_4Br$	160/3.5	83
5	2-bromopyridine	160/2.2	94
6	4-$MeOC_6H_4Cl$	140/16	74
7	PhI	80/20	91
8	4-MeC_6H_4Cl	140/16	39
9	4-AcC_6H_4Br	160/4.4	
10	4-NCC_6H_4Br	160/20	15
11	4-$MeOC_6H_4Cl$	160/4	70
12[(a)]	4-ClC_6H_4Br	160/15	80

[(a)] No reaction of the Ar−Cl bond.

ligand.[183,184] Representative examples of these highly selective monoarylation reactions are shown in Scheme 80.

In 2003, a simple catalyst system composed of $PdCl_2$ and PPh_3 was systematically studied by Huang et al. in the cross-coupling reactions of ethyl cyanoacetate and malononitrile with aryl bromides in pyridine,[259] and it was found that this catalyst system is highly active to produce arylmalononitriles and ethyl arylcyanoacetates in good-to-excellent yields when electron-neutral, electron-rich, and electron-poor aryl bromides are used as arylating reagents and NaH is employed as the base (Table 71).[259]

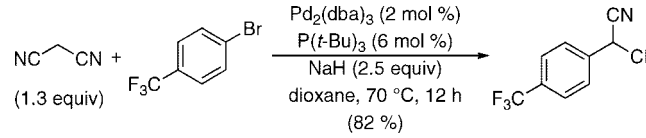
In the past decade, some other catalyst systems have been developed to achieve the selective monoarylation of malononitrile with aryl halides.[260−263] In 2000, Cristeau, Taillefer et al. described that $Ni(PPh_3)_3$, generated in situ from $NiBr_2(PPh_3)_2$, PPh_3, and Zn metal, allows arylation of malononitrile with iodobenzene and aryl bromides or chlorides bearing electron-withdrawing substituents in the presence of KO*t*-Bu as the base in good yields and selectivitites (Scheme 81).[260]

In 2002 and 2003, Huang et al. reported that malononitrile undergoes cross-coupling reactions with aryl chlorides and bromides in pyridine under the influence of catalyst systems obtained by a combination of $Pd(dba)_2$ and the NHC ligand derived from the reaction of imidazolium salt **201**, **202**, or **203** with NaH. Arylmalononitriles were so obtained in 45−94% yield (Scheme 82).[261] It was noticed that a higher loading of the catalyst system was required for reactions involving the use of aryl chlorides instead of the corresponding bromides and that the presence of the electron-donating methoxy group in 2-methoxyphenyl chloride led to a sharp decrease in the yield of the Pd/NHC-catalyzed reaction.[261]

In 2006, Schneider et al. developed a convenient and technically feasible method for the synthesis of hindered arylmalononitriles in high yields consisting of the reaction of malononitrile with aryl halides in xylene in the presence of NaO*t*-Bu and a catalyst system composed of $PdCl_2$ and PCy_3 (Table 72).[262] Remarkably, the arylation reaction involving the use of 2,6-diethyl-4-bromotoluene (entry 1, Table 72) could be carried out on a 100 kg scale, demonstrating that the method is easy to scale up for technical applications.[262]

Kashin et al. had previously reported that the arylation of malononitrile with 4-bromobenzotrifluoride can be achieved in high yield using 2.5 equiv of NaH in dioxane and a catalyst system composed of a mixture of $Pd_2(dba)_3 \cdot CHCl_3$ and P(*t*-Bu)$_3$ (ligand/Pd = 3:1) (Scheme 83).[263] The arylation

Scheme 83. $Pd_2(dba)_3/P(t\text{-}Bu)_3$-Catalyzed Coupling of Malononitrile with 4-Bromobenzotrifluoride



Scheme 84. Pd-Catalyzed Intramolecular Arylation of *β*-Ketoester 204

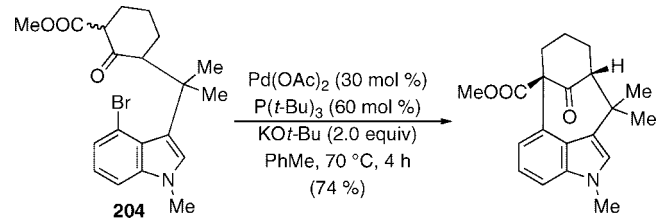
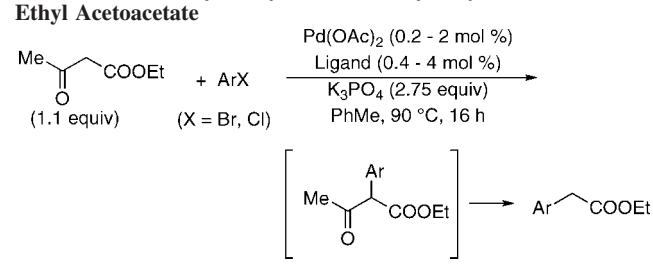
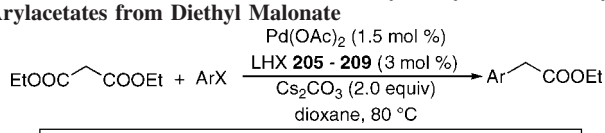


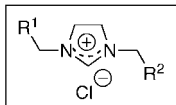
Table 73. Pd-Catalyzed Synthesis of Ethyl Arylacetates from Ethyl Acetoacetate



entry	ArX	mol % $Pd(OAc)_2$	ligand (mol %)	yield (%)
1	PhBr	1	JohnPhos (2)	56
2	PhBr	2	JohnPhos (4)	68
3	PhBr	2	MDBPB (4)	93
4	PhCl	0.2	MDBPB (0.4)	49
5	PhCl	0.5	MDBPB (1)	75
6	4-$MeOC_6H_4Br$	1	HP(*t*-Bu)$_3BF_4$ (2)	40
7	4-AcC_6H_4Br	1	HP(*t*-Bu)$_3BF_4$ (2)	30
8	1-bromonapthalene	1	HP(*t*-Bu)$_3BF_4$ (2)	15
9	PhBr	1	HP(*t*-Bu)$_3BF_4$ (2)	55
10	4-$MeOC_6H_4Cl$	0.5	MDBPB (1)	75

Table 74. $Pd(OAc)_2$/LHX/Cs_2CO_3−Catalyzed Synthesis of Ethyl Arylacetates from Diethyl Malonate





205 : $R^1 = R^2 = 2,4,6\text{-}(Me)_3C_6H_2$
206 : $R^1 = R^2 = 3,4,5\text{-}(MeO)_3C_6H_2$
207 : $R^1 = R^2 = 2,4,6\text{-}(MeO)_3C_6H_2$
208 : $R^1 = MeOCH_2$; $R^2 = 2,4,6\text{-}(Me)_3C_6H_2$
209 : $R^1 = EtOCH_2$; $R^2 = 2,4,6\text{-}(Me)_3C_6H_2$

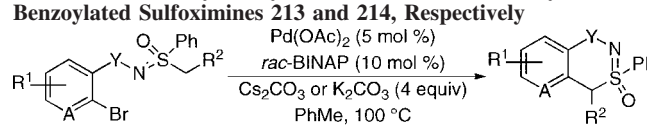
entry	ArX	LHX	reaction time (h)	yield (%)
1	PhI	**205**	24	93
2	PhI	**206**	24	91
3	PhI	**207**	24	89
4	PhI	**208**	24	96
5	PhI	**209**	24	95
6	4-$MeOOCC_6H_4Br$	**208**	24	91
7	4-$O_2NC_6H_4Br$	**205**	24	87
8	4−$OHCC_6H_4Br$	**209**	24	91
9	4-AcC_6H_4Cl	**205**	24	92
10	PhBr	**208**	48	87
11	4-$MeOC_6H_4Cl$	**208**	24	87
12	2,4,6-$(Me)_3C_6H_4Br$	**209**	24	95

reactions of malononitrile and other C−H acids, including certain sulfones and ethyl cyanoacetate, were found to proceed smoothly provided that a base stronger than the initial carbanion was present in the reaction mixture. In fact, in the absence of this type of base, the reactions did not proceed at all.[263]

An interesting example of palladium-catalyzed intramolecular arylation of a β-ketoester was reported by Rawal et al. in 2005.[264] The reaction (Scheme 84), which was used as a key step in an efficient convergent synthesis of the bicyclo[4.3.1]decane ring system of welwitindolinones, a new class of indole alkaloids, gave the best result when $Pd(OAc)_2$, the P(*t*-Bu)$_3$ ligand, and the base were premixed at room temperature, followed by addition of a toluene solution of substrate **204**.[264]

Intriguing examples of syntheses of ethyl arylacetates via palladium-catalyzed intermolecular arylation of ethyl acetoacetate with aryl bromides and chlorides, followed by deacylation under the reaction conditions, were described by Parkinson et al. in 2004.[265] As expected, the deacylation step proved to be dependent on the base concentration. Table 73 illustrates that the bulky and electron-rich phosphine MDBPB was the ligand of choice for the efficient synthesis of ethyl phenylacetate from ethyl acetoacetate and chloro- or bromobenzene in toluene using K_3PO_4 as the base. Remarkably, no arylation of ethyl phenylacetate was observed employing this base, while the use of NaO*t*-Bu under identical reaction conditions furnished ethyl diphenylacetate in a good yield.[265]

Table 75. Pd-Catalyzed Cyclization Reactions of Benzylated and Benzoylated Sulfoximines 213 and 214, Respectively



213 : Y = CH_2
214 : Y = CO
215 : Y = CH_2
216 : Y = CO

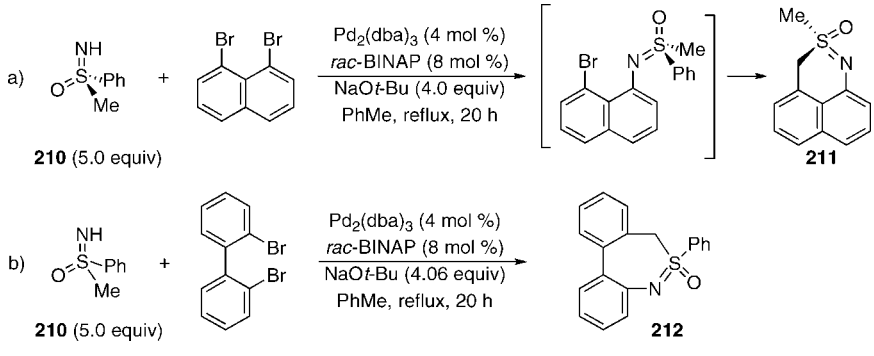
	substrate						
entry	Y	A	R^1	R^2	base	reaction time (h)	yield (%)
1	CH_2	CH	H	H	Cs_2CO_3	16	93
2	CH_2	CH	H	H	K_2CO_3	16	88
3	CH_2	CH	5-NO_2	H	K_2CO_3	16	83
4	CH_2	CH	5-MeO	H	Cs_2CO_3	72	91
5	CH_2	CH	H	*n*-Bu	Cs_2CO_3	16	40
6	CO	CH	H	H	K_2CO_3	16	62
7	CO	CH	5-NO_2	H	K_2CO_3	16	0
8	CO	CH	5-MeO	H	K_2CO_3	16	74
9	CH_2	N	H	H	Cs_2CO_3	16	92
10	CO	N	H	H	Cs_2CO_3	72	16

As previously reported in subsection 9.1, a similar C-arylation followed by an in situ deacylation reaction was recently observed in the copper-catalyzed arylation of ethyl acetoacetate with aryl iodides in DMSO in the presence of K_2CO_3 as the base under ligandless conditions.[246]

It should be noted that ethyl arylacetates have also been prepared by palladium-catalyzed arylation of diethyl malonate with aryl halides, followed by in situ dealkoxycarbonylation.[266] In fact, Özdemir et al. reported that imidazolium salts **205**−**209** are precursors to the most efficient NHC supporting ligands and furnish ethyl arylacetates in high yields also when the Pd-catalyzed reactions are run under an oxygen atmosphere.[266] Representative examples of syntheses of ethyl arylacetates from diethyl malonate and aryl halides in the presence of Cs_2CO_3 as the base and catalytic quantities of $Pd(OAc)_2$ and these 1,3-bis(alkyl)imidazolium halides (LHX) are shown in Table 74.

Recently, attention has also been directed to investigate the palladium-catalyzed α-arylation of sulfoximines,[267,268] a class of compounds that has found widespread interest in the chemical community.[269] In 2002, Bolm et al. reported that the $Pd_2(dba)_3$/*rac*-BINAP-catalyzed reaction between dibromoarenes and sulfoximines in the presence of NaO*t*-Bu as base affords 6- to 8-membered heterocycles in excellent yields.[267a] In fact, the coupling of 1,8-dibromonaphthalene with a molar excess of sulfoximine **210** did not give the expected C_2-symmetric bissulfoximine but furnished compound **211** instead in 99% yield (Scheme 85, eq a).

Scheme 85. Pd-Catalyzed Synthesis of Heterocycles 211 and 212 from Sulfoximine 210



Scheme 86. Synthesis of *N*-Benzoyl Benzyl Sulfoximines 219

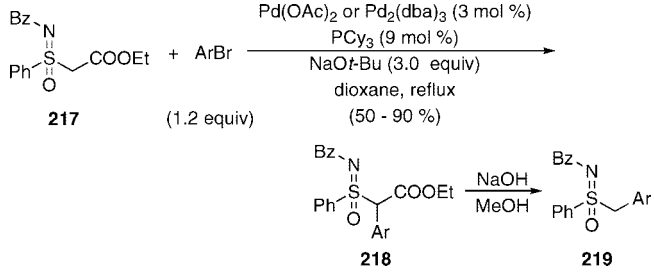
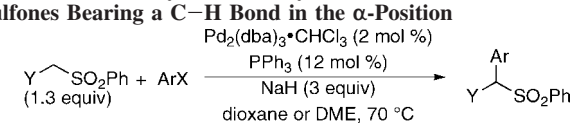


Table 76. Pd-Catalyzed Monoarylation of Functionalized Sulfones Bearing a C−H Bond in the α-Position



entry	Y	ArX	solvent	reaction time (h)	yield (%)
1	SO_2Ph	4-$CF_3C_6H_4Br$	dioxane	3	85
2	SO_2Ph	1-bromonaphthalene	dioxane	6	77
3	SO_2Ph	3-bromoquinoline	dioxane	6	76
4	COOEt	4-MeC_6H_4Br	dioxane	8	91
5	COOEt	4-FC_6H_4Br	dioxane	4	64
6	COOEt	3-bromopyridine	dioxane	6	51
7	CN	4-$CF_3C_6H_4Br$	DME	4.5	30
8	NO_2	4-$CF_3C_6H_4Br$	DME	7.1	72
9	COOEt	4-$MeOC_6H_4I$	dioxane	3	71
10	COOEt	4-$CF_3C_6H_4Cl$	dioxane	27	25
11	SO_2F	3-FC_6H_4Br	dioxane	4	81
12	Bz	4-$CF_3C_6H_4Br$	DME	4.5	30
13	C_6F_5	4-$CF_3C_6H_4Br$	DME	5	0

Analogously, the $Pd_2(dba)_3$/*rac*-BINAP-catalyzed reaction of **210** with 2, 2′-dibromobiphenyl gave **212** in 98% yield (Scheme 85, eq b).

Mechanistic studies revealed that these transformations involve two steps that occur sequentially and without detectable racemization at the stereogenic sulfur atom. First, the sulfoximine undergoes a palladium-catalyzed intermolecular *N*-arylation reaction that then gives the resulting heterocycle by a Pd-catalyzed α-arylation, which involves the acidic protons of the sulfoximine methyl group.[267a]

Bolm et al. also established that sulfoximine derivatives such as *N*-(2-bromobenzyl)- and *N*-(2-bromobenzoyl)sulfoximines **213** and **214**, respectively, which lack the *N*-arylsulfoximine nitrogen bond, are able to undergo palladium-catalyzed cyclization to afford the six-membered heterocycles **215** and **216**, respectively, in moderate-to-good yields.[267b] In both cases, the reactions were performed in the presence of a base such as K_2CO_3 or Cs_2CO_3 and catalytic amounts of $Pd(OAc)_2$ and *rac*-BINAP. Representative examples of these reactions are illustrated in Table 75.

Finally, in 2005, Cho and Bolm investigated the Pd-catalyzed α-arylation of *N*-benzoyl protected sulfoximine ethyl ester **217** with a large variety of electron-poor, electron-rich, and electron-neutral aryl bromides and observed that the reaction, when performed in refluxing dioxane in the presence of NaO*t*-Bu as base and catalytic amounts of PCy_3 and $Pd(OAc)_2$ or $Pd_2(dba)_3$, leads to the α-arylated products **218** in good-to-excellent yields. Interestingly, these derivatives can easily be converted to the corresponding *N*-protected benzyl phenylsulfoximines **219** by treatment with NaOH in methanol (Scheme 86).[268]

In recent years, several examples of intermolecular palladium-catalyzed α-arylation reactions of sulfonyl C−H acids with aryl halides have also been described.[270−273] In 2002, Beletskaya et al. reported that functionalized sulfones bearing a C−H bond at the α-position are able to undergo arylation with (hetero)aryl halides in dioxane or DME in the presence of NaH as the base and catalytic quantities of $Pd_2(dba)_3$ and PPh_3 to give monoarylated products in high yields (Table 76).[270]

Remarkable limitations of the reactions were as follows: (i) A side-process resulting in aryl halides reduction to the corresponding arenes accompanied the reactions, reducing the yield of the required arylated products. (ii) The reactions did not proceed when BuLi was used as the base. (iii) Weak sulfonyl C−H acids, being precursors to highly nucleophilic carbanions, proved unreactive, and the reactions proceeded only in the case of sulfonyl C−H acids possessing pK_a values in DMSO in the range 7.1−12.2.[270,273]

A protocol similar to that illustrated in Table 76 was used by Kashin et al. in 2004 for the α-arylation of benzyl trifluoromethyl sulfones with electron-poor aryl bromides (Scheme 87).[273]

One year later, it was demonstrated that methanesulfonamides **220** can undergo α-arylation by treatment with aryl bromides in toluene in the presence of NaO*t*-Bu as the base and catalytic amounts of $Pd(OAc)_2$ and PPh_3.[271] The required monoarylation products **221** were so obtained in moderate yields, but diarylation to give compounds **222** in varying amounts was also observed (Table 77).[271]

Scheme 87. α-Arylation of Benzyl Trifluoromethyl Sulfones

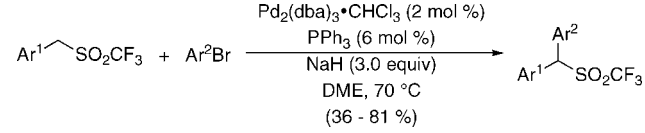
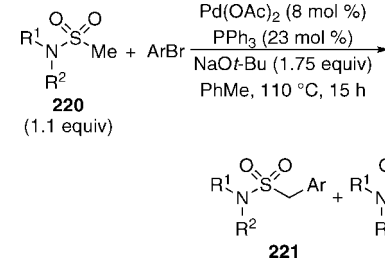


Table 77. α-Arylation of *N*,*N*-Disubstituted Methanesulfonamides with Aryl Bromides



entry	R^1	R^2	Ar	yield (%) of **221**	yield (%) of **222**
1	*i*-Pr	*i*-Pr	Ph	34	14
2	*i*-Pr	*i*-Pr	2-MeC_6H_4	50	10
3	*i*-Pr	*i*-Pr	4-$MeOC_6H_4$	52	2
4	$(CH_2)_4$	Ph	35	6	
5	$(CH_2)-O-(CH_2)_2$	Ph	60	5	
6	Me	Ph	Ph	34	4

Scheme 88. Synthesis of Benzylic Sulfonamides 225 via α-Arylation of Sulfonamide 223

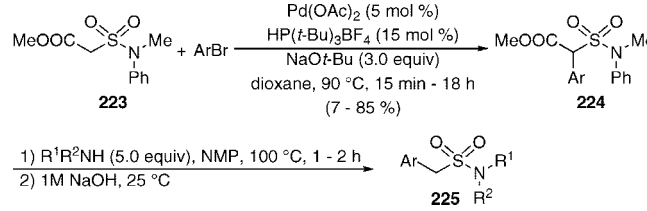
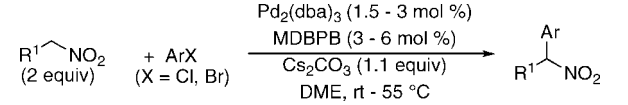
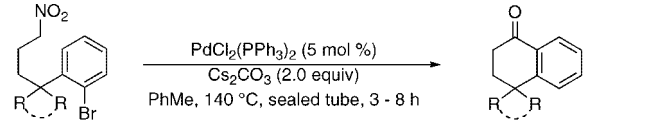


Table 78. Pd-Catalyzed Intermolecular Monoarylation Reactions of Nitroalkanes with Aryl Halides



entry	R^1	ArX	mol % of Pd	reaction temp. (°C)	yield (%)
1	Me	PhBr	3	50	90
2	Me	4-$MeOOCC_6H_4Br$	2	50	85
3	Me	3-*t*-$BuOOCC_6H_4Br$	3	50	82
4	Me	3-$Me_2NC_6H_4Br$	1.5	50	98
5	Et	4-$MeOC_6H_4Cl$	1.5	50	68
6	*n*-Pent	4-*t*-BuC_6H_4Br	2	50	92
7	CH_2=$CH(CH_2)_3$	4-AcC_6H_4Br	3	rt	64
8	$MeOOC(CH_2)_2$	4-$MeOOCC_6H_4Cl$	5	50	67
9	$MeOOC(CH_2)_2$	3-$Me_2NC_6H_4Br$	5	50	75
10	$MeOOC(CH_2)_2$	2-bromonaphthalene	5	50	78
11	Et	4-AcC_6H_4Br	3	45	80
12	Me	3-*t*-$BuOOCC_6H_4Br$	3	50	82
13	Et	3-$MeOOCC_6H_4Cl$	1.5	55	65
14	Et	3-AcC_6H_4Br	3	45	63

Scheme 89. Synthesis of Bicyclic Tetralones 227 and 228



226 : R = H
227 : R-R = $O(CH_2)_2O$

228 : R = H (59 %)
229 : R-R = $O(CH_2)_2O$ (46 %)

Other byproducts frequently found in the final reaction mixtures were the biphenyl derivatives derived from the aryl bromides used as arylating reagents.

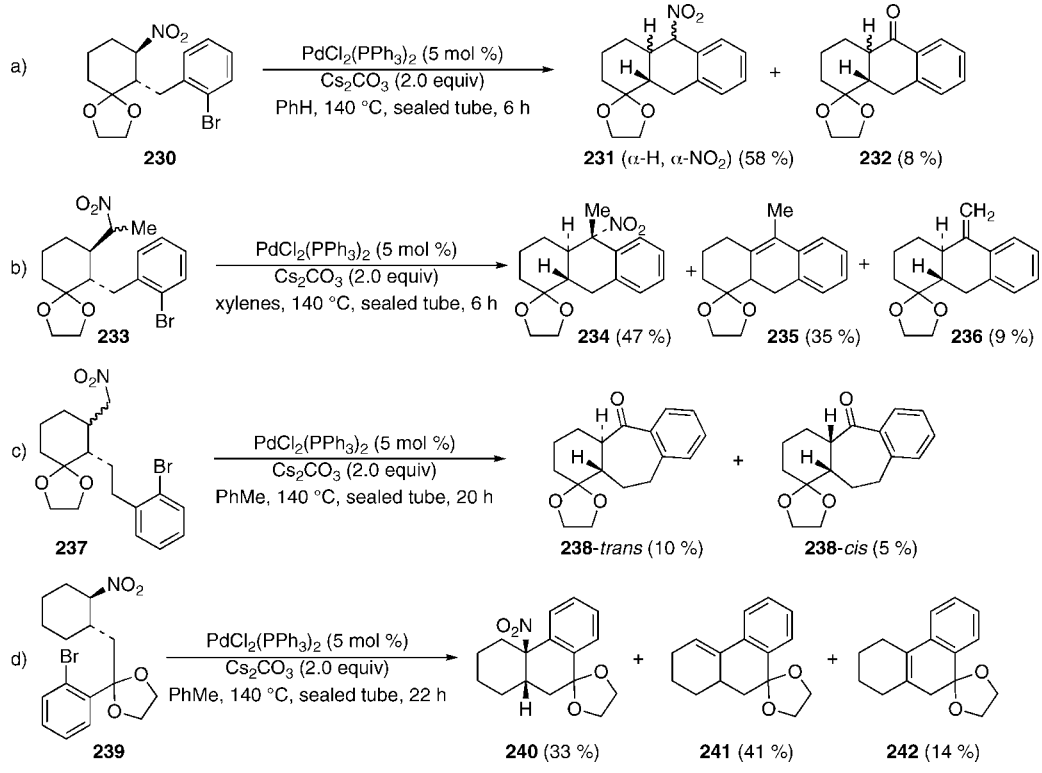
More recently, an efficient two-step strategy to access diversely functionalized benzylic sulfonamides, in which the first step involves the palladium-catalyzed α-arylation of sulfonamide **223** with aryl bromides, has been developed by Northrup et al.[272] These authors found that P(*t*-Bu)$_3$ was the supporting ligand of choice for the preparation of α-arylated sulfonamides **224** from **223** in low-to-good yields. Benzylic sulfonamides **225** were then prepared by a metathesis reaction of compounds **224** with diverse amines followed by saponification (Scheme 88).[272] Importantly, the α-arylation reaction was tolerant of various functionalities including nitriles, esters, and ketones. Moreover, the couplings of chloro-substituted aryl bromides proved to be highly halogen-selective, exclusively furnishing chloro-arylated sulfonamides in good yields.[272]

At the end of this subsection we wish also to mention that, over recent years, the α-arylation chemistry involving substrates bearing activated sp^3-hybridized C−H bonds has been expanded to include nitroalkanes.[45b,128,274] The first intermolecular version of this reaction was described by Vogl and Buchwald in 2002, who found that substituted aryl bromides as well as aryl chlorides can efficiently be coupled with a variety of nitroalkanes in DME in the presence of Cs_2CO_3 as the base and a catalytic system composed of $Pd_2(dba)_3$ and MDBPB to selectively yield monoarylated nitroalkanes in good-to-excellent yields.[274] Several representative examples of these reactions illustrating the ability of the method to tolerate a number of functional groups are reported in Table 78.

The intramolecular version of the α-arylation of properly designed substrates bearing a nitro group was investigated by Muratake et al.[45b,c,128] In 2004, in a conclusive paper, these authors reported that cyclization of compounds **226** and **227**, which are substrates with high stereochemical flexibility, in the presence of Cs_2CO_3 and a catalytic amount of $PdCl_2(PPh_3)_2$ produces bicyclic α-tetralones **228** and **229**, respectively, in moderate yields (Scheme 89).[45c]

In contrast, when similar experimental conditions were employed for cyclization of the stereochemically more restricted substrates **229** and **232**, tricyclic products were

Scheme 90. Pd-Catalyzed Synthesis of Tricyclic Derivatives by Intramolecular Arylation of Properly Designed Nitro Derivatives



obtained in high yields (Scheme 90).[45c] Specifically, a mixture of compounds **231** and **232** was obtained from **230** (Scheme 87, eq a), and cyclization of **233** produced compounds **234**, **235**, and **236** (Scheme 90, eq b). On the other hand, a mixture of stereoisomeric compounds *cis*- and *trans*-**238** was obtained from **237**, but cyclization of **239** gave a mixture of compounds **240**, **241**, and **242** in which the first two substances were the main components (Scheme 90, eqs c and d, respectively). The formation of the ketone derivatives **242**, *cis*-**238**, and *trans*-**238** was explained considering that the cyclization products bearing a secondary nitro group partly undergo a Nef reaction[275] in the presence of an excess of Cs_2CO_3 and a saturated aqueous NH_4Cl solution or an aqueous solution of citric acid used for quenching the reaction.

On the other hand, formation of styrene-type products such as **235**, **236**, **241**, and **242** was rationalized supposing an elimination reaction involving the nitro group present in compounds **234** and **240**.[45c]

10. Conclusions

In this review, we have highlighted the use of transition metal-catalyzed arylation reactions of substrates with activated sp^3-hybridized C−H bonds and some of their synthetic equivalents with aryl halides and pseudohalides as a route of paramount importance toward the formation of alkyl−aryl bonds in the α-position of electron-withdrawing groups including keto, formyl, alkoxycarbonyl, cyano, nitro, sulfoximino, and sulfonyl groups. Over the last few years, this methodology that avoids the preparation and use of organometallic reagents, exploits a broad scope and high functional group tolerance, and allows access to compounds for which conventional synthetic procedures would consist of many tedious and costly steps has evolved into a powerful synthetic tool for the efficient, straightforward, regio- and chemoselective preparation of fine chemicals including pharmacologically active compounds, their synthetic precursors, and some interesting naturally occurring substances. It can also be expected that the application of this cost-effective and environmentally attractive methodology will gain increasing importance in the near future.

Palladium and copper have been the transition metal components of the catalyst systems used in most direct α-arylation reactions, but some very interesting nickel-catalyzed arylations have also been described. However, the high toxicity of Ni catalysts can represent a significant limitation to the use of Ni-catalyzed reactions in industrial applications.

Direct arylations performed in the presence of Pd-catalysts have been particularly investigated, and on the basis of the very important contributions by Miura's, Buchwald's, and Hartwig's research groups, it is now possible to achieve some palladium-catalyzed reactions at room temperature, the use of base-sensitive substrates, and the implementation of highly enantioselective transformations. Nevertheless, it must be pointed out that most of the direct palladium-catalyzed α-arylations of substrates with activated sp^3-hybridized C−H bonds in the α-position, on a par with several protocols developed in recent years for (hetero)aryl−(hetero)aryl bond-forming reactions that involve palladium-catalyzed couplings of (hetero)aryl halides with (hetero)arenes[276] or regard palladium- or palladium/copper-catalyzed decarboxylative cross-coupling reactions of (hetero)aryl iodides with (hetero)arylcarboxylic acids,[277] suffer from problems due to the high catalyst loadings, the high current cost of Pd, and the use of expensive and patented phosphine ligands, which are frequently required at present as catalyst components. Consequently, in order that the palladium-catalyzed alkyl−aryl bond-forming reactions via direct arylation become attractive procedures to be used in crucial steps of commercial production processes, studies aimed at developing more practical, cost-saving, and environmentally benign procedures that involve either very low loadings of air-stable, robust catalyst systems composed of well-defined Pd-complexes with inexpensive ligands or ligandless conditions should be intensified. Ligand-free catalysis in particular offers several advantages that include reduced costs and an easier workup.

In contrast, application for industrial-scale synthesis can already be anticipated for some copper-catalyzed direct arylations of substrates with acidic sp^3-hybridized C−H bonds. In fact, CuI, which is frequently used as a component of catalyst systems for these reactions, is an air-stable salt. In addition, even though the copper-catalyzed arylations require at present high catalyst loadings, they involve the use of inexpensive ligands that can be easily removed from the reaction products. Finally, it should be taken into account that the cost of copper, which is a metal of common occurrence, also defined as a base metal,[278] is significantly lower than that of palladium. In addition, copper can be more easily removed than residual palladium from polar reaction products, particularly in the late stages of the synthesis of drug substances.[279,280] Nevertheless, the palladium-catalyzed arylation reaction of substrates with activated sp^3-hybridized C−H bonds still represents a thriving research area, and very recently, the following major developments have appeared.

Asymmetric versions of palladium-catalyzed intramolecular arylation reactions both of amides in the presence of chiral *N*-heterocyclic carbene ligands to give chiral 3-alkoxy- or 3-aminooxindoles[281] and aldehydes using axially chiral ligands to give α-arylated aldehydes in high yields and enantioselectivities[282] have been reported.

An improved protocol for the palladium-catalyzed intermolecular arylation of aldehydes with aryl halides including challenging electron-rich aryl bromides[283a] has been described. The coupling of electron-rich aryl bromides was better carried out with $Pd(OAc)_2$ as the palladium precursor and SPhos or QPhos as the ligand. On the other hand, the recently developed one-component XPhos precatalyst[283b] was found to be optimal for electron-rich aryl chlorides under reaction conditions identical to those using unbranched aryl aldehydes.[283a]

Benzofurans have been prepared in moderate-to-excellent yields via a one-pot process that utilizes a $Pd(OAc)_2$/*rac*-DTBPB-catalyzed enolate arylation.[284] The method has been used in a key step of the synthesis of the natural product eupomatenoid 6.[284]

An array of substituted isoquinolin-1(2*H*)-ones have been synthesized in moderate yields by a $Pd(OAc)_2$/tri(2,6-dimethoxyphenyl)phosphine-catalyzed cyclization of diethyl (2-iodoaryl)malonates with imidoyl chlorides and carbon monoxide. It has been suggested that the first intermediates of this one-pot process are obtained by α-arylation of diethyl (2-iodoaryl)malonates with imidoyl chlorides.[285]

A new ligand, diphenylmethylcyclopropylphosphine, has successfully been used in the palladium-catalyzed α-arylation of ketones with aryl chlorides.[286] An asymmetric coupling between 2-methylindan-1-one and anisyl chloride has also

been tested, giving 41% ee and 80% yield with 1 mol % palladium.[286]

The bulky and electron-rich MOP-type phosphine ligand 2-di(*tert*-butyl)phosphino-2′-isopropyloxy-1,1′-binaphthyl has been shown to exhibit good catalytic activity in palladium-catalyzed α-arylation of 1,3-dicarbonyl compounds.[287]

β-(2-Iodoanilino) carboxamides have been found to undergo $Pd(PPh_3)_4$-catalyzed intramolecular α-arylation in the presence of large molar excesses of phenol and KO-*t*Bu in refluxing THF.[288] However, *β*-(2-iodoanilino) carboxamides undergo intramolecular acylation when treated with K_3PO_4 and Et_3N in toluene solution at 110 °C in the presence of 20 mol % of $Pd(PPh_3)_4$.[288]

N-Heterocyclic carbene ligands derived from C_2-symmetric diamines with naphthyl side-chains have been recently introduced as chiral monodentate ligands, and their palladium complexes (NHC)Pd(cin)Cl (cin = cinnamyl) have been prepared.[289] These compounds exist as a mixture of diastereoisomers, and the palladium complexes have been successfully separated and their absolute stereochemistry has been established. It has been shown that, when used in the asymmetric intramolecular α-arylation of carboxyamides, oxindoles with quaternary carbon stereocenters can be obtained in high yield and selectivity when correctly matching the chirality of the NHC complexes.[289]

Niwa, Yorimitsu, and Oshima have developed an effective catalyst system consisting of a mixture of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and $P(c\text{-}C_6H_{13})_3$ for the direct arylation of benzyl sulfones with aryl halides.[290] The catalytic reaction provides a facile route to diarylmethyl sulfones.[290] Yorimitsu, Oshima et al. have also described that *N*-benzylxanthone imines undergo $[PdCl(\eta^3\text{-}C_3H_5)]_2/P(c\text{-}C_6H_{13})_3$-catalyzed arylation at the aminated benzylic positions with aryl chlorides in the presence of cesium hydroxide, yielding the corresponding benzhydrylamine derivatives.[291]

The first catalytic method for the high-yielding asymmetric palladium-catalyzed intramolecular α-arylation of α-branched aldehydes with high enantioselectivities has been published by Garcia-Fortanet and Buchwald in October 2008.[292] The reactions were perfomed in the presence of catalytic amounts of $Pd(OAc)_2$ and the tetrafluoroborate salt of a homochiral phospanyloxazoline-based ligand in *t*-BuOH at 80 °C in the presence of Cs_2CO_3 as the base.[292]

An efficient approach to valuable quaternary 3-aminooxindoles, which involves the microwave-assisted $Pd(OAc)_2/HPCy_3BF_4$-catalyzed intramolecular arylation of enolates of substituted amino acids, has been described by Marsden et al.[293] They have found that the cyclization of *N*-indole-substituted substrates is accompanied by direct C−H arylation of the indole, leading to indolofused benzodiazepines.[293]

A new method for the highly diastereoselective $Pd(OAc)_2/P(t\text{-}Bu)_3 \cdot HBF_4$-catalyzed α-arylation of (2*S*,5*S*)-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one, easily obtained from (*S*)-mandelic acid, with aryl and heteroaryl bromides in toluene at room temperature in the presence of LHMDS as the base has been recently described by Jansat et al.[294]

On the other hand, Guo et al. have reported that α-fluoro-α-arylketones can be synthesized by palladium-catalyzed cross-coupling of aryl bromides with either α-fluoroketones or their corresponding silyl enol ethers.[295] The arylation reactions of α-fluoroketones require the use of K−O*t*-Bu as the base, but under these conditions, the presence of a base-sensitive functional group is not compatible. However, good functional group tolerance can be achieved when the anionic coupling moieties are generated from the silyl enol ethers obtained by reaction of α-fluoroketones with tetrabutylammonium(triphenylsilyl)difluorosilicate as the fluoride source.[295]

An intramolecular $Pd(OAc)_2/P(c\text{-}C_6H_{13})_2$-catalyzed α-arylation reaction has been used by Pfefferkorn and Choi for the synthesis of 1,1′-*H*-spiro(indoline-3,3′-piperidine) from a suitable functionalized *o*-bromoanilide in a mixture of dioxane and THF at 85 °C in the presence of K−O*t*Bu as the base.[296]

Barluenga et al. have reported a new modular synthesis of indoles from imines and *o*-dihalobenzenes or *o*-chloroarylsulfinates.[297] The cascade reaction involves two palladium-catalyzed processes, an imine α-arylation followed by an intramolecular C−N bond-forming reaction, both promoted by the same palladium catalyst. Remarkably, the reaction with 1,2-dibromobenzene allows the introduction of aryl, vinyl, and alkyl substituents at different positions of the five-membered ring of the indole.[297]

A telescoped sequence involving $Pd(OAc)_2$-catalyzed intramolecular enolate arylation followed by an in situ Horner−Wadsworth−Emmons olefination has been developed by Taylor et al. to provide rapid access to 3-alkenyloxindoles from readily available bromoanilines and aromatic, heteroaromatic, and aliphatic aldehydes.[298] This one-pot process is greatly accelerated by microwaves and proceeds with low loading of $Pd(OAc)_2$ (0.2−1.0 mol %).[298]

A mild, racemization-free $Pd(OAc)_2$/2-di-*tert*-butylphosphino-2′,4′,6′-trisopropylbiphenyl-catalyzed α-arylation of homochiral tetramic acids (2,4-pyrrolidinediones) with aryl chlorides, bromides, or triflates in THF in the presence of K_2CO_3 or K_3PO_4 as the base has been developed by Tanner et al.[299] However, aryl iodides and tosylates as well as *o*-substituted aryl chlorides do not work in this process.[299]

Finally, it should be noted that the copper-catalyzed direct arylation of substrates with activated sp^3-hybridized C−H bonds is still an active research area. Recently, substituted homophthalimides have been synthesized in good yields by Ma and co-workers via CuI-catalyzed reaction of 2-bromobenzamides and at 90 °C in *i*-PrOH in the presence of Cs_2CO_3 as the base under ligandless conditions.[300] This synthesis involves a cascade coupling/condensation process, which allows assembly of a wide range of substituted homophthalimides by varying *β*-ketoesters and 2-bromobenzamides.

Fu, Jiang et al. have developed a simple and efficient CuI-catalyzed method for the synthesis of 3,4-disubstituted isoquinolin-1(2*H*)-one derivatives via cascade reactions of 2-halobenzamides with *β*-ketoesters under mild conditions without addition of any ligand or additive.[301]

Very recently, an excellent account concerning the main results obtained in Ma's laboratory on the copper/amino acid-catalyzed cross-coupling of aryl and vinyl halides with nucleophiles has been published.[302]

11. Acknowledgments

We thank the University of Pisa for financial support.

12. References

(1) For leading references, see: (a) Morrell, D. C.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. (c) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221. (d) Peng, S.; Qing, F. L.; Li, Y.-Q.; Hu, C.-M. *J. Org. Chem.* **2000**, *65*, 694. (e) Gray, M.; Andrews, I. P.; Hook, D. F.;

Kitteringham, J.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 6237. (f) Zou, G.; Reddy, Y. K.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 7213. (g) Negishi, E.-i.; Gagneur, S. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i. Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 597; (h) Marriere, E.; Rouden, J.; Tadino, V.; Lasne, M.-C. *Org. Lett.* **2000**, *2*, 1121. (i) Gagneur, S.; Montchamp, J.-L.; Negishi, E.-i *Organometallics* **2000**, *19*, 2417. (j) Yus, M.; Gomis, J. *Eur. J. Org. Chem.* **2002**, 1989. (k) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609. (l) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (m) Molander, G. A.; Yun, C.-S. *Tetrahedron* **2002**, *58*, 1465. (n) Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* **2004**, *60*, 3813. (o) Herve, A.; Rodriguez, A. L.; Fouquet, E. *J. Org. Chem.* **2005**, *70*, 1953. (p) Walters, I. A. S. *Tetrahedron Lett.* **2005**, *47*, 341. (q) Cho, C.-H.; Sun, M.; Park, K. *Bull. Korean Chem. Soc.* **2005**, *26*, 1410. (r) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538. (s) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, 624. (t) Rueping, M.; Ieawsuwan, W. *Synlett* **2007**, 247. (u) Luo, X.; Zhang, H.; Duan, H.; Liu, Q.; Zhu, L.; Zhang, T.; Lei, A. *Org. Lett.* **2007**, *9*, 4571. (v) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013. (w) Klapars, A.; Campos, K. R.; Waldman, J. H.; Zewge, D.; Dormer, P. G.; Chen, C. *J. Org. Chem.* **2008**, *73*, 4986. (x) Coldham, I.; Leonori, D. *Org. Lett.* **2008**, *10*, 3923. (y) Xu, H.; Ekoue-Kovi, K.; Wolf, C. *J. Org. Chem.* **2008**, *73*, 7638.

(2) For leading references, see: (a) Jones, P. R.; Young, J. R. *J. Org. Chem.* **1968**, *33*, 1675. (b) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273. (c) Kosugi, M.; Negishi, Y.; Kameyama, M.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3383. (d) Yuan, K.; Scott, W. J. *Tetrahedron Lett.* **1991**, *32*, 189. (e) Watson, A. T.; Park, K.; Wiemer, D.; Scott, W. J. *J. Org. Chem.* **1995**, *60*, 5102. (f) Goossen, L. J. *Chem. Commun.* **2001**, 669. (g) Duan, Y.-Z.; Deng, M.-Z. *Tetrahedron Lett.* **2003**, *44*, 3423. (h) Rodríguez, N.; Cuenca, A.; Ramírez, de Arellano, C.; Medio-Simón, M.; Asensio, G. *Org. Lett.* **2003**, *5*, 1705. (i) Rodríguez, N.; Cuenca, A.; Ramírez, de Arellano, C.; Medio-Simón, M.; Peine, R.; Asensio, G. *J. Org. Chem.* **2004**, *69*, 8070. (j) Liu, C.; He, C.; Shi, W.; Chen, M.; Lu, A. *Org. Lett.* **2007**, *9*, 5601. (k) Rodríguez, N.; Ramírez, de Arellano, C.; Asensio, G.; Medio-Simón, M. *Chem.—Eur. J.* **2007**, *13*, 4223. (l) Yasuda, S.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 287.

(3) (a) Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525. (b) Ref 2h. (c) Ref 2i.

(4) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, *21*, 691.

(5) For leading references, see: (a) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056. (b) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (c) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527. (d) Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5079. (e) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2003**, *32*, 890. (f) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403. (g) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616. (h) Brenstrum, T.; Gerristma, D. A.; Adjabeng, G. M.; Frampton, C. S.; Britten, J.; Robertson, A. J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 7635. (i) Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6180. (j) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Chem.—Eur. J.* **2006**, *12*, 4749. (k) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Commun.* **2007**, 825. (l) Negishi, E.-i; Hu, Q.; Huang, Z.; Wang, G.; Yin, N. In *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds; Wiley-Interscience: New York, 2007; Chapter 11, p 457.

(6) For leading references, see: (a) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186. (b) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N *J. Am. Chem. Soc.* **2002**, *124*, 4222. (c) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340. (d) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788. (e) Terao, J.; Kambe, N. *Catalysts for Fine Chemicals*; Roberts, S. M., Ed.; Wiley: Chichester, U.K., 2004; Vol. 3, p 128. (f) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510. (g) Gonzalez-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360. (h) Ref 5l. (i) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556. (j) Duncton, M. AZ. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G. *Org. Lett.* **2008**, *10*, 3259.

(7) Takahashi, H.; Inagaki, S.; Nishihara, Y.; Shibata, T.; Takagi, K. *Org. Lett.* **2006**, *8*, 3037.

(8) For eading references, see: (a) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. (b) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (c) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297. (d) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, 1794. (e) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161. (f) Fürstner, A.; Rubén, M. *Chem. Lett.* **2005**, *34*, 624. (g) Bica, K.; Gaertner, P. *Org. Lett.* **2006**, *8*, 733. (h) Chowdhury, R. R.; Crane, A.; Fowler, C.; Kwong, P.; Kozak, C. M. *Chem. Commun.* **2008**, 94.

(9) Yasuda, S.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 287.

(10) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886.

(11) (a) Cahiez, G.; Chaboche, C.; Jezequel, M. *Tetrahedron* **2000**, *56*, 2733. (b) Terao, J.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646. (c) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086.

(12) For reviews on transition metal-catalyzed cross-coupling reactions of unactivated alkyl halides and pseudohalides with organometallic compounds, see: (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *36*, 1525. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674.

(13) For leading references, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (c) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657. (d) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2373. (e) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.

(14) For leading references, see: (a) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78. (b) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *18*, 12634. (c) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (d) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882.

(15) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596.

(16) For leading references, see: (a) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13418. (b) Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043. (c) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485. (d) Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D. G.; Jafarpour, F.; Joushagham, A.; Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 1888.

(17) (a) Pastine, S. J.; Gribskov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (c) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661.

(18) For leading references, see: (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450. (b) Tsuchimoto, T.; Ozawa, Y.; Negoro, R.; Shirakawa, E.; Kawekami, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 4231. (c) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 609. (d) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (e) Li, Z.; Bohle, S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8929. (f) Li, C.-J.; Li, Z. *Pure Appl. Chem.* **2006**, *78*, 935. (g) Liegault, B.; Fagnou, K. *Organometallics* **2008**, *27*, 4841. (h) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

(19) Scolastico, C.; Poli, G. *Chemtracts* **1999**, *12*, 498.

(20) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 212.

(21) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

(22) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953.

(23) Kametani, T.; Seino, C.; Yamaki, K.; Shibuya, S.; Fukumoto, K.; Kigasawa, K.; Satoh, F.; Hiiragi, M.; Hayasaka, T. *J. Chem. Soc., C* **1971**, 1047.

(24) For a review on the nucleophilic coupling with arynes, see: Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 2.3.

(25) (a) Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* **1973**, *14*, 4519. (b) Rossi, R. A.; Bunnett, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 112. (c) Semmelhack, M. F.; Bargar, T. *J. Org. Chem.* **1977**, *42*, 1481. (d) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (e) Semmelhack, M. F.; Bargar, T. *J. Am. Chem. Soc.* **1980**, *102*, 7765. (f) Scamehorn, R. G.; Hardacre, J. H.; Lukanich, J. M.; Sharpe, L. R. *J. Org. Chem.* **1984**, *49*, 4881. (g) Beugelmans, R.; Ginsburg, H. *Heterocycles* **1985**, *23*, 1197. (h) Norris, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4,Chapter 2.2.

(26) (a) Abramovitch, R. A.; Barton, D. H. R.; Finet, J.-P. *Tetrahedron* **1988**, *44*, 3039. (b) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J. P.; Atenson, P. H. *Tetrahedron* **1988**, *44*, 6387. (c) Finet, J. P. *Chem. Rev.* **1989**, *89*, 1487.

(27) Jones, P. R.; Young, J. R. *J. Org. Chem.* **1968**, *33*, 1675.

(28) (a) Sacks, C. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7372. (b) Sakurai, H.; Shiribata, A.; Araki, Y.; Hosoni, A. *Tetrahedron Lett.* **1980**, *21*, 2325. (c) Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114. (d) Marino, J. P.; Jaén, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165. (e) Rathke, M. W.; Vogiaroglou, D. *J. Org. Chem.* **1987**, *52*, 3697.

(29) (a) Pinhey, J. T.; Rowe, B. A. *Aust. J. Chem.* **1983**, *36*, 789. (b) Pinhey, J. T. In *Comprehensive Organometallic Chemistry II*; McKillop, A., Ed.; Pergamon Press: Oxford, U.K., 1995; Vol. 11, Chapter 11 and references cited therein. (c) Pinhey, J. T. *Pure Appl. Chem.* **1996**, *68*, 819. (d) Morgan, J.; Pinhey, J. T.; Rowe, B. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1005.

(30) (a) Brown, H. C.; Nambu, H.; Rogic, M. M. *J. Am. Chem. Soc.* **1969**, *91*, 6852. (b) Liu, C.; He, W.; Chen, M.; Lei, A. *Org. Lett.* **2007**, *9*, 5601.

(31) (a) McCague, R.; Kuroda, R.; Leclercq, G.; Stoessel, S. *J. Med. Chem.* **1986**, *29*, 2053. (b) Mino, T.; Matsuda, T.; Murahashi, K.; Yamashita, M. *Organometallics* **1997**, *16*, 3241.

(32) Al Adel, I.; Adeoti Salami, B.; Levisalles, J.; Rudler, H. *Bull. Soc. Chim. Fr.* **1976**, 930.

(33) (a) Varvoglis, A. *Synthesis* **1984**, 709. (b) Chen, K.; Koser, G.-F. *J. Org. Chem.* **1991**, *56*, 5764. (c) Gao, P.; Portoghese, P. S. *J. Org. Chem.* **1995**, *60*, 2276. (d) Ryan, J. H.; Stang, P. J. *Tetrahedron Lett.* **1997**, *38*, 5061. (e) Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673. (f) Aggarwal, V. K.; Olofsson, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5516.

(34) Newman, M. S.; Farbman, M. D. *J. Am. Chem. Soc.* **1944**, *66*, 1550.

(35) Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1993**, *49*, 235.

(36) Pandey, G.; Krishna, A.; Girija, K.; Karthlkeyan, M. *Tetrahedron Lett.* **1993**, *34*, 6631.

(37) Justik, M. W.; Koser, G. F. *Tetrahedron Lett.* **2004**, *45*, 6159.

(38) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 4508.

(39) Ryan, J. H.; Stang, P. J. *Tetrahedron Lett.* **1997**, *38*, 5061.

(40) Molinaro, C.; Mowat, J.; Gosselin, F.; O'Shea, P. D.; Marcoux, J.-F.; Angeland, R.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 1856.

(41) Aléman, J.; Jacobsen, C. B.; Frisch, K.; Overgaard, J.; Jørgensen, K. A. *Chem. Commun.* **2008**, 632.

(42) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507.

(43) Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577.

(44) Muratake, H.; Hayakawa, A.; Natsume, M. *Chem. Pharm. Bull.* **2000**, *48*, 1558.

(45) (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581. (b) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355. (c) Muratake, H.; Natsume, M.; Nakai, H. *Tetrahedron* **2004**, *60*, 11783.

(46) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

(47) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

(48) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740.

(49) Whitesides, G. M.; Gaasch, J. F.; Stedronsky, E. R. *J. Am. Chem. Soc.* **1972**, *94*, 5258.

(50) (a) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (b) Prashad, M.; Liu, Y.; Repic, O. *Adv. Synth. Catal.* **2003**, *345*, 533.

(51) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(52) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209.

(53) Grasa, G. A.; Colacot, T. J. *Org. Lett.* **2007**, *9*, 5489.

(54) (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (b) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Organometallics* **2008**, *27*, 1679.

(55) (a) Carril, M.; SanMartin, R.; Churruca, F.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2005**, *7*, 4787. (b) Carril, M.; SanMartin, R.; Domínguez, E. *Chem. Soc. Rev.* **2008**, *37*, 639.

(56) Limbeck, M.; Wamhoff, H.; Rölle, T.; Griebenow, N. *Tetrahedron Lett.* **2006**, *47*, 2945.

(57) (a) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2345. (b) Satoh, T.; Miura, M.; Nomura, M. *J. Organomet. Chem.* **2002**, *653*, 161.

(58) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Eur. J. Org. Chem.* **2005**, 2481.

(59) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *ARKIVOC* **2007**, 270.

(60) (a) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Tetrahedron* **2006**, *62*, 11513. (b) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett.* **2004**, *6*, 4755.

(61) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2002**, *4*, 1591.

(62) (a) Churruca, F.; SanMartin, R.; Carril, M.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2004**, *60*, 2393. (b) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron Lett.* **2003**, *44*, 5925. For a review on the synthesis and cross-coupling catalysis applications of polyethylene or polypropylene supported palladium complexes, see: (c) Colacot, T. J. *Top. Catal.* **2008**, *48*, 91.

(63) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2000**, *56*, 1315.

(64) (a) Ooi, T.; Kondo, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 3039. (b) Thorn, M. G.; Vilardo, J. S.; Fanwick, R. E.; Rothwell, I. *Chem. Commun.* **1998**, 2427. (c) Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943.

(65) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345.

(66) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2001**, *57*, 5967.

(67) For reviews on *N*-heterocyclic carbenes (NHCs) and their applications in transition metal catalysis, see: (a) Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *600*, 12. (b) Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2000**, *46*, 181. (c) Hillier, A. C.; Nolan, S. P. *Platinum Met. Rev.* **2002**, *46*, 50. (d) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69. (e) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (f) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247. (g) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239. (h) Viciu, M. S.; Nolan, S. P. *Top. Organomet. Chem.* **2005**, *8*, 241. (i) Crabtree, R. H. *J. Organomet. Chem.* **2005**, *690*, 5451. (j) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Aldrichim. Acta* **2006**, *39*, 97. (k) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: New York, 2006. (l) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768. (m) Sommer, W. J.; Weck, M. *Coord. Chem. Rev.* **2007**, *251*, 860. (n) Colacino, E.; Martinez, J.; Lamaty, F. *Coord. Chem. Rev.* **2007**, *251*, 726. (o) Kuhl, O. *Chem. Soc. Rev.* **2007**, *36*, 592. (p) Díez-González, S.; Nolan, S. P. *Top. Organomet. Chem.* **2007**, *21*, 47. (q) Organ, M. G.; Chass, G. A.; Fang, D.-C.; Hopkinson, A. C.; Valente, C. *Synthesis* **2008**, 2776. (r) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523. (s) Marion, N.; Nolan, S. *Acc. Chem. Res.* **2008**, *41*, 1440.

(68) (a) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053. (b) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470.

(69) Singh, R.; Nolan, S. P. *J. Organomet. Chem.* **2005**, *690*, 5832.

(70) Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, A. R., III; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685.

(71) Navarro, O.; Marion, N.; Scott, N. M.; González, J.; Amoroso, D.; Bell, A.; Nolan, S. P. *Tetrahedron* **2005**, *61*, 9716.

(72) Marion, N.; de Frémont, P.; Puijk, I. M.; Ecarnot, E. C.; Amoroso, D.; Bell, A.; Nolan, S. P. *Adv. Synth. Catal.* **2007**, *349*, 2380.

(73) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816.

(74) Matsubara, K.; Okazaki, H.; Senju, M. *J. Organomet. Chem.* **2006**, *691*, 3693.

(75) Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479.

(76) For recent reviews on the potential of palladacycles in synthesis, see: (a) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23. (b) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Org. Chem.* **2001**, 1917. (c) Bedford, R. B. *Chem. Commun.* **2003**, 1787. (d) Dumina, V. V.; Gorunova, O. N. *Russ. Chem. Rev.* **2004**, *73*, 309. (e) Cheprakov, A. V.; Beletskaya, I. P. *J. Organomet. Chem.* **2004**, *689*, 4055. (f) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527. (g) *Palladacycles: Synthesis, Characterization and Applications*; Dupont, J., Pfeffer, M., Eds.; Wiley-VCH: Weinheim, Germany, 2008.

(77) Nguyen, H, N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

(78) Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H.-U. *Angew. Chem., Int. Ed.* **2002**, *41*, 3668.

(79) Lavallo, V.; Canac, Y.; Präsang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705.

(80) Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 5082.

(81) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron Lett.* **2006**, *47*, 3233.

(82) For reviews on the reactivity and catalytic performances of metal complexes based on pincer framework, see: (a) Albrecht, M.; van Koten, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 3750. (b) Singleton, J. T. *Tetrahedron* **2003**, *59*, 1837. (c) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239. (d) Morales-Morales, D. *Rev. Soc. Quim. Mex.* **2004**, *48*, 338. (e) Schuster, E. M.; Botoshansky, M.; Gandelman, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4555.

(83) Ackermann, L.; Spatz, J. H.; Gschrei, C. J.; Born, R.; Althammer, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7627.

(84) Abrams, M. B.; Scott, B. L.; Baker, R. T. *Organometallics* **2000**, *19*, 4944.

(85) Matsubara, K.; Ueno, K.; Koga, Y.; Hara, K. *J. Org. Chem.* **2007**, *72*, 5069.

(86) Sido, A. S. S.; Boulanger, L.; Désaubry, L. *Tetrahedron Lett.* **2005**, *46*, 8017.

(87) Willis, M. C.; Brace, G. N.; Holmes, J. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403.
(88) Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168.
(89) Diedrichs, N.; Ragot, J. P.; Thede, K. *Eur. J. Org. Chem.* **2005**, 1731.
(90) For reviews on rocaglaols and rocaglamides, see: (a) Proksch, P.; Edrada, R.; Ebel, R.; Bohnenstengel, F. I.; Nugroho, B. W. *Curr. Org. Chem.* **2001**, *5*, 923. (b) Pikarsky, E.; Porat, R. M.; Stein, I.; Abramovitch, R.; Amit, S.; Kasen, S.; Gutkovich-Pyest, E.; Urili-Shoval, S.; Galun, E.; Ben-Neriah, Y. *Nature* **2004**, *431*, 461.
(91) Honda, T.; Sakamaki, Y. *Tetrahedron Lett.* **2005**, *46*, 6823.
(92) Mutter, R.; Campbell, I. B.; Martin de la Nava, E. M.; Merritt, A. T.; Wills, M. *J. Org. Chem.* **2001**, *66*, 3284.
(93) (a) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardía, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587. (b) Solé, D.; Vallverdú, L.; Peidró, E.; Bonjoch, J. *Chem. Commun.* **2001**, 1888. (c) Solé, D.; Vallverdú, L.; Bonjoch, J. *Adv. Synth. Catal.* **2001**, *343*, 439.
(94) Khartulyari, A. S.; Maier, M. E. *Eur. J. Org. Chem.* **2007**, 317.
(95) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918.
(96) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261.
(97) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195.
(98) Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413.
(99) For reviews on the stereoselective construction of all-carbon quaternary centers, see: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad Sci. U.S.A.* **2004**, *101*, 5363. (c) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (d) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (e) *Quaternary Stereocenters. Challenges and Solutions in Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2006. (f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969.
(100) For a review on the synthesis and applications of P-Phos, see: Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711.
(101) Jeulin, S.; Duprat de Paulo, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320.
(102) (a) Akuamoah, R. K.; Brown, P. E.; Marcus, W. Y.; Steele, J. E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 197. (b) Klapash, B. N.; Shar, R. C.; Wheeler, T. S. *J. Indian Chem. Soc.* **1942**, *19*, 117.
(103) For leading references on the regioselective synthesis of silyl enol ethers of ketones, see: (a) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979. (b) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (c) Kato, M.; Mori, A.; Oshino, H.; Enda, J.; Kobayashi, K.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1773. (d) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495. (e) Davis, F. A.; Lal, G. S.; Wei, J. *Tetrahedron Lett.* **1988**, *29*, 4269. (f) Bonafoux, D.; Bordeau, D.; Biran, C.; Cazeau, P.; Dunogues, J. *J. Org. Chem.* **1996**, *61*, 5532. (g) Okada, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 8023. (h) Huang, C.-H.; Chang, S.-Y.; Wang, N.-S.; Tsai, Y.-M. *J. Org. Chem.* **2001**, *66*, 8983. (i) Maekawa, H.; Sakai, M.; Uchida, T.; Kita, Y.; Nishiguchi, I. *Tetrahedron Lett.* **2004**, *45*, 607. (j) Ooguri, A.; Ikeda, Z.; Matsubara, S. *Chem. Commun.* **2007**, 4761.
(104) Kuwajima, I.; Uribe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831.
(105) For arylation reactions of silyl enol ethers of ketones with aryl electrophiles that do not involve Pd-catalysis, see: (a) Chen, K.; Koser, G. F. *J. Org. Chem.* **1991**, *56*, 5764. (b) Sakakura, T.; Hara, M.; Tanaka, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 283. (c) Pandy, G.; Karthikeyan, M.; Muragan, A. *J. Org. Chem.* **1998**, *63*, 2867. (d) Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673.
(106) Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809.
(107) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797.
(108) Iwama, T.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 5725.
(109) Guo, Y.; Twamley, B.; Shreeve, J. M. *Chem. Commun.* **2007**, 3583.
(110) Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 5852.
(111) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.
(112) Chobanian, H. R.; Liu, P.; Chioda, M. D.; Guo, Y.; Lin, S. L. *Tetrahedron Lett.* **2007**, *48*, 1213.
(113) Battace, A.; Feuerstein, M.; Lemhadri, M.; Zair, T.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2007**, 3122.
(114) (a) House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514. (b) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.
(115) For leading references on the synthesis of enol esters of ketones, see: (a) Hauthal, H. G.; Kluge, P.; Schmidt, H. *J. Prakt. Chem.* **1965**, *29*, 296. (b) Rodig, O. R.; Zanati, G. *J. Org. Chem.* **1967**, *32*, 1423. (c) Hudrlik, P. F.; Hudrlik, A. M. *J. Org. Chem.* **1973**, *38*, 4254. (d) Bessodes, M.; Ollapally, A.; Antonakis, K. *J. Chem. Soc., Chem Commun.* **1979**, 835. (e) Masuda, Y.; Hoshi, M.; Arase, A. *Chem. Lett.* **1980**, 413. (f) Larock, R. C. *Comprehensive Organic Transormations*; VCH: New York, 1989; (g) Abe, S.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2863. (h) Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1997**, 507. (i) Kalita, D. J.; Borah, R.; Sharma, J. C. *J. Chem. Res., Synop.* **1999**, 404. (j) Kalita, B.; Bezbarua, M. S.; Barua, N. C. *Synth. Commun.* **2002**, *32*, 3181. (k) Opstal, T.; Verpoort, F. *Tetrahedron Lett.* **2002**, *43*, 9259. (l) Makagawa, H.; Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, *44*, 103.
(116) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5535.
(117) Saito, R.-i.; Izumi, T.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1776.
(118) Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Saitoh, K.; Migita, T. *Chem. Lett.* **1982**, 939.
(119) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *J. Chem. Soc., Chem. Commun.* **1983**, 344.
(120) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242.
(121) Gupta, M.; Nair, V. *Tetrahedron Lett.* **2005**, *46*, 1165.
(122) Nicolaou, K. C.; Xu, H. *Chem. Commun.* **2006**, 600.
(123) Liu, P.; Lanza, T. J., Jr.; Hewell, J. P.; Jones, C. P.; Hagmann, W. K.; Lin, L. S. *Tetrahedron Lett.* **2003**, *44*, 8869.
(124) Jean, M.; Renault, J.; Uriac, P.; Capet, M.; van de Weghe, P. *Org. Lett.* **2007**, *9*, 3623.
(125) Mitsudo, T.-a.; Kadokura, M.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 3186.
(126) Barluenga, J.; Jiménez-Aquino, A.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1529.
(127) De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N.; Charpenitier-Morize, M. *Tetrahedron Lett.* **1982**, *23*, 2853.
(128) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355.
(129) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **2002**, *43*, 2913.
(130) Muratake, H.; Natsume, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4646.
(131) (a) Muratake, H.; Natsume, M. *Tetrahedron* **2006**, *62*, 7056. (b) Muratake, H.; Natsume, M. *Tetrahedron* **2006**, *62*, 7071. (c) Muratake, H.; Natsume, M.; Nakai, H. *Tetrahedron* **2006**, *62*, 7093.
(132) Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1996**, 823.
(133) Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101.
(134) Martín, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236.
(135) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127.
(136) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.
(137) Alemán, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5520.
(138) Lednicer, D.; Mitscher, L. A. In *The Organic Chemistry of Drug Synthesis*; John Wiley: New York, 1980; Vol. 2, p 62.
(139) Takeda, T.; Gonda, R.; Hatano, K. *Chem. Pharm. Bull.* **1997**, *45*, 697.
(140) Kong, F.; Andersen, R. J. *J. Org. Chem.* **1993**, *58*, 6924.
(141) Durandetti, M.; Nédélec, J.-Y.; Périchon, J. *J. Org. Chem.* **1996**, *61*, 1748.
(142) Conan, A.; Sibille, S.; d'Incan, E.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1990**, 48.
(143) Durandetti, M.; Gosmini, C.; Périchon, J. *Tetrahedron* **2007**, *63*, 1146.
(144) Millard, A. A.; Rathke, M. V. *J. Am. Chem. Soc.* **1977**, *99*, 4833.
(145) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273.
(146) Orsini, F.; Pellizzoni, F. *Synth. Commun.* **1987**, *17*, 1389.
(147) Orsini, F.; Pellizzoni, F.; Vallarino, L. M. *J. Organomet. Chem.* **1989**, *367*, 375.
(148) Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557.
(149) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176.
(150) Bentz, E.; Moloney, M. G.; Wetway, S. M. *Tetrahedron Lett.* **2004**, *45*, 7395.
(151) (a) Kosugi, M.; Negishi, Y.; Kameyama, M.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3383. For a review on the use of organotin enolates in organic synthesis, see: (b) Shibata, I.; Baba, A. *Org. Prep. Proced. Int.* **1994**, *26*, 85.
(152) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1549.
(153) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996.
(154) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410.
(155) For leading references on the Pd-catalyzed hydrodehalogenation reaction of aryl halides, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009. (b) Rahaim, R. J.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **2002**, *43*, 8823. (c) Cellier, P. P.; Spindler, J.-F.; Taillefer, M.; Cristeau, H.-J. *Tetrahedron Lett.* **2003**, *44*, 7191. (d) Selvam, P.; Mohapatra, S. K.; Sonovame, S. U.; Jayram, R. V. *Appl. Catal., B* **2004**, *49*, 251. (e) Logan, M. E.; Oinen, M. E. *Organometallics* **2006**, *25*, 1052. (f) Caló, V.; Nacci, A.; Monopoli,

A.; Damascelli, A.; Ieva, E.; Cioffi, N. *J. Organomet. Chem.* **2007**, *692*, 4397. (g) Ohlin, C. A.; Béni, Z.; Laurenczy, G.; Ruiz, N.; Masdeu-Bultó, A. M. *Appl. Organomet. Chem.* **2007**, *21*, 156. (h) Wawisza, A. M.; Muzart, J. *Tetrahedron Lett.* **2007**, *21*, 156.
(156) Bercot, E. A.; Caille, S.; Bostick, T. M.; Ranganathan, K.; Jensen, R.; Faul, M. M. *Org. Lett.* **2008**, *10*, 5251.
(157) (a) Hocek, M. *Heterocycles* **2004**, *63*, 1673. (b) Lagerlund, O.; Odell, L. R.; Mowbray, S. L.; Nilsson, M. T.; Krajewski, W. W.; Nordqvist, A.; Karlen, A.; Larhed, M. *Comb. Chem. High Throughput Screening* **2007**, *10*, 783.
(158) Liu, X.; Hartwig, J. F. *Org. Lett.* **2003**, *5*, 1915.
(159) Trost, B. M.; Aeiza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727.
(160) Wang, Y.; Nair, R. *Tetrahedron Lett.* **2007**, *48*, 1191.
(161) Shetty, R.; Moffett, K. K. *Tetrahedron Lett.* **2006**, *47*, 8021.
(162) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465.
(163) Taylor, S. R.; Ung, A. T.; Pyne, S. G. *Tetrahedron* **2007**, *63*, 10889.
(164) Solé, D.; Serrano, O. *J. Org. Chem.* **2008**, *73*, 2476.
(165) Malcom, S. C.; Ribe, S.; Wang, F.; Hewitt, M. C.; Bhongle, N.; Bakale, R. P.; Shao, L. *Tetrahedron Lett.* **2005**, *46*, 6871.
(166) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500.
(167) Carfagna, C.; Musco, A.; Sallese, G.; Santi, R.; Fiorani, T. *J. Org. Chem.* **1991**, *56*, 261.
(168) Galarini, R.; Musco, A.; Pontellini, R.; Santi, R. *J. Mol. Catal.* **1992**, *72*, L11.
(169) (a) Sakamoto, T.; Kondo, Y.; Masumoto, K.; Yamanaka, H. *Heterocycles* **1993**, *36*, 2509. (b) Sakamoto, T.; Kondo, Y.; Masumoto, K.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 235.
(170) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182.
(171) Agnelli, F.; Sulikowski, G. A. *Tetrahedron Lett.* **1998**, *39*, 8807.
(172) Koch, K.; Melvin, L. S., Jr.; Reiter, L. A.; Biggers, M. S.; Showell, H. J.; Griffiths, R. J.; Pettipher, E. R.; Cheng, J. B.; Milici, A. J.; Breslow, R.; Conklyn, M. J.; Smith, M. A.; Hacjman, B. C.; Doherty, N. S.; Salter, E.; Farrell, C. A.; Schultz, G. *J. Med. Chem.* **1994**, *37*, 3197.
(173) For leading references on the synthesis of *O*-silyl ketene acetals, see: (a) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67. (b) Kita, Y.; Haruta, J.; Segawa, J.; Tamura, Y. *Tetrahedron Lett.* **1979**, *20*, 4311. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650. (d) Magot-Cuvru, A.; Blanco, L.; Drouin, J. *Tetrahedron* **1991**, *47*, 8311. (e) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 5301. (f) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3099. (g) Su, K.-H.; Choo, D.-J. *Bull. Korean Chem. Soc.* **1995**, *16*, 1003. (h) Takikawa, G.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2005**, *70*, 8811. (i) Okabayashi, T.; Iida, A.; Takai, K.; Nawate, Y.; Misaki, T.; Tanabe, Y. *J. Org. Chem.* **2007**, *72*, 8142.
(174) Johnson, P. D.; Sohn, J.-H.; Rawal, V. H. *J. Org. Chem.* **2006**, *71*, 7899.
(175) Friederich, K.; Wallenfels, K. *The Chemistry of the Cyano Group*; Wiley-Interscience: New-York, 1970.
(176) Prisant, L. M. *Heart Dis.* **2001**, *3*, 55.
(177) Jeffery, P. *Pulm. Pharmacol. Ther.* **2005**, *18*, 9.
(178) For leading references, see: (a) Fresneda, P. M.; Lidon, M. J.; Molina, P.; Vilaplana, M. J. *Synthesis* **1981**, 711. (b) Tamura, Y.; Choi, H. D.; Mizutani, M.; Ueda, Y.; Ishibashi, H. *Chem. Pharm. Bull.* **1982**, *30*, 3574. (c) Stamos, I. K. *Tetrahedron Lett.* **1985**, *26*, 477. (d) Frejd, T.; Klingstedt, T. *Synthesis* **1987**, 40. (e) Kitahawa, T.; Kawaguchi, M.; Ikiuchi, M. *Chem. Pharm. Bull.* **1991**, *39*, 187. (f) Starosotnikov, A. M.; Lobach, A. V.; Shelev, S. A. *Synthesis* **2005**, 2830. (g) Kamila, S.; Koh, B.; Biehl, E. R. *Synth. Commun.* **2006**, *36*, 3493.
(179) For leading references, see: (a) Sperber, N.; Papa, D.; Schwenk, E.; Sherlok, M.; Fricano, R. *J. Am. Chem. Soc.* **1951**, *73*, 5752. (b) Carver, D. R.; Greenwood, T. D.; Hubbard, J. S.; Komin, A. P.; Sachdeva, Y. P.; Wolfe, J. F. *J. Org. Chem.* **1983**, *48*, 1180. (c) Rose-Munch, F.; Aniss, K.; Rose, E. *J. Organomet. Chem.* **1990**, *385*, C1. (d) Loupy, A.; Philippon, N.; Pigeon, P.; Galons, H. *Heterocycles* **1991**, *32*, 1947. (e) Sleevi, M. C.; Cale, A. D.; Gero, T. W.; Jacques, L. W.; Welstead, W. J.; Johnson, A. F.; Kilpatrick, B. F.; Demian, I.; Nolan, J. C.; Jenkins, H. *J. Med. Chem.* **1991**, *34*, 1314. (f) Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712. (g) Skerlj, R. T.; Bogucki, D.; Bridger, G. J. *Synlett* **2000**, 1488. (h) Klapars, A.; Waldman, J. H.; Campos, K. R.; Jensen, M. S.; McLaughlin, M.; Chung, J. Y. L.; Cvetovich, R. J.; Chen, C.-y. *J. Org. Chem.* **2005**, *70*, 10189.
(180) Satoh, T.; Inoh, J.-i.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239.
(181) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330.
(182) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003.
(183) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051.
(184) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.
(185) For representative examples, see: (a) Rivara, S.; Lodola, A.; Mor, M.; Bedini, A.; Spadoni, G.; Lucini, V.; Pannacci, M.; Frascini, F.; Scaglione, F.; Ochoa Sanchez, R.; Gobbi, G.; Tarzia, G. *J. Med. Chem.* **2007**, *50*, 6618. (b) Bhattacharya, A.; Scott, B. P.; Nasser, M.; Ao, H.; Maher, M. P.; Dubin, A. E.; Swanson, D. M.; Shankley, M. P.; Wickenden, A. D.; Chaplan, S. R. *J. Pharmacol. Exp. Ther.* **2007**, *323*, 665.
(186) Johansson, I. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 5th ed.; Wiley: New York, 2004; Vol. 2, p 442.
(187) (a) *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley-Interscience: New York, 1970. (b) *The Amide Linkage: Structural Significance, Chemistry, Biochemistry and Material Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley: New York, 2000.
(188) Southwick, P. L. *Synthesis* **1970**, 628.
(189) Stewart, J. D.; Fields, S. C.; Kochar, K. S.; Pinnick, H. W. *J. Org. Chem.* **1987**, *52*, 2110.
(190) (a) Rossi, R. A.; Alonso, R. A. *J. Org. Chem.* **1980**, *45*, 1239. (b) Palacios, S. M.; Asis, S. E.; Rossi, R. A. *Bull. Soc. Chim. Fr.* **1993**, *130*, 111.
(191) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.
(192) Freund, R.; Mederski, W. W. K. R. *Helv. Chim. Acta* **2000**, *83*, 1247.
(193) Botuha, C.; Galley, C. M. S.; Gallagher, T. *Org. Biomol. Chem.* **2004**, *2*, 1825.
(194) Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631.
(195) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.
(196) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 1363.
(197) Hillgren, J. M.; Marsden, S. P. *J. Org. Chem.* **2008**, *73*, 1413.
(198) Marsden, S. P.; Watson, E. L.; Raw, S. A. *Org. Lett.* **2008**, *10*, 2905.
(199) Bignan, G. C.; Battista, K.; Connolly, P. J.; Orsini, M. J.; Liu, J.; Middleton, S. A.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5022.
(200) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 193.
(201) (a) Kündig, E. P.; Seidel, T. M.; Jia, Y.-X.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484. (b) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040.
(202) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehman, C. *Chem. Commun.* **2002**, 2704.
(203) Arao, T.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2006**, *47*, 1417.
(204) Arao, T.; Sato, K.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 1576.
(205) Arao, T.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 1743.
(206) Bertogg, A.; Campanovo, F.; Togni, A. *Eur. J. Inorg. Chem.* **2005**, 347.
(207) Bonnet, L. G.; Douthwaite, R. E.; Hodgson, R. *Organometallics* **2003**, *22*, 4384.
(208) Durbin, M. J.; Willis, M. C. *Org. Lett.* **2008**, *10*, 1413.
(209) Altmann, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613.
(210) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218.
(211) Cossy, J.; de Filippis, A.; Pardo, D. G. *Synlett* **2003**, 2171.
(212) Cossy, J.; de Filippis, A.; Pardo, D. G. *Org. Lett.* **2003**, *5*, 3037.
(213) (a) De Filippis, A.; Pardo, D. G.; Cossy, J. *Synthesis* **2004**, 2930. (b) De Filippis, A.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2004**, *60*, 9757.
(214) Satynarayana, G.; Maier, M. E. *Tetrahedron* **2008**, *64*, 356.
(215) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976.
(216) (a) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652. (b) Badioli, M.; Ballini, R.; Bartolacci, M.; Bosica, G.; Torregiani, E.; Marcantoni, E. *J. Org. Chem.* **2002**, *67*, 8938. (c) Kurosu, M.; Kishi, Y. *Tetrahedron Lett.* **1998**, *39*, 4793.
(217) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(218) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
(219) (a) Bruggink, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607. (b) Bruggink, A.; McKillop, A. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 340. (c) Bruggink, A.; Ray, S. J.; McKillop, A. *Org. Synth.* **1978**, *58*, 52. (d) McKillop, A.; Rao, D. P. *Synthesis* **1977**, 759.
(220) (a) Setsune, J.; Matsukawa, K.; Wakemoto, H.; Kitao, T. *Chem. Lett.* **1981**, 367. (b) Setsune, J.; Matsukawa, K.; Kaito, T. *Tetrahedron Lett.* **1982**, *23*, 663.
(221) Suzuki, H.; Kobayashi, T.; Yoshida, Y.; Osuka, A. *Chem. Lett.* **1983**, 193.
(222) Suzuki, H.; Yi, Q.; Inoue, J.; Kusume, K.; Ogawa, T. *Chem. Lett.* **1987**, 887.
(223) Suzuki, H.; Koide, H.; Ogawa, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 501.
(224) Ugo, R.; Nardi, P.; Baro, R.; Roberto, D. *Gazz. Chim. Ital.* **1992**, *122*, 511.
(225) Rosenau, B.; Krieger, C.; Staab, H. A. *Tetrahedron Lett.* **1985**, *26*, 2081.
(226) Hurtley, W. R. H. *J. Chem. Soc.* **1929**, 1870.

(227) For a review up to 2004 on the developments of the Hurtley reaction, see: Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, E. V. *J. Organomet. Chem.* **2004**, *689*, 3810.
(228) Bryson, T. A.; Stewart, J. J.; Gibson, J. M.; Thomas, P. S.; Berch, J. K. *Green Chem.* **2003**, *5*, 174.
(229) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606.
(230) Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, 398.
(231) Shinkwin, A. E.; Wish, W. J. D.; Threadgill, M. D. *Bioorg. Med. Chem.* **1999**, *7*, 297.
(232) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269.
(233) For noncatalytic procedures to prepare dialkyl arylmalonates, see: (a) Cope, A. C.; Field, L. *J. Org. Chem.* **1949**, *14*, 856. (b) Ismail, M. T.; El-Khawaga, A. H.; Abdel-Wahib, A. M. A.; Khalaf, A. A. *Ann. Chim.* **1982**, *72*, 269. (c) Ghosh, S.; Pardo, S. N.; Salomon, R. G. *J. Org. Chem.* **1982**, *47*, 4692. (d) Baciocchi, E.; Dell'Aira, D.; Ruzziconi, R. *Tetrahedron Lett.* **1986**, *27*, 2763. (e) Chen, Z.-C.; Jin, Y.-Y.; Stang, P. J. *J. Org. Chem.* **1987**, *52*, 4115. (f) Tona, M.; Sánchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1994**, *50*, 8117. (g) Deutsch, J.; Bartoszek, M.; Scneider, M.; Zabel, V.; Niclas, H. J. *J. Prakt. Chem.* **1997**, *339*, 261. (h) Terao, Y.; Ijima, Y.; Kakidani, H.; Ohta, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2395.
(234) Cristeau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607.
(235) Jiang, Y.; Wu, N.; Wu, H.; He, H. *Synlett* **2005**, 2731.
(236) (a) Xie, X.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 4693. (b) Wang, Y.; Sun, Z.; Ma, D. *Org. Lett.* **2008**, *10*, 625.
(237) Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050.
(238) Deng, W.; Wang, Y. F.; Liu, L.; Guo, Q. X. *Chin. Chem. Lett.* **2006**, *17*, 595.
(239) Fang, Y.; Li, C. *J. Org. Chem.* **2006**, *71*, 6427.
(240) (a) Chen, Y.; Xie, X.; Ma, D. *J. Org. Chem.* **2007**, *72*, 9329. (b) Tanimori, S.; Ura, H.; Kirihata, M. *Eur. J. Org. Chem.* **2007**, 3977.
(241) Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469.
(242) Lu, B.; Ma, D. *Org. Lett.* **2006**, *8*, 6115.
(243) (a) Parkes, K. E. B.; Ermert, P.; Fässler, J.; Ives, J.; Martin, J. A.; Merrett, J. H.; Obrecht, D.; Williams, G.; Klumpp, K. *J. Med. Chem.* **2003**, *46*, 1153. (b) Robinson, R. P.; Reiter, L. A.; Barth, W. E.; Campeta, A. M.; Cooper, K.; Cronin, B. J.; Destito, R.; Donahue, K. H.; Falkner, F. C.; Fiese, E. F.; Johnson, D. L.; Kupermann, A. V.; Liston, T. P.; Malloy, D.; Martin, J. J.; Mitchell, D. Y.; Rusek, F. W.; Shamblin, S. L.; Wright, C. F. *J. Med. Chem.* **1996**, *39*, 10.
(244) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1994**, *50*, 12697.
(245) (a) Pores-Makkay, M.; Simig, G. *Org. Prep. Res. Dev.* **2000**, *4*, 10. (b) Sechi, M.; Sannia, L.; Carta, F.; Palomba, M.; Dallocchio, R.; Dessi, A.; Derudas, M.; Wawahir, Z.; Neamati, N. *Antiviral Chem. Chemother.* **2005**, *16*, 41.
(246) Zeevaart, J. G.; Parkinson, C. J.; de Koning, C. B. *Tetrahedron Lett.* **2007**, *48*, 3289.
(247) Wang, B.; Lu, B.; Jiang, Y.; Zhang, Y.; Ma, D. *Org. Lett.* **2008**, *10*, 2761.
(248) Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1984**, 506.
(249) Uno, M.; S.; Seto, K.; Masuda, M.; Ueda, W.; Takahashi, S. *Tetrahedron Lett.* **1985**, *26*, 1553.
(250) Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932.
(251) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171.
(252) Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4151.
(253) Huang, X.; Jiang, S. *Chin. Chem. Lett.* **1993**, *4*, 317.
(254) Djakovitch, L.; Köhler, K. *J. Organomet. Chem.* **2000**, *606*, 101.
(255) For a recent review on carbon—carbon bond-forming reactions catalyzed by heterogeneous Pd catalysts, see: Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.
(256) Aramendia, M. A.; Borau, V.; Jiménez, C.; Marinas, J. M.; Ruiz, J. R.; Urbano, F. J. *Tetrahedron Lett.* **2002**, *43*, 2847.
(257) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.
(258) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641.
(259) Gao, C.; Tao, X.; Qian, Y.; Huang, J. *Synlett* **2003**, 1716.
(260) Cristeau, H. J.; Vogel, R.; Taillefer, M.; Gadras, A. *Tetrahedron Lett.* **2000**, *41*, 8457.
(261) (a) Gao, C.; Tao, X.; Qian, Y.; Huang, J. *Chem. Commun.* **2003**, 1444. (b) Gao, C.; Tao, X.; Liu, T.; Huang, J.; Qian, Y. *Chin. J. Chem.* **2002**, *20*, 819.
(262) Schnyder, A.; Indolese, A. F.; Maetzke, T.; Wenger, J.; Blaser, H.-U. *Synlett* **2006**, 3167.
(263) Mitin, A. V.; Kashin, A. N.; Beletskaya, I. P. *J. Organomet. Chem.* **2004**, *689*, 1085.
(264) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421.
(265) Zeevaart, J. G.; Parkinson, C. J.; de Koning, C. B. *Tetrahedron Lett.* **2004**, *45*, 4261.
(266) Özdemir, I.; Yigit, M.; Cetinkaya, E.; Cetinkaya, B. *Tetrahedron Lett.* **2004**, *45*, 5823.
(267) (a) Bolm, C.; Martin, M.; Gibson, L. *Synlett* **2002**, 832. (b) Bolm, C.; Okamura, H.; Verrucci, M. *J. Organomet. Chem.* **2003**, *687*, 444.
(268) Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 1351.
(269) For reviews, see: (a) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. (b) Huang, S. L.; Swern, D. *Phosphorus, Sulfur Silicon Relat. Elem.* **1976**, *1*, 309. (c) Pyne, S. G. *Sulfur Rep.* **1992**, *12*, 57. (d) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.
(270) Kashin, A. N.; Mitin, A. V; Beletskaya, I. P. *Tetrahedron Lett.* **2002**, *43*, 2539.
(271) Zeevaart, J. G.; Parkinson, C. J.; de Koning, C. B. *Tetrahedron Lett.* **2005**, *46*, 1597.
(272) Grimm, J. B.; Katcher, M.; Witter, D. J.; Northrup, A. B. *J. Org. Chem.* **2007**, *72*, 8135.
(273) Mitin, A. V.; Kashin, A. N.; Beletskaya, I. P. *J. Organomet. Chem.* **2004**, *689*, 1085.
(274) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106.
(275) For a recent review on the Nef reaction, see: Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.
(276) For reviews on this topic, see: (a) Kachiuchi, K.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (c) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (f) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (g) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35. (h) Bellina, F.; Cauteruccio, S.; Rossi, R. *Curr. Org. Chem.* **2008**, *12*, 774. (i) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548.
(277) For leading references, see: (a) Forgione, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350. (b) Goossen, L. J.; Deng, G.; Levy, L. *Science* **2006**, *313*, 662. (c) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373. (d) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (e) Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781. (f) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103.
(278) *Dictionary of Chemistry*; Daintith, J., Ed.; Oxford University Press: Oxford, U.K., 2000; p 61.
(279) For leading references on removal of palladium from reaction products, see: (a) Ishihara, K.; Nakayama, M.; Kurihara, H.; Itoh, A.; Haraguchi, H. *Chem. Lett.* **2000**, *29*, 1218. (b) Manley, P. W.; Acemoglu, M.; Marterer, W.; Pachinger, W. *Org. Process Res. Dev.* **2003**, *7*, 436. (c) Chen, C.-y.; Dagneau, P.; Grabowski, E. J. J.; Oballa, R.; O'Shea, P.; Prasit, P.; Robicheaud, J.; Tillyer, R.; Wang, X. *J. Org. Chem.* **2003**, *68*, 2633. (d) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889. (e) Guino, M.; Hii, K. K. *Tetrahedron Lett.* **2005**, *46*, 6911. (f) Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev.* **2005**, *9*, 198. (g) Wong, H.; Pink, C. J.; Ferreira, F. C.; Livingston, A. G. *Green Chem.* **2006**, *8*, 373. (h) Crudden, C. M.; McEleney, K.; MacQuarrie, S. L.; Blanc, A.; Sateesh, M.; Webb, J. D. *Pure Appl. Chem.* **2007**, *79*, 247. (i) Galaffu, N.; Man, S. P.; Wilkes, R. D.; Wilson, R. H. *Org. Process Res. Dev.* **2007**, *11*, 406. (j) Flahive, E. J.; Ewanicki, B. L.; Sach, N. W.; O'Neill-Slawecki, S. A.; Stankovic, N. S.; Yu, S.; Guiness, S. M.; Dunn, J. *Org. Process Res. Dev.* **2008**, *12*, 637. (k) Bullock, K. M.; Mitchell, M. B.; Toczko, J. F. *Org. Process Res. Dev.* **2008**, *12*, 896.
(280) For leading references on removal of copper from reaction mixtures and products, see: (a) Neuberger, A.; Sanger, F. *Biochem. J.* **1943**, *37*, 515. (b) Zahn, H.; Zuber, H.; Ditscher, W.; Wegerle, D.; Meinhofer, J. *Chem. Ber.* **1956**, *89*, 407. (c) Zairal, M. *Collect. Czech. Chem. Commun.* **1965**, *30*, 1853. (d) Prestidge, R. L.; Harding, D. R. K.; Battersby, J. E.; Hancock, W. S. *J. Org. Chem.* **1975**, *40*, 3287. (e) Scott, J. W.; Parker, D.; Parrish, D. R. *Synth. Commun.* **1981**, *11*, 303. (f) Taylor, U. F.; Dyckes, D. F.; Cox, J. R., Jr. *Int. J. Pept. Protein Res.* **1982**, *19*, 158. (g) Bunegar, M. J.; Dyer, U. C.; Green, A. P.; Gott, G. G.; Jaggs, C. M.; Lock, C. J.; Mead, B. J. V.; Spearing, W. R.; Tiffin, P. D.; Tremayne, N.; Woods, M. *Org. Process Res. Dev.* **1998**, *2*, 334. (h) Wiejak, S.; Masiukiewicz, E.; Rzeszotarska, B. *Chem. Pharm. Bull.* **2001**, *49*, 1189. (i) Sailaja, G.; Nowshuddin, S.; Rao, M. N. A. *Tetrahedron Lett.* **2004**, *45*, 9297.
(281) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040.
(282) García-Fortanet, J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8108.

(283) (a) Martin, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561. (b) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.
(284) Eidamshaus, C.; Burch, J. D. *Org. Lett.* **2008**, *10*, 4211.
(285) Zheng, Z.; Alper, H. *Org. Lett.* **2008**, *10*, 4903.
(286) Suzuki, K.; Sawaki, T.; Hori, Y.; Kobayashi, T. *Synlett* **2008**, 1809.
(287) Jiang, H.; Ma, F.-F.; Xie, X.-M.; Zhang, Z.-G. *Youji Huaxue* **2008**, *28*, 1410.
(288) Solé, D.; Serrano, O. *J. Org. Chem.* **2008**, *73*, 9372.
(289) Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Linden, A.; Dorta, R. *Org. Lett.* **2008**, *10*, 5569.
(290) Niwa, T.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2009**, *65*, 1971.
(291) (a) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 4689. (b) Niwa, T.; Suehiro, T.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2009**, *65*, 5125.
(292) Garcia-Fortanet, J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8108.
(293) Marsden, S. P.; Watson, E. L.; Raw, S. A. *Org. Lett.* **2008**, *10*, 2905.
(294) Jiang, L.; Weist, S.; Jansat, S. *Org. Lett.* **2009**, *11*, 1543.
(295) Guo, Y.; Twamley, B.; Shreeve, J. S. *Org. Biomol. Chem.* **2009**, *7*, 1716.
(296) Pfefferkorn, J. A.; Choi, C. *Tetrahedron Lett.* **2008**, *49*, 4372.
(297) Barluenga, J.; Jiménez-Aquino, A.; Aznar, F.; Valdés, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031.
(298) Millemaggi, A.; Perry, A.; Whitwood, A. C.; Taylor, R. J. K. Eur. J. Org. Chem. 2009, DOI: 10.1002/ejoc.200900294.
(299) Storgaard, M.; Dörwald, F. Z.; Peschke, B.; Tanner, D. J. Org. Chem. 2009, DOI: 10.1021/jo900799y.
(300) Wang, H.; Gao, K.; Jiang, Y.; Ma, D. *Heterocycles* **2009**, *79*, 695.
(301) Wang, F.; Liu, H.; Fu, H.; Jiang, Y.; Zhao, Y. Org. Lett. 2009, *11*, DOI: 10.1021/ol900847t.
(302) Ma, D.; Cai, Q. *Acc. Cheet m. Res.* **2008**, *41*, 1450.

CR9000836