T. J. Colacot and C. C. C. Johansson

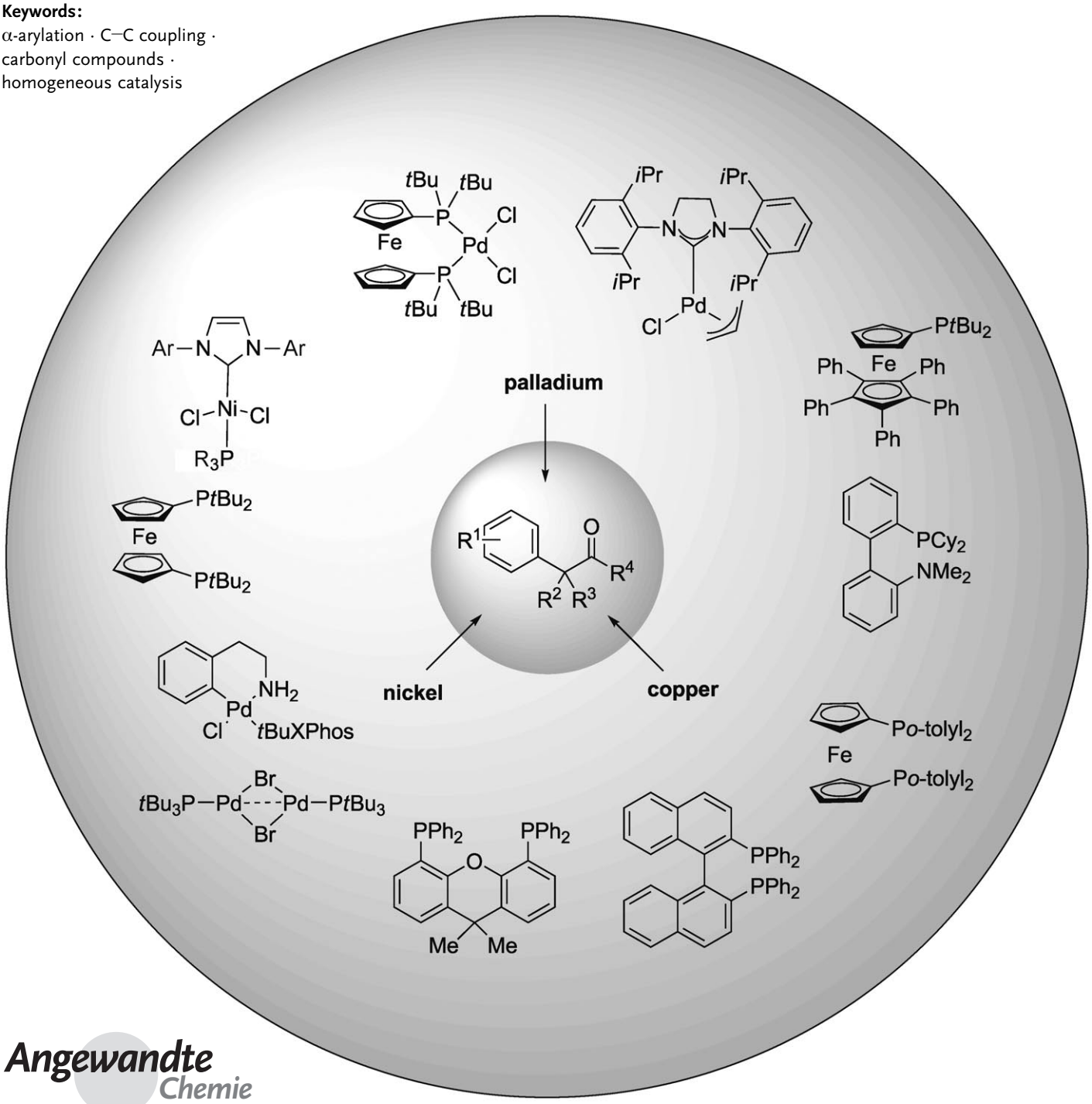
DOI: 10.1002/anie.200903424

α-Arylation

Metal-Catalyzed α-Arylation of Carbonyl and Related Molecules: Novel Trends in C–C Bond Formation by C–H Bond Functionalization

*Carin C. C. Johansson and Thomas J. Colacot**

Keywords:
α-arylation · C–C coupling · carbonyl compounds · homogeneous catalysis

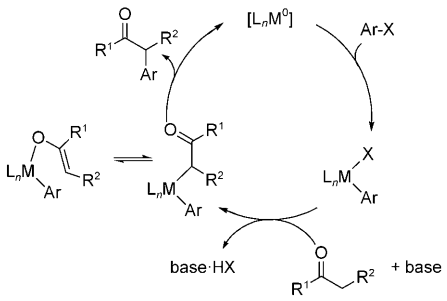


***α*-Arylated** *carbonyl compounds are commonly occurring motifs in biologically interesting molecules and are therefore of high interest to the pharmaceutical industry. Conventional procedures for their synthesis often result in complications in scale-up, such as the use of stoichiometric amounts of toxic reagents and harsh reaction conditions. Over the last decade, significant efforts have been directed towards the development of metal-catalyzed α-arylations of carbonyl compounds as an alternative synthetic approach that operates under milder conditions. This Review summarizes the developments in this area to date, with a focus on how the substrate scope has been expanded through selection of the most appropriate synthetic method, such as the careful choice of ligands, precatalysts, bases, and reaction conditions.*

From the Contents

1. Introduction

The metal-catalyzed α-arylation of carbonyl compounds has been extensively studied over the last decade as a method to form C–C bonds. This is because of the importance of α-aryl carbonyl moieties in many organic compounds which possess interesting pharmacological and biological properties.[1] Prior to this technology, a number of classical organic reactions were employed to construct some of these important structural motifs. Conventional nucleophilic aromatic substitution was only suitable when highly activated aryl halides were employed,[2] while other methods involved the use of stoichiometric amounts of metal catalysts with preformed enolates.[3] These transformations, however, suffer from many practical drawbacks, such as functional-group compatibility, air and moisture sensitivity, and toxicity of the reagents. It was therefore highly desirable to develop efficient catalytic methods to address the arylation of various carbonyl compounds with unactivated, less-reactive aryl halides or pseudohalides. The end result of an α-arylation reaction is a formal sp^2–sp^3 coupling through cleavage of a C–H bond. In most processes, an intermediate metal enolate is formed, which undergoes transmetalation to allow the final reductive elimination to achieve the C–C coupling. The general catalytic cycle for the α-arylation of carbonyl compounds is depicted in Scheme 1.[4] The mechanism of the reaction follows the conventional coupling pathway, although the equilibrium between the Pd–O and Pd–C species in the transmetalation can be the rate-determining step once the oxidative addition is accomplished.



Scheme 1. General catalytic cycle for α-arylation reactions. L = ligand.

Several factors can determine the success of a metal-catalyzed α-arylation reaction: the use of in situ generated versus preformed metal complexes as catalysts, the nature of the aryl halide, carbonyl compound, base, and solvent, the stoichiometry of the reagents, and the reaction temperature. Once the metal is fixed (usually palladium), the ligands can influence the rate of several steps in the catalytic cycle, especially the oxidative addition and the subsequent reductive elimination step. In general, as in any other cross-coupling reaction, both the steric and electronic properties of the ligands are important. The more electron-rich ligands tend to stabilize the palladium(II) intermediate, thereby facilitating oxidative addition of the aryl halide, while the sterically hindered ligands make the reductive elimination more facile by pushing the aryl and enolate group at the palladium center closer together in space so that they coordinate in a *cis* mode.

During the past few years, significant understanding of the various factors influencing the α-arylation reaction has been gained, although the area is still under development in terms

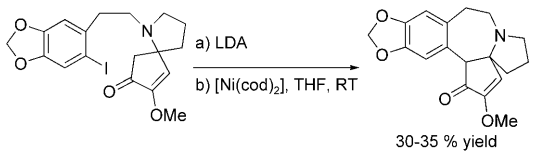
[*] Dr. T. J. Colacot
Catalysis and Chiral Technologies, Johnson Matthey
2001 Nolte Drive, West Deptford, NJ 08066 (USA)
Fax: (+1) 856-384-7035
E-mail: colactj@jmusa.com
Homepage: http://www.jmcatalysts.com/pharma/site.asp?siteid=485
Dr. C. C. C. Johansson
Protech Building, Johnson Matthey Plc
Orchard Road, Royston, SG8 5HE (UK)

of improving the activity, selectivity, and tolerance of the substrate to bases.

The main focus of this Review is to provide up-to-date information on the metal-catalyzed arylation of carbonyl compounds with an emphasis on, but not limited to, palladium-based catalysts under in situ and preformed conditions.[5] However, the reactions discussed are limited to the use of aryl halides or pseudohalides with enolates generated in situ from various carbonyl compounds such as ketones, amides, esters, aldehydes, as well as the few reported examples of the α-arylation of nitriles, sulfones, and nitro alkanes. Section 9 focuses enantioselective catalysis, as enantiopure compounds are extremely important in the pharmaceutical industries.

2. α-Arylation of Ketones

During the early 1970s, Semmelhack et al. proposed a nickel(0)-mediated C–C bond formation as the key step in the total synthesis of cephalotaxinone (Scheme 2).[6] Since this



Scheme 2. Final step in the nickel-catalyzed synthesis of cephalotaxinone by Semmelhack et al. LDA = lithium diisopropylamide, cod = cyclooctadiene.

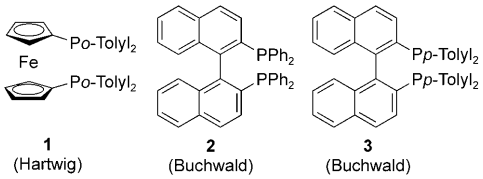
pathway did not follow the classical reactivity pattern for a nucleophilic aromatic substitution, an activation of the aryl ring by the oxidative addition of ArI onto a nickel(0) species was proposed. Subsequent reaction of the σ-aryl nickel complex with a carbanion generated with a base such as LDA, resulted in the desired ring closure to form the pentacyclic core structure of cephalotaxinone in 30–35% yield. This is one of the earliest examples of metal-catalyzed α-arylation reactions (the same research group has also found that a photostimulated SR_N1 activation pathway can effect the ring-closing reaction in a higher yield).

The metal-catalyzed α-arylation reactions of enolates derived from carbonyl compounds subsequently sparked interest to understand the potential scope and generality of this transformation. The most widely used catalysts for the α-arylation of ketones are palladium complexes, although a few nickel catalysts have been reported. There are three main groups of ligands that have been studied: tertiary phosphines, N-heterocyclic carbenes, and cyclic alkyl aminocarbenes. A number of methods have also been applied to the synthesis of biologically interesting molecules.[7]

2.1. Palladium Catalysis

2.1.1. First Generation Ligands

The research groups of Miura,[8,9] Buchwald,[10] and Hartwig[11] concurrently reported the intermolecular palladium-catalyzed direct α-arylation of ketones. In their initial studies, the more-reactive aryl iodides or aryl bromides were utilized as the coupling partners for C–C coupling of a ketone. Whereas Miura and co-workers used a $PdCl_2$ catalyst without a ligand, the choice of ligands employed by Palucki and Buchwald as well as Hamann and Hartwig proved to be crucial. Hamann and Hartwig used [$Pd(dba)_2$] in combination with 1,1′-bis(di-*o*-tolylphosphino)ferrocene (dtpf; **1**),[12] while Palucki and Buchwald observed superior results with a palladium and binap (**2**) or tol-binap (**3**) system (Scheme 3).



Scheme 3. First generation ligands employed in the α-arylation of ketones.

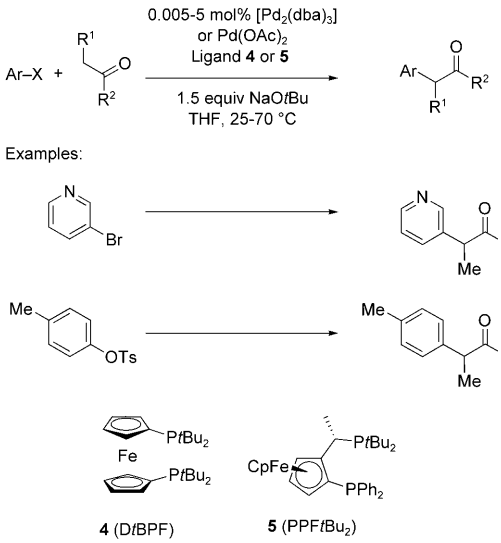
Prior to these reports, the majority of methods developed for this transformation involved the use of preformed main-group enol ethers[13] or toxic bismuth and lead reagents.[14] Therefore, the findings of the research groups of Miura, Buchwald, and Hartwig constituted a milestone in this field of

Dr Thomas J. Colacot obtained his PhD from the Indian Institute of Technology, Madras (1989) and an MBA from Penn State University (2004) in Strategy & New Venture. Before joining Johnson Matthey in 1995 he carried out postdoctoral research and undergraduate teaching at UAB and SMU (both US). Since 2003 he has been Development Manager in Homogeneous Catalysis (Global) of Johnson Matthey Catalysis & Chiral Technologies business unit, and occasionally teaches a graduate course in catalysis relevant to Organic Synthesis at Rutgers University (US). He is on the editorial board of Platinum Metals Review and The Open Catalysis Journal.

Carin Johansson studied at the University of Manchester Institute of Science and Technology, including a year abroad at l'Ecole Superieure Chimie, Physique, Electronique de Lyon (France), and in 2003 received her MChem. She then moved to the University of Cambridge (UK), where in 2006 she received her PhD while working for Dr. Matthew Gaunt. After further research with Dr. Gaunt, in 2008 she joined the Catalysis and Chiral Technologies division of Johnson Matthey in Royston (UK), where she is working on the development of novel homogeneous metal catalysts for organic transformations.

research, which opened up the possibility for the simple direct intermolecular arylation of ketones through the use of readily available starting materials without the need for stoichiometric amounts of reagents to generate the carbanion species. During this period, Buchwald also demonstrated the use of aryl chlorides in α-arylation reactions.[23] The research groups of Buchwald and Hartwig observed that palladium complexes of chelating ligands afforded the products in good yields. This was speculated to be due to the prevention of β-hydrogen elimination from the palladium enolate by the use of bulky chelating ligands, which force the palladium complex to be in a four-coordinate state. Also, it was generally observed that the bulkier the phosphine ligand was, the better the yield of the reaction. In addition, Palucki and Buchwald also hypothesized that diarylation may be suppressed by the use of very bulky ligands.[10]

A number of other research groups also showed an early interest in this field of catalysis. For example, Muratake et al. developed a palladium-catalyzed intramolecular α-arylation reaction of ketones,[15] and Miura and co-workers extended their work on the arylation of 2-phenylphenol to include the selective α-arylation of acetophenone.[8,16] Both methods were based on the use of a palladium/PPh_3 catalyst system.



Scheme 4. α-Arylation of ketones by Kawatsura and Hartwig. Cp = cyclopentadienyl, Ts = toluene-4-sulfonyl.

2.1.2. *Bulky Electron-Rich Phosphine Ligands*

For the rational design and development of more-active catalyst systems for the arylation of carbonyl compounds, Hartwig and co-workers tried to understand the catalyst properties relevant for this transformation. On the basis of previous findings, they suggested that two factors play major roles: Firstly, sterically demanding ligands should be able to stabilize the palladium center and thereby decrease the energy of the reactive low-coordinate palladium(0) intermediates. Secondly, alkyl phosphines are known to donate more electron density to the metal and, therefore, are less prone to undergo P–C cleavage than their respective aryl analogues, thereby resulting in higher turnover numbers. In addition, chelating ligands inhibit β-hydrogen elimination from the intermediates—a pathway that prevents the formation of the desired α-aryl ketone as previously observed by the research groups of Hartwig and Buchwald.[10,11] Based on these hypotheses, Kawatsura and Hartwig evaluated palladium sources in conjunction with a number of different phosphine ligands in the α-arylation of ketones (Scheme 4).[17] It was found that the bulky chelating bisphosphine ligand D*t*BPF (**4**) in conjunction with a palladium source provided a very effective catalyst system for the arylation of ketones with both bromo- and chloroarenes. Interestingly, arylation reactions could be carried out with aryl tosylates when the D*t*BPF ligand was substituted by the related PPF*t*Bu_2 bisphosphine ligand **5**.

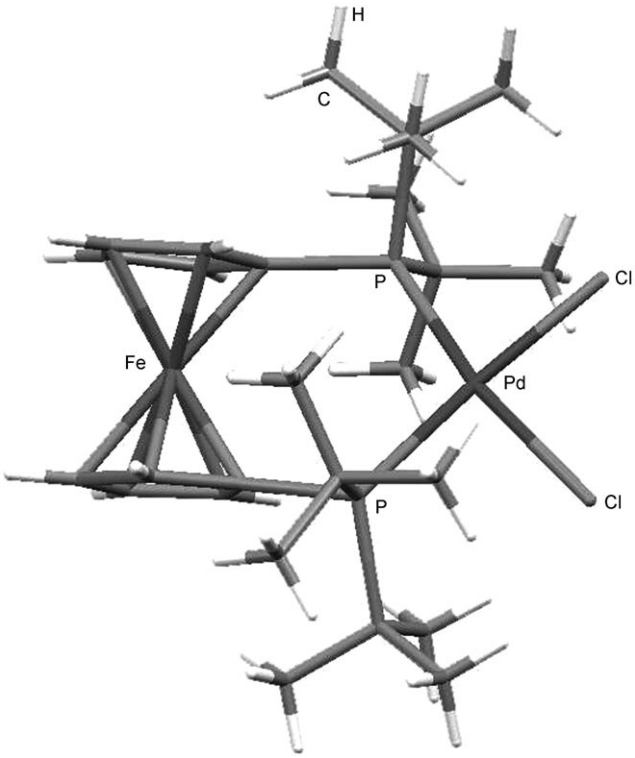
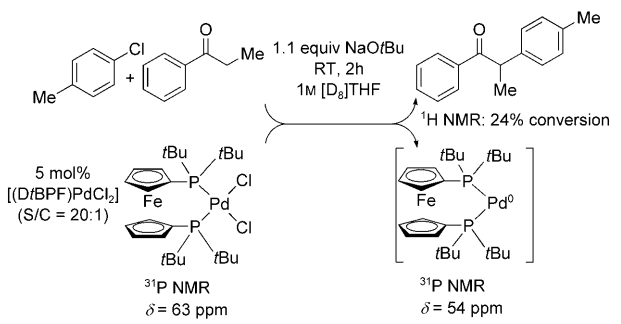


Figure 1. X-ray structure of **6** (P-Pd-P bite angle 104.22°).

Grasa and Colacot also investigated the utility of D*t*BPF in the α-arylation of ketones.[18] Following the successful application of the air-stable precatalyst [$PdCl_2$(D*t*BPF)] (**6**; Figure 1) in the Suzuki reaction,[19] the same complex was initially explored in the arylation of propiophenone. It was found that the activity of the preformed catalyst was significantly superior than the complex formed in situ from [Pd_2(dba)$_3$] and D*t*BPF. The in situ catalysis using Pd and D*t*BPF in a ratio of 1:1 gave very poor conversion. Interestingly, the preformed [$PdCl_2$(D*t*BPF)] catalyst was very active, even though the palladium/D*t*BPF ratio was 1:1.[18]

To gain insight into the differences between the reactions with an in situ catalyst and the one with a preformed complex the reaction mixture was monitored by NMR spectroscopy

(Scheme 5). The fact that only one ^{31}P NMR resonance ($<\iota\tau>\delta<\iota\tau>=54$ ppm) was observed during the catalysis suggests that both P atoms are coordinated to the palladium



Scheme 5. NMR spectroscopic monitoring of the reaction of *p*-chlorotoluene with propiophenone in the presence of [$PdCl_2$(D*t*BPF)].

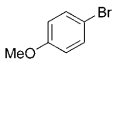
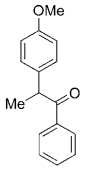
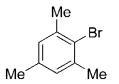
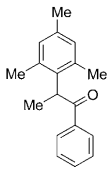
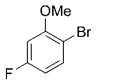
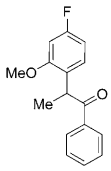
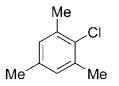
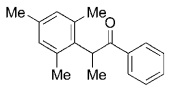
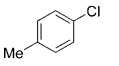
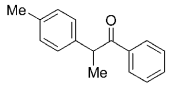
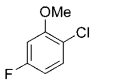
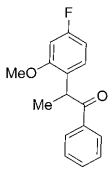
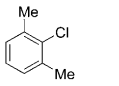
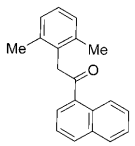
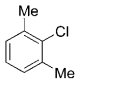
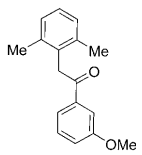
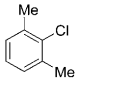
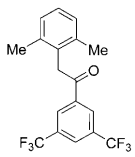
center, at least in the ground state of the catalytically active species.[18] The lower activity of the in situ catalyst system, where the palladium/ligand ratio was 1:1, might be due to the formation of the thermodynamically stable 18-electron species [$Pd(DtBPF)_2$], which may not equilibriate back to the 14-electron species[Pd(D*t*BPF)], as observed by Buchwald and co-workers in the case of the palladium/XantPhos (**12**) system for C–N coupling (for the structure of XantPhos see Scheme 8).[20]

The products of the [$PdCl_2$(D*t*BPF)]-catalyzed coupling between various aryl halides and propiophenone were isolated in yields up to 97% (Table 1). The monoarylation of acetophenone derivatives using sterically demanding aryl halides was achieved in good yield.

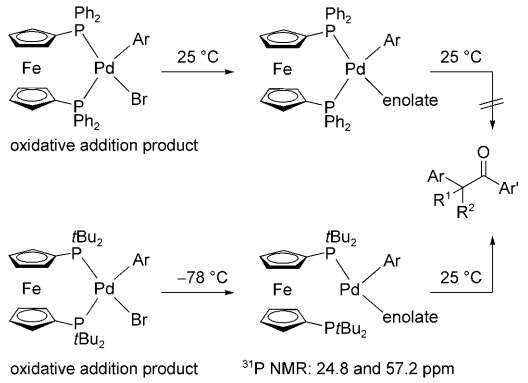
Subsequent improvement of this process indicated that these reactions can be carried out at significantly lower catalyst loadings within 1–3 h, even on a 10 g scale, with a simple work-up.[21] The catalyst is also useful for room-temperature arylations. At lower catalyst loadings, the purity of the ether-based solvents such as THF and dioxane seems to be important. Lower activities were observed when using older bottles of solvents which had been opened for a few months; this finding might be due to the formation of peroxides. A trace amount of moisture does not seem to have any negative effect.

In contrast to the reaction carried out with the preformed palladium complex **6**,[18,21] Kawatsura and Hartwig had earlier suggested that the intermediate palladium enolate complex formed in the in situ reaction remains monocoordinated to one of the phosphorus atoms of the bidentate ligand,[17] thereby maintaining a tricoordinate palladium state when the bulky D*t*BPF ligand was used (Scheme 6). This is somewhat contradictary to work carried out by Colacot et al. (see Scheme 5). When less-bulky diphenylphosphinoferrocene (DPPF) was used, the palladium center remained tetracoordinate, with no reductive elimination at room temperature. Therefore, Hartwig and co-workers recommended that one could use sterically hindered monophosphines instead of using a bulky bidentate ligand such as D*t*BPF in the α-arylation reactions.

Table 1: Arylation of Ar-X (X = Br, Cl) with propiophenone.

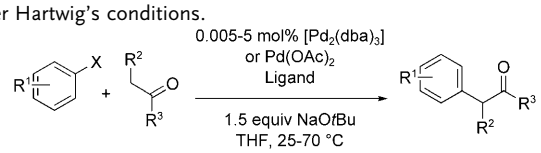
Entry	ArX	Product	Yield [%]
1			97
2			81
3			65
4			90
5			95
6			61
7			95
8			91
9			60

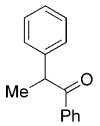
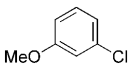
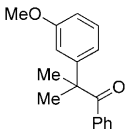
To prove the hypothesis, commercially available monophosphines such as P*t*Bu_3 and PCy_3 (Cy = cyclohexyl) in conjunction with [$Pd_2(dba)_3$] or $Pd(OAc)_2$ were evaluated in the α-arylation reactions.[5b,17] The coupling processes were observed to proceed in high yields when various aryl bromides or chlorides were employed (Table 2). It was noteworthy that two equivalents of base were required for selective monoarylation: the α-hydrogen atom in the product is more acidic than that in the starting material, and the excess base ensures complete deprotonation of both product and starting ketone. As a consequence of the more sterically



Scheme 6. A tricoordinate palladium species observed in the enolate step prior to the reductive elimination (according to Kawatsura and Hartwig).

Table 2: Palladium-monophosphine-catalyzed α-arylation of ketones under Hartwig's conditions.



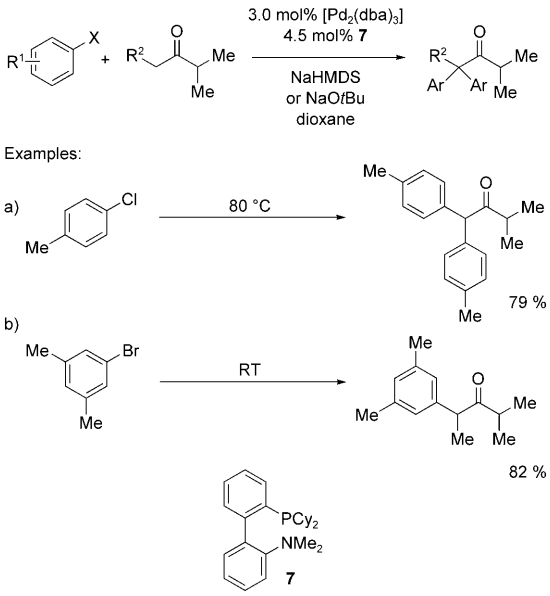
Entry	ArX	Product	Ligand	Yield [%]
1	PhBr		$PtBu_3$	98
2			PCy_3	93
3			$PtBu_3$	82

hindered α position in the product, the enolate of the starting material reacts preferentially to facilitate the monoarylation selectivity.

Beller and co-workers also used bulky electron-rich monophosphines as ligands for the α-arylation of a number of ketones in the presence of a $Pd(OAc)_2/n$BuPAd$_2$ (Ad = adamantyl) catalyst system.[22] Generally, this method afforded the α-arylated products in lower yields than those obtained by using the Hartwig method.

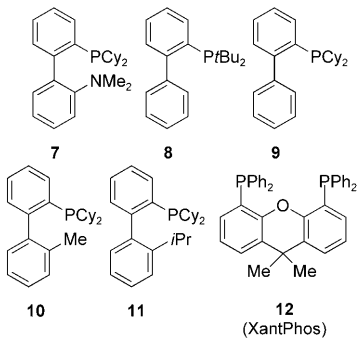
2.1.3. *Biaryl Electron-Rich Phosphine Ligands*

The hypothesis by Palucki and Buchwald that bulky phosphine ligands suppress diarylation[10] was subsequently investigated in a number of cases. The study substantiated that the use of less-bulky ligand **7** in the α-arylation reaction resulted exclusively in the diarylation product when methyl ketones were used as substrates (Scheme 7 a).[23] By using ligand **7**, Buchwald and co-workers also demonstrated for the first time, an effective room-temperature arylation (Scheme 7 b).[23] The high catalytic activity of the catalyst generated from this ligand could be due to the more electron-rich nature of the cyclohexyl groups on the phosphine compared to the aryl substituents on the binap ligand. This finding indicates, as in the studies by Hartwig and co-workers, that both the steric and the electronic properties of the ligand are important in the palladium-catalyzed α-arylation reactions.



Scheme 7. Diarylation of methyl ketones and room-temperature monoarylation at the α position by using Buchwald's ligand.

Subsequently, Buchwald and co-workers used their newly designed biaryl ligands, such as **7**–**11**, as well as the known XantPhos (**12**), in α-arylation reactions of ketones. Previous studies indicated that in some cases the presence of ligands **8** and **9** resulted in more active catalysts than did ligand **7** (Scheme 8). For the reactions where ligand **7** was necessary for high catalytic activity, it had been noted that the alternative phosphines **10** and **11** provided activities comparable to **7**, but with the advantage of a more facile synthesis. It is interesting that prior to exploring the newly developed ligands in α-arylation chemistry, Buchwald and co-workers had investigated the reaction in the absence of any ligands.[24] Surprisingly, the limited number of aryl bromides tested gave α-arylated propiophenone in moderate to good yields.



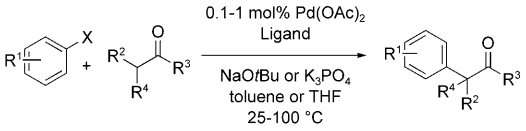
Scheme 8. Structures of the arylation ligands **7**–**11** and of XantPhos (**12**).

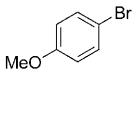
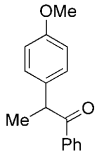
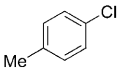
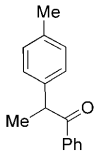
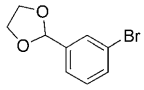
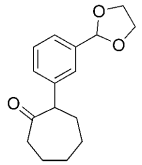
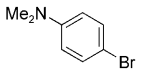
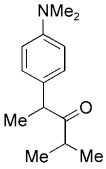
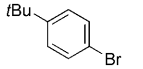
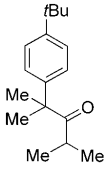
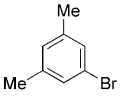
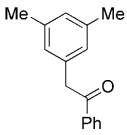
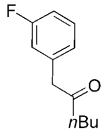
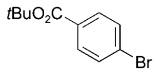
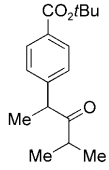
Although phosphines **8** and **9** in combination with a palladium source served as effective catalysts for reactions with a number of substrates, in many cases, however, the yields were unsatisfactorily low. To elucidate whether there is a need in these cases for a second coordinating group on the ligand (ligand **7** has a coordinating NMe_2 group, while **8** and **9** can form palladacycles), ligand **10** was synthesized in which one *ortho* position is blocked with a Me group. It was found that ligand **10** in conjunction with $Pd(OAc)_2$ acted as an active catalyst for the α-arylation of a variety of different substrates with catalyst loadings as low as 0.1 mol%. As Kawatsura and Hartwig had observed earlier,[17] the use of two equivalents of base suppressed diarylation of the substrates and provided cleaner reactions when carried out at room temperature. When the Me group was replaced by an *i*Pr group, ligand **11** in combination with $Pd(OAc)_2$ (1 mol%) provided the monoarylated product in good yield. A detailed study was carried out using the bidentate phosphine ligands to understand the increase in regioselectivity obtained with ketones containing acidic protons in both the α and α′ positions.[24] Buchwald and co-workers also developed a very efficient method for these type of substrates by using a $[Pd_2(dba)_3]$/XantPhos (**12**) catalyst system,[23] where XantPhos (**12**) has a relatively large bite angle (111°)[25] compared to many bidentate ligands. Catalyst loadings as low as 0.2 mol% palladium could be used.[23] Generally, the substrate scope could be improved by substituting NaO*t*Bu for a milder base, such as K_3PO_4. Interestingly, in the case of *o*-halonitroarenes, a phenol additive significantly improved the efficiency of the reaction: The use of $[Pd_2(dba)_3]$/ligand **7** in the presence of a phenol (20 mol%) enabled a number of methyl ketones to be efficiently arylated and subsequently transformed to polysubstituted indoles by a reductive cyclization reaction.[26]

The above studies illustrate how a careful combination of ligand and base could improve the reactivity and selectivity of a coupling reaction such as α-arylation. The choice of catalyst system is dictated by the nature of both substrates—the ketone and the aryl halide. A few examples of the optimized systems are listed in Table 3. In their recent studies, Biscoe and Buchwald used palladacycle **13**, which contains one of the ligands from the Buchwald research group (X-Phos **14**), to increase the selectivity of the monoarylation of methyl ketones (Scheme 9).[27]

Since phenols, like aryl chlorides, are also very readily available starting materials, the development of methods in which aryl triflates are employed was of great importance, although these compounds are relatively expensive to prepare and sometimes difficult to handle. The reactivity of ArX increases in the order: ArOTs < ArCl < ArOTf < ArBr; however, aryl tosylates are easy to handle and cheaper than aryl triflates. Kawatsura and Hartwig reported the first example of the use of an aryl tosylate in the α-arylation of propiophenone in which a catalyst generated from $Pd(OAc)_2$ and PPF*t*Bu_2 was employed.[17] Buchwald and co-workers later expanded the substrate scope for this transformation by using $Pd(OAc)_2$ in combination with X-Phos (**14**).[28] A fairly efficient α-arylation of ketones was demonstrated (75–85% yield; Scheme 10).

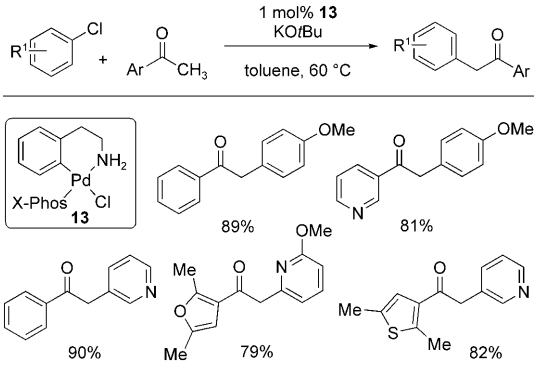
Table 3: Palladium-catalyzed α-arylation of ketones under Buchwald's conditions.



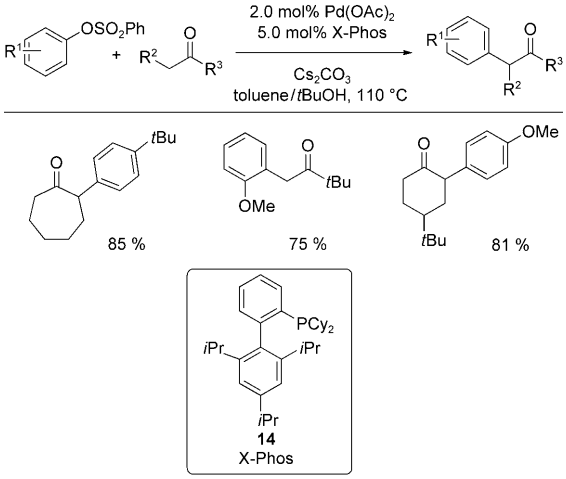
Entry	ArX	Product	Ligand	Yield [%]
1			–	93
2			**8**	91
3			**9** **10**	66 80
4			**10**	70
5			**10**	61
6			**11**	88
7			**12**	74
8			**12**	67

2.1.4. *Other Bulky Monophosphines*

Capretta and co-workers have described successful Suzuki cross-coupling reactions catalyzed by $[Pd_2(dba)_3]$ in the presence of a bulky tertiary phosphine with a phosphaadamantane ligand.[29] They also described the efficient α-arylation of ketones, this time by employing the preformed



Scheme 9. Monoarylation of methyl ketones under Buchwald's conditions.



Scheme 10. Arylation of aryl benzenesulfonates.

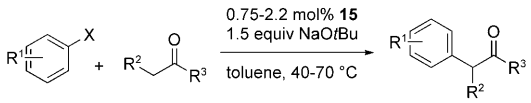
air-stable catalyst **15**.[29] In this way, the α-arylation of propiophenone or isobutyrophenone with a number of aryl bromides or chlorides was achieved in good to excellent yield (Table 4). Notably, the majority of substrates could be coupled even at 40 °C, which demonstrates the good activity of this catalyst.

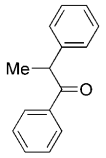
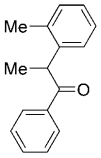
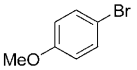
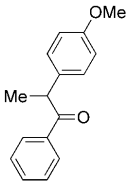
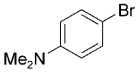
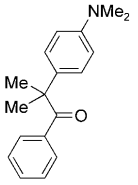
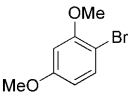
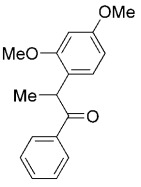
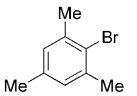
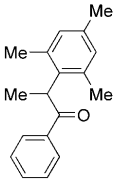
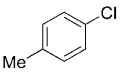
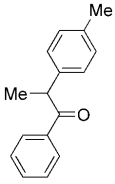
2.1.5. *N-Heterocyclic Carbene Ligands*

Although the majority of palladium catalysts employed in α-arylation reactions contain tertiary phosphines, Nolan and co-workers reported the use of N-heterocyclic carbenes (NHCs), which are highly σ-donating ligands, in the α-arylation of ketones.[30] In addition to the strong basicity, the substituents on the imidazole nitrogen atoms can provide the crucial steric bulkiness.

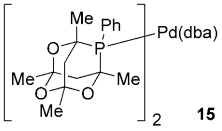
Nolan et al. had previously reported the formation of monomeric palladium species bearing only one NHC ligand by making the 16-electron [(NHC)Pd(allyl)Cl] complex **16**.[30a] It was proposed that the activation step of these catalysts involves the inter- or intramolecular nucleophilic attack of a base such as NaO*t*Bu or KO*t*Bu on the allylic moiety (Scheme 11).[31] This palladium complex was investigated in the α-arylation of ketones by using aryl chlorides and triflates (Table 5).

Table 4: Catalyzed α-arylation reactions using ArBr substrates according to Capretta and co-workers.

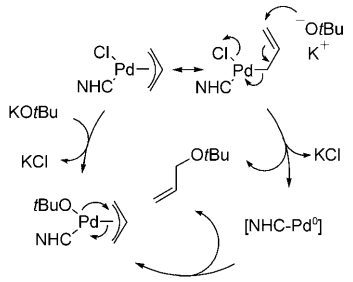


Entry	ArX	Product	Yield[a] [%]
1			93
2			95
3			96
4			93
5			80
6			87
7			78

[a] Yield of isolated product.



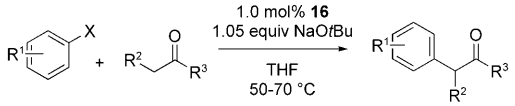
Nolan and co-workers also later discovered a second group of metal complexes with NHC ligands, this time by combining the beneficial properties of the carbene ligands with the robustness of palladacycles,[32] similar to the original

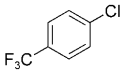
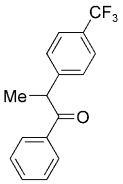
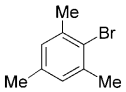
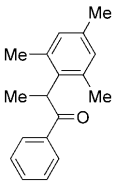
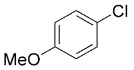
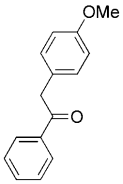
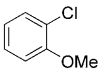
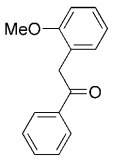
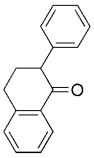
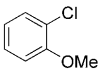
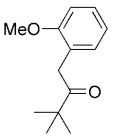
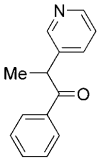
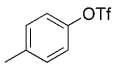
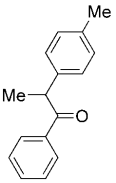
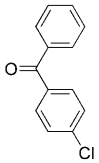
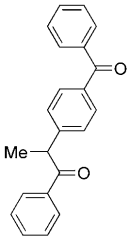
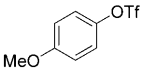
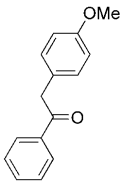


Scheme 11. Catalyst activation pathway proposed by Nolan and co-workers.

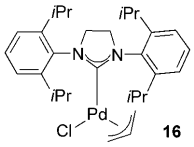
strategy of Buchwald and co-workers. The results obtained using catalyst **17** (Scheme 12) are comparable to those with allyl complex **16**. Here, the catalyst activation could occur by an attack of an alkoxide on the palladium center, thereby giving a palladium alkoxide species. Subsequent reductive elimination of this aryl palladium alkoxide intermediate would generate the active catalyst species. Alternatively, activation could occur through the formation of a palladacycle-NHC-aryl complex, which would undergo reductive elimination to form an arylated aminoaryl fragment and generate the [Pd(NHC)] species. Nolan and co-workers also reported the use of air- and moisture-stable palladium(II) precatalyst **18** (Scheme 12) in α-arylation reactions.[33] The

Table 5: Arylation of ketones according to Nolan and co-workers.

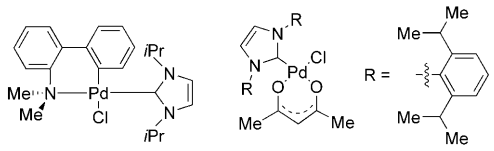


Entry	ArX	Product	Yield[a] [%]	Entry	ArX	Product	Yield[a] [%]
1			81	6			72
2			78	7			80
3			50[b]	8			91[a]
4			60	9			93
5			71	10			87

[a] Yield of isolated product. [b] Yield determined by NMR spectroscopic analysis.



16



17 **18**

Scheme 12. N-Heterocyclic carbene ligands developed by Nolan and co-workers.

yields of the α-arylated ketones in this process were slighly improved in comparison to their previous methods.

A nice application of N-heterocyclic carbenes in α-arylation is shown in the study by Matsubara et al. on step-growth polymerization.[34] Prior to this report, Wu and co-workers had explored the use of the bulky phosphine ligands P*t*Bu$_3$, P(*o*-tolyl)$_3$, and binap (**2**) in the polycondensation reactions of haloaryl ketones; however, the catalyst loading was relatively high (10 mol% Pd(OAc)$_2$ or [Pd$_2$(dba)$_3$]).[35]

2.1.6. Cyclic Alkylaminocarbenes

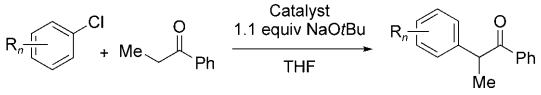
In addition to bulky electron-rich phosphines and cyclic diaminocarbenes (N-heterocyclic carbenes), a third group of ligands was developed by Bertrand and co-workers.[36] These ligands are stable cyclic alkylaminocarbenes (CAACs), where one of the electronegative amino susbtituents has been replaced by an alkyl group to take advantage of the σ-donor ability of the amino group, hence making them more electron-rich than both NHCs and tertiary phosphine ligands. Furthermore, the presence of the tertiary carbon atom, which forms part of the cyclohexane ring, provides a "flexible steric bulk" that differs from the steric bulk of the other two classes of ligands.[37] The strong σ-donating properties combined with the flexible steric bulk should, in theory, further accelerate the oxidative addition, transmetalation, and reductive elimination in the catalytic cycle of the α-arylation reaction compared to NHCs.

Bertrand and co-workers explored the effect of these air-stable CAAC ligands in the α-arylation reaction of ketones at room temperature (Table 6).[36] Prior to this study, no α-arylation was successful at room temperature with aryl chlorides, especially with sterically hindered, *ortho*-disubstituted aryl chlorides. A dramatic difference in activity was observed with catalysts **19**–**21** (Scheme 13): While **21** proved to be the most effective catalyst for the coupling of unhindered aryl chlorides, complex **20** was more active for bulky aryl chlorides. This difference can be rationalized on the basis of the "steric and electronic match" between the substrate and the catalysts bearing different ligands.

2.1.7. Other Ligands

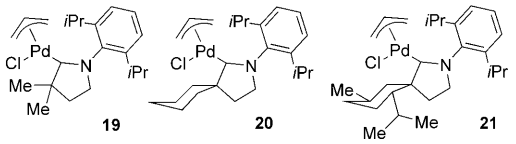
During the course of the studies on the in situ generation of diaminooxophosphine (daop) ligands through salt elimination from the corresponding chlorophosphine (Scheme 14), Ackermann et al. instead observed an oxidative addition of the chloride to the palladium center, with formation of a phosphenium cation.[38]

Table 6: Carbene-catalyzed α-arylation according to Bertrand and co-workers.



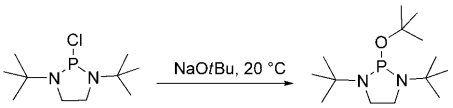
Entry	ArCl	Cat. (mol%)	*T* [°C]	Yield [%][a]
1	PhCl	**19** (0.5)	23	22
2	PhCl	**20** (0.5)	23	29
3	PhCl	**21** (0.5)	23	100
4	PhCl	**21** (0.01)	23	72
5	2-MePhCl	**19** (0.5)	23	0
6	2-MePhCl	**20** (0.5)	23	10
7	2-MePhCl	**21** (0.5)	23	82
8	2,6-Me$_2$PhCl	**19** (0.5)	23	0
9	2,6-Me$_2$PhCl	**20** (1.0)	50	81
10	2,6-Me$_2$PhCl	**21** (0.5)	50	0

[a] Yields as determined by NMR spectroscopy.



19 **20** **21**

Scheme 13. Palladium catalysts from Bertrand and co-workers.



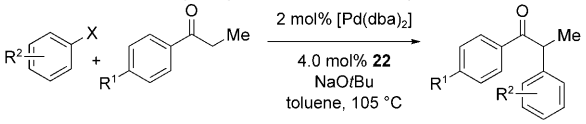
Scheme 14. Salt elimination from diaminochlorophosphine.

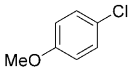
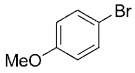
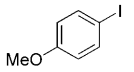
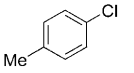
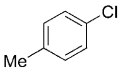
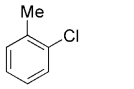
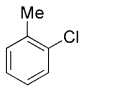
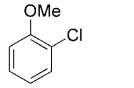
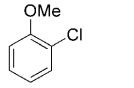
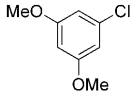
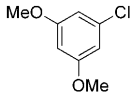
The oxidative addition products are isolobal with N-heterocyclic carbenes, which are ligands frequently used in coupling reactions. Ackermann et al. explored the activity of these novel phosphine ligands in the α-arylation of ketones. Crucially, no salt elimination was observed with phosphine chloride **22** in the presence of NaO*t*Bu, which would ensure that the desired oxidative addition of the chloride to the palladium center would occur. The α-arylated products could be obtained in good to very good yields (75–98%; Table 7) by using [Pd(dba)$_2$] and **22**. However, no examples with electron-poor aryl halides were demonstrated, and the loadings and reaction temperatures were significantly higher than for the [PdX$_2$(D*t*BPF)] (X = Br and Cl) catalyst employed for similar systems.[21]

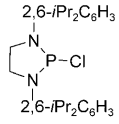
2.2. Nickel-Catalyzed Reactions

Nickel catalysts have also been gaining some attention, since nickel is cheaper than palladium. However, only a limited number of examples of useful reactions have been reported, as the starting nickel(II) salts are not easy to reduce to the nickel(0) species. Furthermore, the active nickel(0) compounds are toxic and/or highly air sensitive.

Table 7: Diaminochlorophosphine-mediated α-arylation.[a]



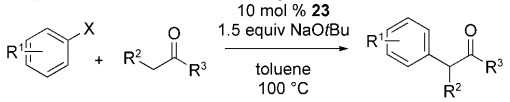
Entry	ArX	R^1	Yield [%]
1		H	90
2		H	98
3		H	96
4		H	92
5		OMe	90
6		F	90
7		OMe	89
8		F	80
9		OMe	78
10		H	75
11		OMe	87

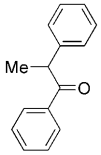
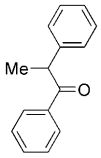
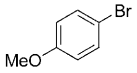
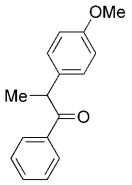
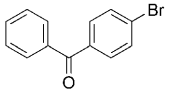
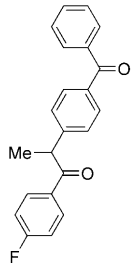
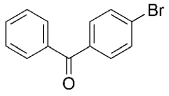
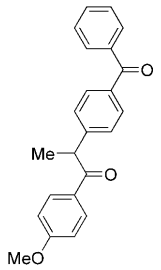
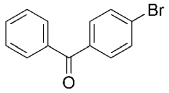
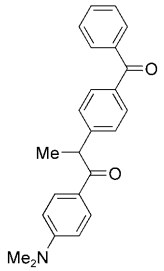
[a] 

22

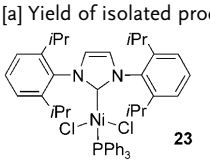
Buchwald and co-workers[39]and Chan and co-workers[40] had previously reported the asymmetric α-arylation of cyclic esters and cyclic ketones in the presence of a nickel(0) precursor and chiral ligands (see Section 9). Inspired by their success, Matsubara et al. developed the active, easy to prepare, and stable nickel catalyst **23** by incorporating an NHC as the stabilizing ligand.[41] NHC ligands also possess strong σ-donor properties and steric bulk. The activity of this catalyst may be attributed to its ability to eliminate triphenylphosphine, thereby creating a vacant coordination site on the nickel center. This mechanism is analogous to the activation of the Grubbs second generation metathesis catalyst, where Cy_3P dissociates to create a vacant site on the ruthenium center.[42]

Table 8: Arylation of ketones according to Matsubara et al.



Entry	ArX	Product	Yield[a] [%]
1			54
2			42
3			78
4			70
5			66
6			48

[a] Yield of isolated product.



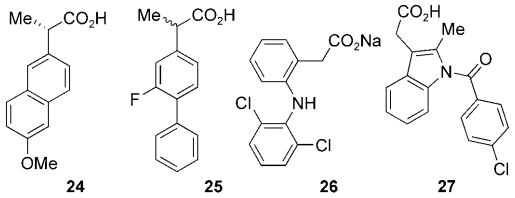
23

Efficient α-arylation of a number of propiophenone derivatives could be achieved using 10 mol% of **23** to afford the product in moderate to good yield (Table 8). Notably,

these are the only examples of nickel-catalyzed α-arylation reactions of acyclic ketones. However, these reactions may not be suitable for industrial applications because of the potential toxicity of the nickel catalysts.

3. Palladium-Catalyzed α-Arylation of Esters

α-Aryl esters and their derivatives are of great synthetic importance in organic chemistry because of the prevalence of this motif in several pharmacologically active ingredients with analgesic and anti-inflammatory properties.[5c] Some examples are naproxen (**24**), flurbiprofen (**25**), dichlofenac (**26**), and indomethacin (**27**; Scheme 15).

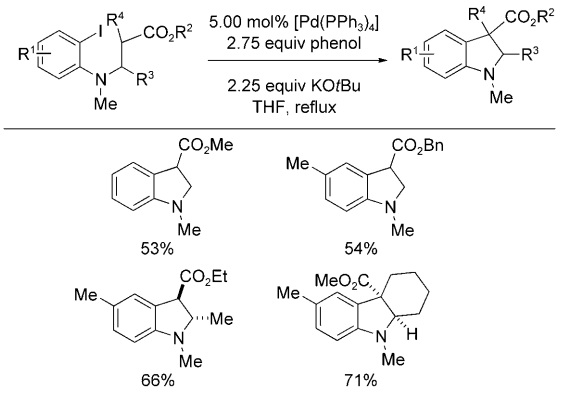


Scheme 15. Examples of anti-inflammatory drugs.

Prior to the development of the direct metal-catalyzed arylation of esters, which will be discussed in this section, very few catalytic and economically viable methods were available to construct α-aryl esters. While there are no regioselectivity issues associated with the α-arylation of esters, their lower reactivity and relative sensitivity to basic conditions makes this transformation intrinsically challenging. The potential for ester enolates to undergo a Claisen condensation also complicates the synthesis. Significant recent developments in this area have mostly been demonstrated by the research groups of Hartwig and Buchwald. In this section, the major focus will be on the syntheses of α-aryl esters by metal-catalyzed coupling reactions between aryl halides and in situ formed enolates of esters. However, there are a few alternatives to these syntheses, such as Goossen's approach, wherein an α-bromo ester is treated with an aryl boronic acid in the presence of a palladium catalyst.[43]

3.1. Triphenylphosphine-Based First Generation Catalysts

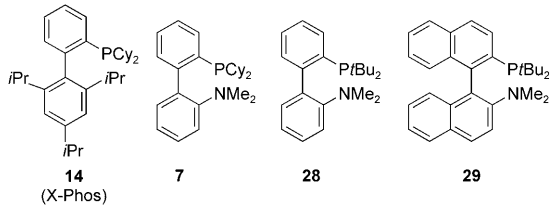
In the late 1990s, Satoh et al. reported, concurrently with their findings on the arylation of ketones, one of the first examples of the α-arylation of esters (Section 2).[44] They employed a palladium/triphenylphosphine-based catalyst system, as was also employed recently by Solé and Serrano in their intramolecular α-arylation reaction.[45] They demonstrated the cyclization of β-(2-iodoanilino) esters in the presence of $[Pd(PPh_3)_4]$ and potassium phenoxide to afford the indoline products in low to good yields (Scheme 16). Since a good background on the use of first generation catalysts was provided in Section 2.1.1 on ketone arylation, the discussion will not be further elaborated because of space limitation and limited synthetic relevance.



Scheme 16. Synthesis of indoline-3-carboxylic acid derivatives according to Solé and Serrano. Bn = benzyl.

3.2. Bulky Electron-Rich Biaryl Phosphines

Following the finding that bulky electron-rich *o*-biphenyl phosphines significantly improved the α-arylation reaction of ketones, Moradi and Buchwald reported an extensive study on the palladium-catalyzed α-arylation of esters.[46] A similar positive effect was also observed when these types of ligands were used in the arylation of nitroalkanes, malonoesters, and 1,3-diketones. In addition, a good functional-group tolerance and high regioselectivities were observed. The efficient arylation of a number of esters was achieved by employing $Pd(OAc)_2$ in combination with ligands **7**, **28**, or **29** (Scheme 17 and Table 9).

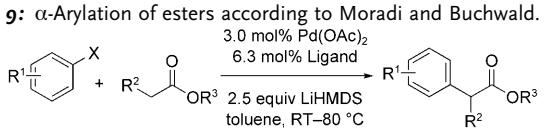


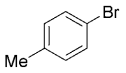
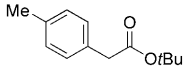
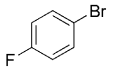
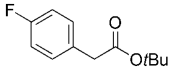
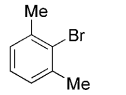
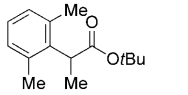
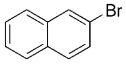
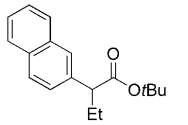
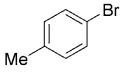
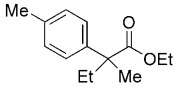
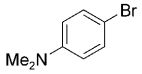
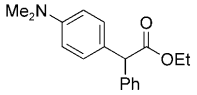
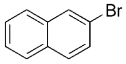
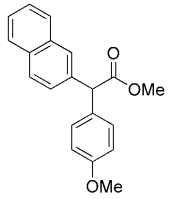
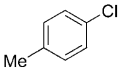
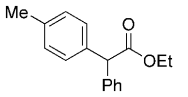
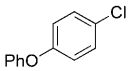
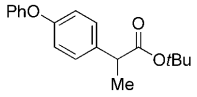
Scheme 17. Ligands employed by Moradi and Buchwald for the arylation of esters.

In accordance with previous results obtained in the alkylation of β-diketones,[47] the choice of counterion seems to be important to form a M–O bond with a more covalent character and thus provide selective monofunctionalization of the esters. As it is known that Li–O bonds are more covalent than Na–O bonds,[48] the use of lithium hexamethyldisilazide (LiHMDS) has resulted in the formation of monoarylated esters in good yields. The most general ligand for the coupling reaction of aryl bromides was **7**, while ligand **28** provided the best results for aryl chlorides.

Less attention has been paid to the development of intramolecular α-arylation reactions than the respective intermolecular versions. The research groups of Ciufolini,[49] Muratake,[15] Reissig,[50] Hartwig, and Buchwald have an interest in this field. Buchwald et al. reported the intramolecular arylation of α-amino acid esters in the presence of

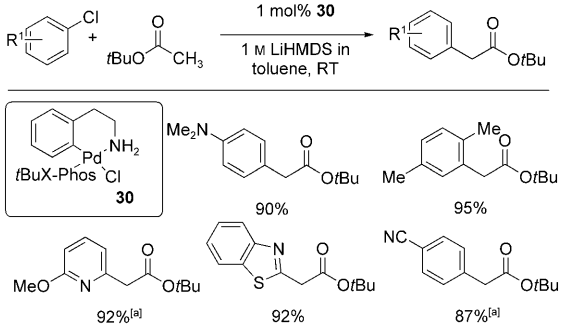
Table 9: α-Arylation of esters according to Moradi and Buchwald.



Entry	ArX	Product	Ligand	Yield [%]
1			**7**	81
2			**7**	71
3			**7**	68
4			**7**	81
5			**29**	48
6			**7** **28**	49 90[a]
7			**7**	83
8			**28**	82
9			**28**	54

[a] 1.5 mol% $[Pd(dba)_2]$ and 6.3 mol% **28** was used.

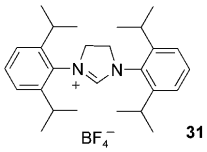
their highly effective biaryl P,N ligands to form isoindoline or tetrahydroisoquinoline carboxylic acid esters.[51] The reaction proceeded in high yields when the more sterically hindered biphenyl-based phosphine ligands were employed. The use of other simpler aryl phosphines or alkyl phosphines resulted in lower yields. It was proposed that the high activity of the biaryl phosphine ligands might arise from weak coordination between the biaryl moiety or the amino group and the metal center. It was also noted that the use of $[Pd_2(dba)_3]$ as a catalyst precursor resulted in superior results than $Pd(OAc)_2$, which could be explained by the potential of dibenzylideneacetone to act as a supporting ligand to the intermediate palladium(0) complexes. Buchwald and co-workers also demonstrated the first and only example of the use of aryl benzenesulfonates as coupling partners in the α-arylation of an ester.[28] For this transformation, $Pd(OAc)_2$/X-Phos (**14**) was used as the catalyst system to arylate ethyl phenyl acetate in very good yield (88%). Recently, Biscoe and Buchwald accomplished the selective monoarylation of methyl esters by employing palladacycle **30**, which bears a *t*BuX-Phos ligand, as the catalyst (Scheme 18).[27]



Scheme 18. Monoarylation of methyl esters using the palladacyle developed by Biscoe and Buchwald. [a] Reaction conducted at 0°C.

3.3. Other Bulky Electron-Rich Monodentate Ligands

In addition to the biaryl P,N ligands, there are two very prominent classes of ligands that have been shown to result in effective α-arylations, namely bulky alkyl monophosphines and nucleophilic carbenes. Hartwig and co-workers noticed that the α-arylation of esters could be carried out at room temperature by using 2 mol% $[Pd(dba)_2]$ and *N*-*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium (**31**; Scheme 19) or $PtBu_3$.[52]

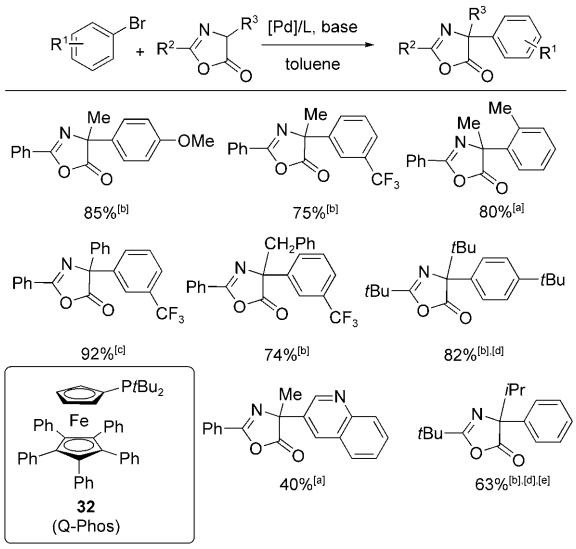


Scheme 19. Carbene ligand for the α-arylation of esters and amides.

While the method of Moradi and Buchwald required the use of two equivalents of ester[46] relative to each aryl halide, Hartwig and co-workers used only a slight excess of the ester.[52] However, 2.3 equivalents of the base were needed to ensure that the more acidic product would not quench the enolate of the starting material. Hartwig and co-workers subsequently improved this protocol by using $PtBu_3$ as a ligand and $LiNCy_2$ as a base. In many cases, the catalyst loadings could be reduced, and the number of equivalents of the base was lowered to 1.3.

While Gaertzen and Buchwald reported the intramolecular arylation of α-substituted amino acid derivatives,[51] Liu and Hartwig demonstrated the first intermolecular version of this reaction.[53] They used azlactones as amino acid derivatives, with the arylation carried out using $[Pd(dba)_2]$ or $Pd(OAc)_2$ in combination with $Ad_2P(tBu)$ or Q-Phos (**32**).[53] The arylation of azlactones derived from alanine, phenylalanine, phenylglycine, leucine, and valine underwent reaction in good yields (Scheme 20). Importantly, the azlactones can be readily hydrolyzed to generate α-aryl-α-substituted amino acids.[54]

Although significant advances in the metal-catalyzed arylation reactions of alkali metal enolates had been made in terms of reaction efficiency, the basic conditions required for this transformation limited the substrate scope. Components bearing nitro, cyano, carboxy, and keto groups were not



Scheme 20. α-Arylation of azlactones according to Liu and Hartwig. [a] 5.0 mol% $[Pd(dba)_2]$, 10 mol% Ad_2PtBu, 3.3 equiv K_2CO_3, 100 °C. [b] 5 mol% $Pd(OAc)_2$, 5 mol% Ad_2PtBu, 3.3 equiv K_3PO_4, 80 °C. [c] 5 mol% $Pd(OAc)_2$, 5 mol% Q-Phos (**32**), 3.3 equiv K_2CO_3, 80 °C. [d] 10 mol% Ad_2PtBu. [e] 100 °C.

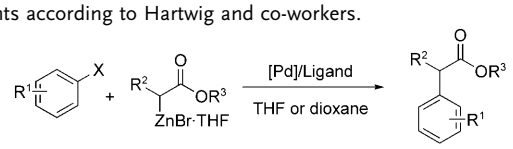
amenable to the reaction conditions. It was also difficult to achieve arylation at the more-hindered position of substrates bearing two acidic α protons. In addition, strong basic conditions also had an adverse effect on the enantioselective catalysis, as it favored the racemization of the newly formed tertiary stereocenters.

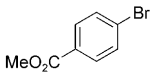
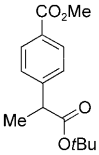
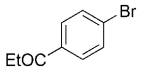
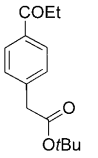
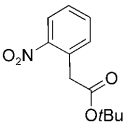
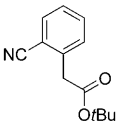
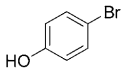
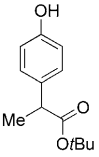
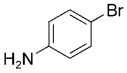
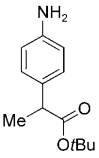
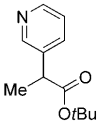
To alleviate such complications, Hartwig and co-workers developed an α-arylation reaction of esters and amides under less basic conditions,[55] which paralleled the cross-coupling reactions of zinc enolates. However, the range of aryl halides was very limited and the yields were generally low.[56] Hartwig and co-workers mostly utilized zinc enolates and aryl bromides as coupling partners in the presence of either $[Pd(dba)_2]$/Q-Phos (**32**) and the palladium(I) dimer $[\{Pd(\mu\text{-}Br)(tBu_3P)\}_2]$ (**33**). These are both highly efficient commercially available catalyst systems.[57] This significantly expanded the substrate scope of esters. Notably, most of the reactions could be carried out at room temperature with no formation of diarylated product (Table 10).

The discovery that **33** was an effective catalyst for the α-arylation of zinc enolates prompted Hama and Hartwig to further explore the use of this catalyst for the arylation of alkali metal enolates of esters with both aryl bromides and chlorides (Table 11).[58,59] The preformed catalyst **33** was found to be more efficient than the in situ $Pd/PtBu_3$ system. Generally, catalyst loadings were reduced to 0.2–0.25 mol%, while obtaining higher yields of the arylated products compared to those with the in situ $[Pd(dba)_2]/PtBu_3$ catalyst system, which used a loading of 0.4–1 mol% (Table 12).

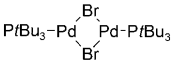
Moloney and co-workers also investigated the use of Reformatsky reagents in α-arylation reactions. They reported a microwave-assisted, $[Pd(PPh_3)_4]$-catalyzed arylation of the zinc reagent of *tert*-butyl acetate to give products in moderate yields.[60]

Table 10: Arylation of esters under mild conditions using Reformatsky reagents according to Hartwig and co-workers.



Entry	ArBr	Conditions[a]	Product	Yield [%]
1		A		87
2		A		94
3		A		87
4		B		81
5		C		95
6		C		66
7		A[b]		91

[a] A) 1 mol% $[Pd(dba)_2]$, 1 mol% Q-Phos (**32**), THF, RT; B) 0.5 mol $[\{[P(tBu)_3]PdBr\}_2]$ (**33**), THF RT; C) 0.5 mol **33**, 1.05 equiv KH, THF, RT. [b] 70 °C.

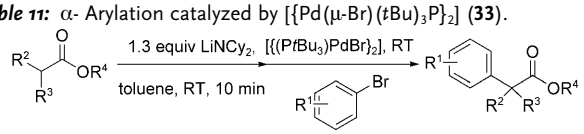


33

4. β-Difunctionalized Compounds

The difficulties encountered in the α-arylation of β-difunctionalized compounds are highlighted by the limited number of reports that can be found in the literature. The reactions prior to the recent palladium-catalyzed methods were carried out using stoichiometric or catalytic amounts of copper, mostly by using the more-reactive substrates such as aryl iodides.[61] Rawal and co-workers demonstrated the use

Table 11: α- Arylation catalyzed by [{Pd(μ-Br)(*t*Bu)$_3$P}$_2$] (**33**).



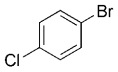
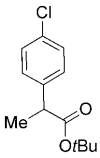
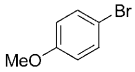
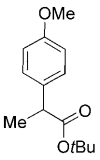
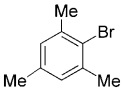
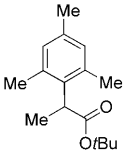
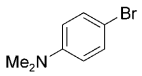
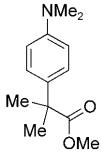
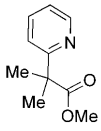
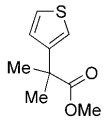
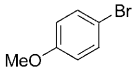
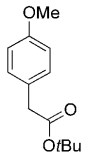
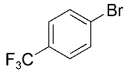
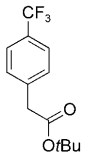
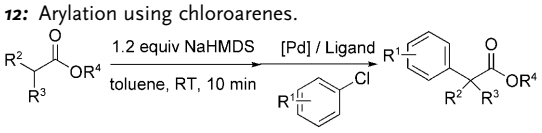
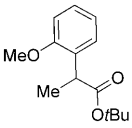
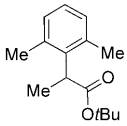
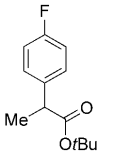
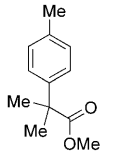
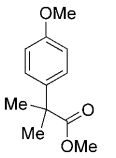
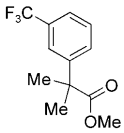
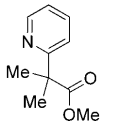
Entry	ArBr	Catalyst loading [mol%]	Product	Yield [%]
1		0.2		83
2		0.25		87
3		0.05		72
4		0.05		88
5		0.5		71
6		0.5		75
7		0.2		86
8		0.4		73

Table 12: Arylation using chloroarenes.



Entry	Conditions	Product	Yield [%]
1	1% [Pd(dba)$_2$]/1% P*t*Bu$_3$[a] 0.4% **33**		62 77
2	0.4% [Pd(dba)$_2$]/0.4% P*t*Bu$_3$[b] 0.2% **33**[b]		42 81
3	0.15% **33**[b]		73
4	0.4% [Pd(dba)$_2$]/0.4% P*t*Bu$_3$[c] 0.2% **33**[c]		79 84
5	0.4% [Pd(dba)$_2$]/0.4% P*t*Bu$_3$[c] 0.2% **33**[c]		69 73
6	0.4% [Pd(dba)$_2$]/0.4% P*t*Bu$_3$[c] 0.2% **33**[c]		81 75
7	0.4% [Pd(dba)$_2$]/0.4% P*t*Bu$_3$[c] 0.2% **33**[c]		66 71

[a] RT. [b] 60 °C. [c] 100 °C.

of an intramolecular α-arylation reaction of a β-ketoester to form the bicyclic framework of the welwitindolinones,[62] a family of indole alkaloids exhibiting potent biological (such as antifungal, larvacidal, and insecticidal) activities.[62]

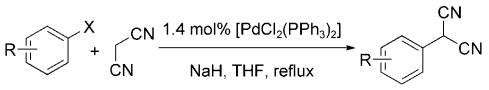
In this section, the α-arylation of malononitriles, malonoesters, and malonates by using palladium, copper, and nickel catalysts will be discussed.

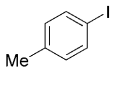
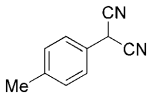
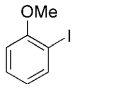
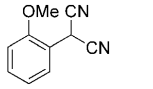
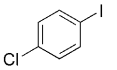
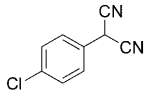
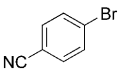
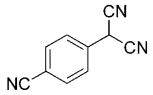
4.1. Palladium-Catalyzed α-Arylation

4.1.1. Palladium/PPh$_3$-Based First Generation Catalysts

Motivated by their successful development of a palladium-catalyzed method to couple aryl halides with ethynyl compounds,[63] Takahashi and co-workers reported one of the first examples of intermolecular α-arylation of dicarbonyl compounds through the use of the simple first generation catalyst [PdCl$_2$(PPh$_3$)$_2$] (Table 13).[64,65] Sakamoto et al.[66] and Ciufolini and Browne[49] independently reported the [Pd(PPh$_3$)$_4$]-catalyzed α-arylation of malononitriles and malonoesters in moderate yields. Ciufolini and Browne also demonstrated the intramolecular arylation of malonates.[49]

Table 13: α-Arylation of malononitriles according to Takahashi and co-workers.



Entry	ArX	Product	Yield [%]
1			92
2			72
3			86
4			56

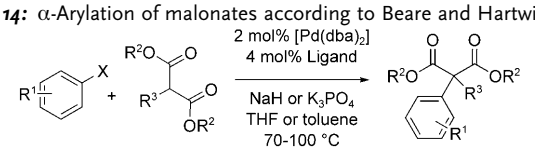
4.1.2. *Electron-Rich Alkyl Monophosphines*

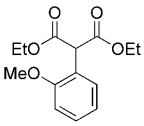
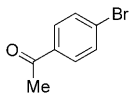
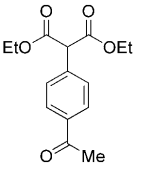
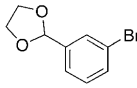
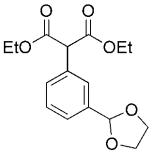
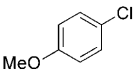
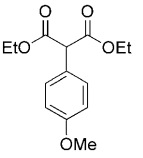
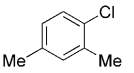
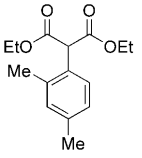
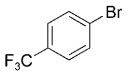
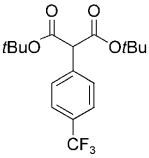
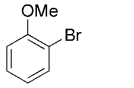
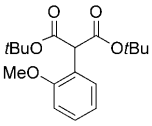
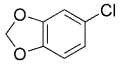
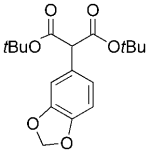
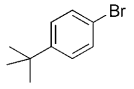
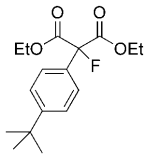
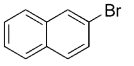
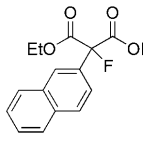
Kawatsura and Hartwig found that D*t*BPF or P*t*Bu$_3$ in combination with [Pd$_2$(dba)$_3$] or Pd(OAc)$_2$ can provide an effective catalyst system to arylate malonates under milder conditions.[17] Notably, the use of less electron-rich ligands, such as DPPF, **2**, PPh$_3$, and P(*o*-tolyl)$_3$, were not useful for this reaction. Kondo et al. subsequently also investigated the arylation of malonates by employing a [Pd$_2$(dba)$_3$]/P*t*Bu$_3$ system.[67] Changing the base from NaO*t*Bu to Cs$_2$CO$_3$ resulted in an accompanying decarboxylation of the arylated products.

To extend the substrate scope of the α-arylation of malonates, Beare and Hartwig carried out a more extensive ligand screen, even including **32** and P*t*Bu$_2$Ad (Table 14).[68] From this study, it was evident that both P*t*Bu$_3$ and D*t*BPF generated the most generally active palladium catalysts, although **32** or P*t*Bu$_2$Ad proved to be more successful ligands for aryl chloride substrates. It was even possible to decrease the palladium loading to 1 mol%, as was shown in the arylation of diethyl malonate with bromobenzene in the presence of a [{Pd(allyl)Cl}$_2$]/D*t*BPF combination. However, the reactions involving pyridyl halides as electrophiles and diethyl alkyl malonates failed to provide any of the desired products.

Following the successful development of α-arylation conditions for malonates, Hartwig and co-workers turned their attention to the arylation of the more-challenging cyanoacetates. Previously, the same research group demonstrated the use of fluorescence resonance energy transfer to screen the catalysts and conditions for this transformation.[69] By using this high-throughput screening technique, the use of [Pd(dba)$_2$] in combination with P*t*Bu$_3$ or P*t*Bu$_2$Ad was identified as the most active catalytic system for these types of arylation reactions. A wider range of substrates for this transformation was subsequently investigated (Table 15). In contrast to malonates, ethyl cyanoacetate could form the diarylated products under similar conditions.[68]

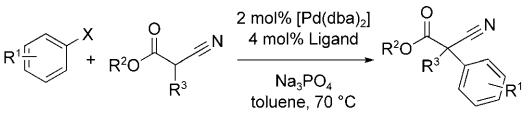
Table 14: α-Arylation of malonates according to Beare and Hartwig.

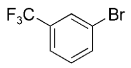
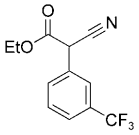
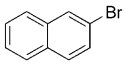
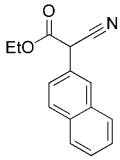
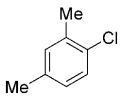
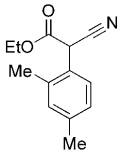
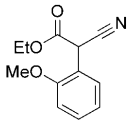
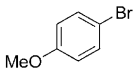
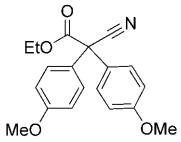
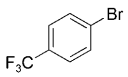
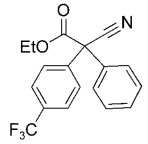
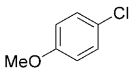
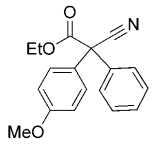
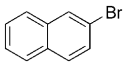
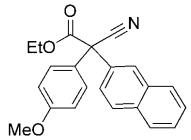


Entry	ArX	Ligand	Product	Yield [%]
1		D*t*BPF		89
2		D*t*BPF		89
3		D*t*BPF		87
4		P*t*Bu$_2$Ad		90
5		**32**		86
6		P*t*Bu$_3$		88 90[a]
7		P*t*Bu$_3$		86
8		P*t*Bu$_3$		87[b]
9		P*t*Bu$_3$		86
10		P*t*Bu$_3$		79

[a] 1 mol% [{Pd(allyl)Cl}$_2$], 1.1 equiv NaO*t*Bu, dioxane, 45 °C. [b] 1 mol% [{Pd(allyl)Cl}$_2$], 1.1 equiv NaO*t*Bu, dioxane, 100 °C.

Table 15: α-Arylation of cyanoacetates according to Hartwig and co-workers.

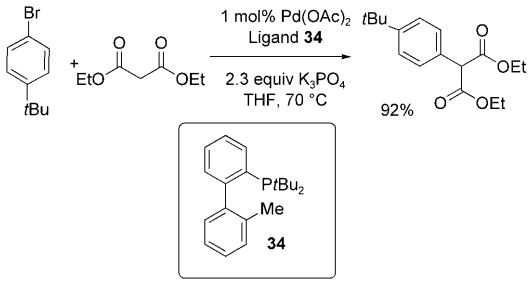


Entry	ArX	Ligand	Product	Yield [%]
1		P*t*Bu$_3$		87
2		**32**		91[a]
3		P*t*Bu$_3$		87
4		**32**		81
5		P*t*Bu$_3$		93[b]
6		P*t*Bu$_3$		91
7		P*t*Bu$_3$		91[c]
8		P*t*Bu$_3$		91

[a] 1 mol% [{Pd(allyl)Cl}$_2$], 100 °C. [b] 0.5 equiv cyanoacetate, 1.1 equiv aryl bromide, 4 mol% [Pd(dba)$_2$], 8 mol% P*t*Bu$_3$. [c] At 100 °C.

4.1.3. *Biaryl Phosphine Ligands*

There are few limited reports on the α-arylation of dicarbonyl compounds with the dialkylaryl phosphine systems developed by Buchwald and co-workers. Buchwald and co-workers reported one isolated example, where Pd(OAc)$_2$ in combination with ligand **34** catalyzed the α-arylation of diethyl malonate in good yield (Scheme 21).[24] Parkinson and co-workers later employed this catalytic system to α-arylate acetoacetate esters, which was followed by a subsequent decarboxylation to obtain 2-aryl acetic acid esters.[70]



Scheme 21. α-Arylation of malonates according to Buchwald and co-workers.

4.1.4. *Other Palladium-Catalyzed Reactions*

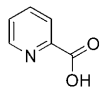
Urbano and co-workers have reported an α-arylation of malonates in which a heterogeneous base was used rather than a typical homogeneous base.[71] Na$_2$[PdCl$_4$] in combination with Ba(OH)$_2$ gave the highest conversions (97–98%), with high selectivity observed for the monoarylation products from various halobenzenes.

Verkade and co-workers also demonstrated the effective α-arylation of cyanoacetates by employing a [Pd$_2$(dba)$_3$]/proazaphosphatrane (**35**) catalyst system, as illustrated by the arylation of nitriles (see Scheme 39 in Section 7.2).[72,73]

4.2. *Copper-Catalyzed Arylation*

Although palladium catalysts are the most widely employed catalysts for α-arylation, the use of copper catalysts has also received some attention. Hurtley reported a pioneering study on the copper-catalyzed arylation of activated methylene compounds.[74] Initially, *o*-bromobenzoic acids had to be used as the coupling partners, which significantly narrowed the substrate scope. In a number of subsequent methods stoichiometric amounts of a copper complex were used at high reaction temperatures in polar solvents. In most cases reproducibility problems were encountered, although reasonably good yields were obtained in the cases of highly activated aryl halides.[75]

Miura and co-workers reported an improved process whereby arylation could be achieved by using a catalytic amount of copper iodide.[76] This method, however, suffered from low yields and narrow substrate scope. Hennessy and Buchwald subsequently improved the process by using a CuI/2-phenylphenol catalyst system to arylate malonates.[77] Ma and co-workers later developed a method in which CuI was used in combination with L-proline to efficiently arylate diethyl malonate in DMSO.[78] Kwong and co-workers subsequently reported a copper-catalyzed α-arylation of diethyl malonate that could be carried out at room temperature in dioxane.[79] A number of monodentate oxygen donor ligands and bidentate O,S and O,N ligands were explored in



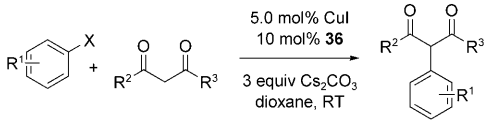
36

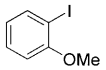
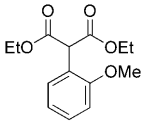
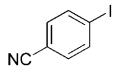
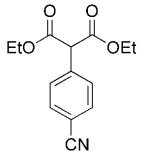
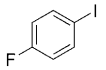
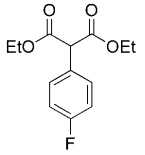
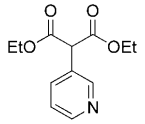
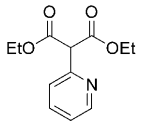
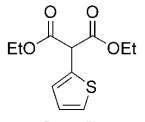
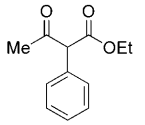
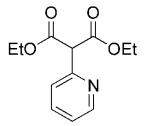
Scheme 22. Ligand used by Kwong and co-workers.

the coupling reaction. The use of 2-picolinic acid (**36**; Scheme 22) resulted in efficient arylation.

A number of aryl iodides and bromides, including heterocyclic iodides, afforded the arylated products in good yield (Table 16). Kwong and co-workers also demonstrated that their CuI/picolinic acid system can be applied in the arylation of a β-ketoester.[79]

Table 16: Copper-catalyzed arylation according to Kwong and co-workers.



Entry	ArI	Product	Yield [%]
1			92
2			82
3			73
4			77
5			90
6			68
7			78[a]
8			88[b]

[a] 70 °C. [b] 100 °C.

4.3. Nickel-Catalyzed Arylation

Cristau et al. reported the only example of a nickel-catalyzed α-arylation reaction of β-difunctionalized compounds.[80] The reaction of malononitrile with a number of aryl halides in the presence of in situ generated $[Ni(PPh_3)_3]$ afforded the products in moderate to good yields.

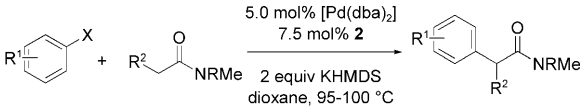
5. α-Arylation of Amides

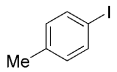
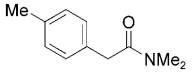
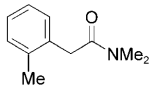
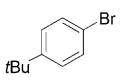
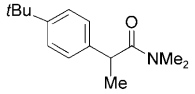
Following the successful arylation of ketone enolates, the search was then on to extend the methodology to enolates derived from amides. The higher pK_a values of amides compared to ketones meant that it was necessary to significantly modify the conditions for the arylation reaction. It was thus clear that this difference in acidity affected the rate of many steps in the catalytic cycle. A series of examples show the applicability of the α-arylation of amides to the total synthesis of biologically active compounds. Freund and Mederski demonstrated the rapid construction of 1,2-dihydro[indole-3,4′-piperidin]-2-ones,[81] which are present in a number of biologically active compounds, for example, neurokinin antagonists,[82] oxytocin antagonists,[83] and monoamine transporter inhibitors.[84] The intramolecular α-arylation of amides was similarly demonstrated by Honda et al. in the total syntheses of cherylline and latifine.[85]

5.1. First Generation Ligands

Hartwig and co-workers carried out a preliminary screen which showed that a $[Pd(dba)_2]$/**2** combination gave the best results for the α-arylation of amides (Table 17).[86] In all cases, a small amount of the diarylated product (ca. 10%) was also isolated. This method was also extended to intramolecular arylation to obtain oxindoles with complete regioselectivity.[86]

Table 17: Intermolecular arylation of amides according to Hartwig and co-workers.

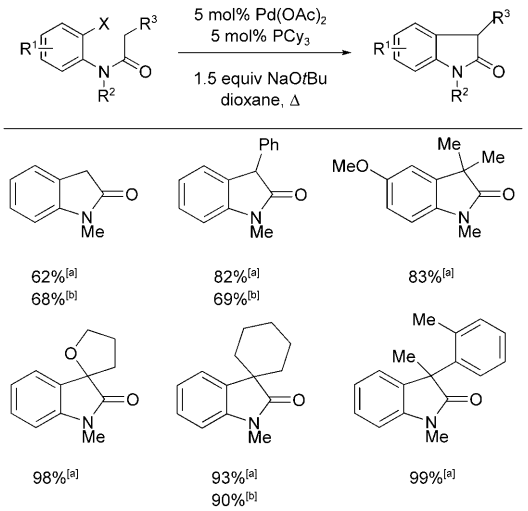


Entry	ArX	Product	Yield [%][a]
1			70
2			72
3			16[b,c]
4			49

[a] Yield of monoarylated product, although diarylation was observed in all cases. [b] $PtBu_3$ ligand was used. [c] GC yield.

5.2. Electron-Rich Monophosphine Ligands

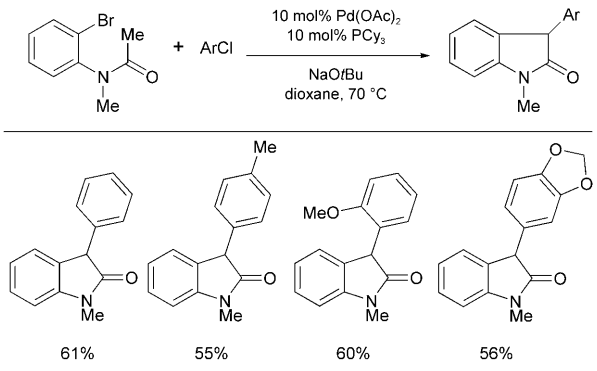
Encouraged by the results obtained with the [Pd(dba)$_2$]/**2** catalyst system, Lee and Hartwig investigated the use of the electron-rich monophosphine ligands that had provided good results in other α-arylation reactions.[87] It was found that a combination of Pd(OAc)$_2$ and PCy$_3$ efficiently promoted the oxindole formation. Notably, the PCy$_3$ ligand was not particularly effective in the arylation of ketones or malonates.[17] A wide range of α,α-disubstituted oxindoles could be synthesized effectively by using this method (Scheme 23). In



Scheme 23. Synthesis of oxindoles according to Lee and Hartwig. [a] X = Br, 50 °C [b] X = Cl, 70 °C.

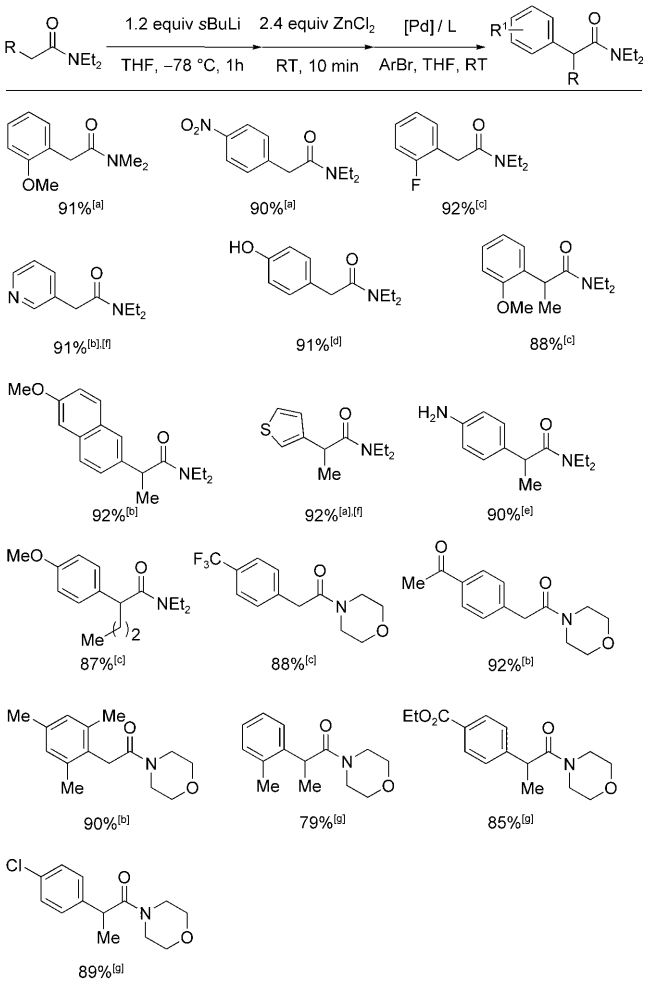
addition, the substrate scope was extended to include various aryl chlorides.[87] The same catalyst system could be employed at slightly increased catalyst loadings for tandem intra- and intermolecular arylation processes, through which α-arylated oxindoles could be prepared in moderate yields in two steps (55–61 %; Scheme 24).

The intermolecular arylation of acyclic amides presents problems since a stronger base is required for this transformation than for the α-arylation of ketones and esters. Other complications involve decomposition of the catalyst



Scheme 24. Intra- and intermolecular arylation according to Lee and Harwig.

caused by the strong base, which resulted in high catalyst loadings, in addition to the quenching of the starting enolate by the α-arylated product. Furthermore, diarylations are often observed as minor side reactions. To alleviate these problems, Hartwig and co-workers used zincamide enolates as starting materials rather than using alkali metal enolates.[55,88] These preformed Reformatsky reagents could be arylated effectively at room temperature by employing a catalyst formed from [Pd(dba)$_2$] and Q-Phos (**32**). Encouraged by these results, Hartwig and co-workers developed an α-arylation method in which the Reformatsky reagents would be generated in situ, thereby avoiding the problematic isolation of the zinc amide enolates.[88] The enolates were formed by the addition of activated zinc metal to a solution of the α-bromoamide at room temperature. This could be subsequently arylated using either [Pd(dba)$_2$]/Q-Phos (**32**) or the palladium(I) dimer **33**, depending on the nature of the amide enolate. A final modification to this methodology provided a very mild general method for the α-arylation of amides. The use of the in situ generated Reformatsky

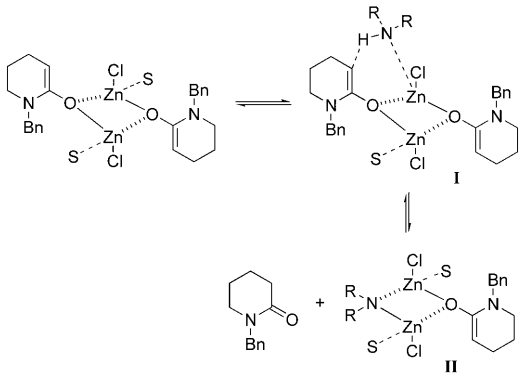


Scheme 25. α-Arylation of amides accordong to Hartwig et al. [a] 1 mol% [Pd(dba)$_2$], 1 mol% Q-Phos (**32**). [b] 2 mol% [Pd(dba)$_2$], 2 mol% Q-Phos (**32**). [c] 3 mol% [Pd(dba)$_2$], 3 mol% Q-Phos (**32**). [d] 0.5 mol% [{Pd(μ-Br)(*t*Bu$_3$P)}$_2$] (**33**), 1.05 equiv KH. [e] 1 mol% [{Pd(μ-Br)(*t*Bu$_3$P)}$_2$] (**33**), 1.05 equiv KH. [f] 70 °C. [g] 4 mol% [Pd(dba)$_2$], 4 mol% Q-Phos (**32**).

reagents (reaction of the amide with *sec*BuLi formed the lithium enolate, which was followed by the reaction with $ZnCl_2$) was also employed in many cases. Again, the palladium complex based on the Q-Phos ligand or **33** were used as catalysts to effect the arylation reaction (Scheme 25). Examples of microwave-mediated arylation of Reformatsky reagents generated from amides have been reported by Moloney and co-workers; however, this method afforded significantly lower yields than those observed by using the method developed by Hartwig and co-workers.[60]

5.4. Biaryl Monophosphine Ligands

Cossy and co-workers developed a process based on the use of a palladium catalyst derived from biphenyl monophosphine ligand **7** to extend the substrate scope of the α-arylation reactions to include Reformatsky reagents formed from cyclic amides.[89] It was postulated that amines such as hexamethyldisilazane (HMDS) present in the reaction mixture could chelate to the zinc enolate dimer to form **I** (Scheme 26). Furthermore, the zinc enolate may be proton-



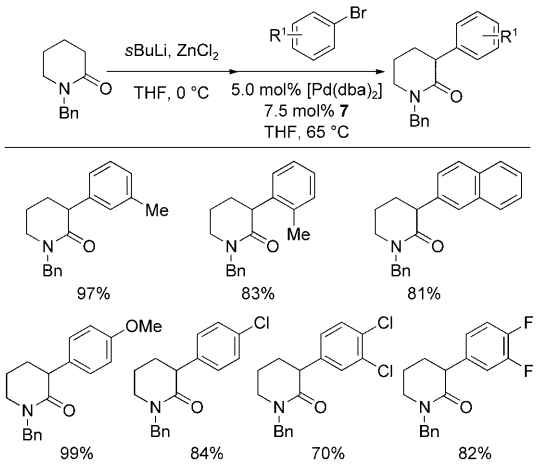
Scheme 26. Proposed species in the Reformatsky reaction.

ated by the amine to generate the amide and species **II**. It is possible that **I** and **II** are less prone to undergo the desired α-arylation reaction. On the basis of this assumption, the HMDS base was changed to *sec*BuLi so as to avoid the formation of complexes **I** and **II.** Indeed, carrying out the α-arylation reactions with *sec*BuLi afforded the products in high yields (Scheme 27).

Durbin and Willis reported a second application of a system based on **14** for the α-arylation of amides (Table 18). Oxindoles were generally arylated in lower yields than with Hartwig's Pd/PCy_3 system.[90]

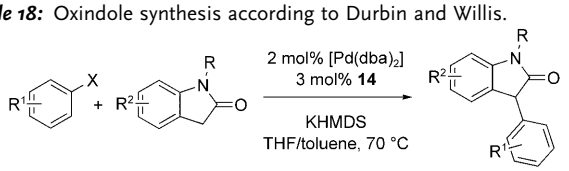
5.5. Carbene Ligands

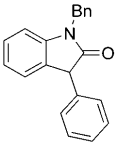
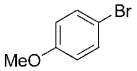
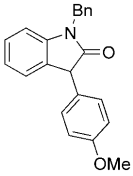
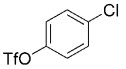
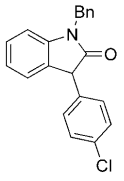
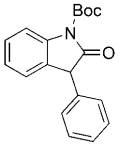
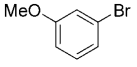
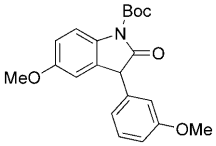
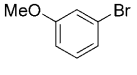
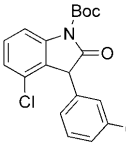
Lee and Hartwig, during their evaluation of phosphine ligands, also demonstrated the first α-arylation of amides with NHC-based complexes.[87] Although PCy_3 generally performed better, in certain cases the use of ligand **31** provided the α-arylated products in higher yields. Subsequently, Zhang and co-workers developed a $[Pd_2(dba)_3]$/ligand **37** catalyst



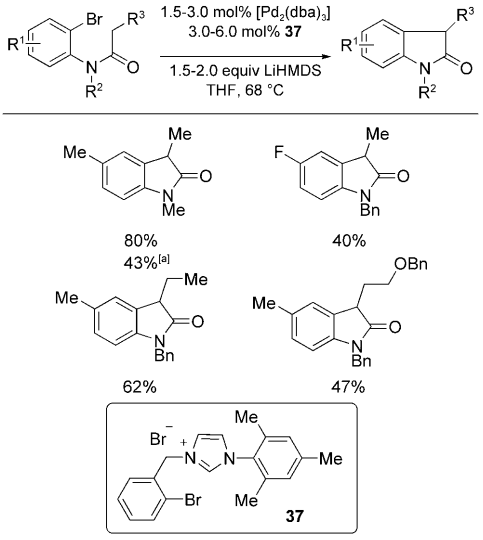
Scheme 27. α-Arylation of N-protected 2-piperidinones according to Cossy and co-workers.

Table 18: Oxindole synthesis according to Durbin and Willis.



Entry	ArX	Product	Yield [%]
1			70
2			85
3			70
4			60
5			76
6			61

system that could effectively mediate formation of an oxindole.[91] In analogy with observations made by Nolan and co-workers,[92] it was suggested that two close coordination sites on the metal were necessary for the formation of a C–C bond. Instead of having two carbene ligands bound to the palladium center, the oxidative addition of ligand **37** to the palladium(0) center provided a precatalyst that was less bulky, and could mediate the formation of an oxindole from several substrates. In general, the $[Pd(dba)_2]$/**37** catalyst system was more active than the $[Pd(dba)_2]$/**2** system, which is evident from the lower catalyst loadings (1.5–3 mol%), and afforded moderate to high yields of the oxindoles (Scheme 28).



Scheme 28. Oxindole formation according to Zhang and Huang. [a] Starting from the aryl chloride.

6. α-Arylation of Aldehydes

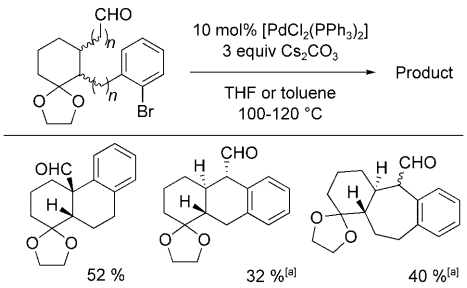
Metal-catalyzed α-arylation of aldehydes is notoriously difficult because of its propensity to readily undergo aldol condensation under the basic conditions. Alhough this area is not fully developed, significant developments have recently been made. This transformation is of great importance, as illustrated in the total synthesis of nominine.[93]

6.1. First Generation Aryl Phosphine Ligands

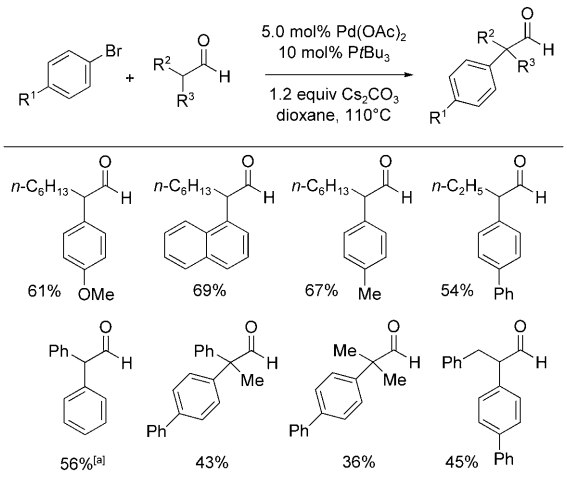
Muratake et al. first demonstrated that the intramolecular α-arylation reaction of aldehydes was possible in the presence of the $[PdCl_2(PPh_3)_2]/Cs_2CO_3$ system (Scheme 29).[94] The use of Cs_2CO_3 is a common theme in all the subsequent methods for the α-arylation of aldehydes.

6.2. Electron-Rich Alkyl Phosphines

Miura and co-workers first evaluated the use of bulky electron-rich monophosphines in the α-arylation of aldehydes.[95] The desired transformation occurred in moderate yields when $Pd(OAc)_2$/P*t*Bu$_3$ was used as the catalyst system (Scheme 30). Subsequently, Vo and Hartwig reported the α-arylation reaction of aldehydes through the use of a



Scheme 29. Intramolecular α-arylation according to Muratake et al. [a] Yield of alcohol after reduction with $NaBH_4$.

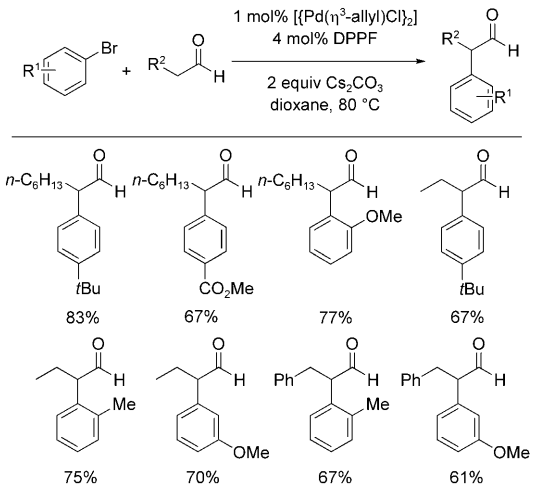


Scheme 30. α-Arylation of aldehydes according to Miura and co-workers. In each case the yield of the isolated product is given. [a] K_2CO_3 was used instead of Cs_2CO_3.

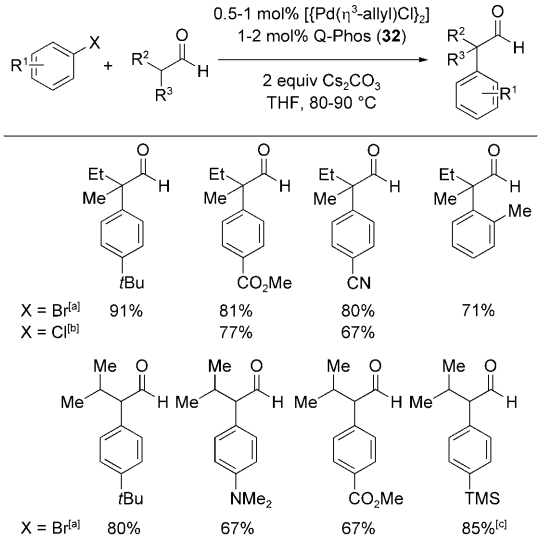
palladium(π-allyl) chloride dimer (APC) catalyst in combination with the less-electron-rich bidentate ligand DPPF (Scheme 31) or the bulky monodentate electron-rich Q-Phos ligand (**32**; Scheme 32).[96] It was found that the arylation of linear aldehydes proceeded in excellent yields with a [Pd]/DPPF system, whereas the arylation of branched aldehydes required the use of the Q-Phos (**32**) ligand. A few examples of the use of aryl chlorides as substrates have also been reported.

A number of palladium precursors and ligands were evaluated for activity in the study. Both $[Pd(dba)_2]$ and $Pd(OAc)_2$ resulted in lower yields than APC. It was observed that APC in conjunction with bulky electron-rich phosphine ligands provided a facile generation of the active, presumably a 12-electron, $[L_nPd^0]$ species in the catalytic cycle.[97]

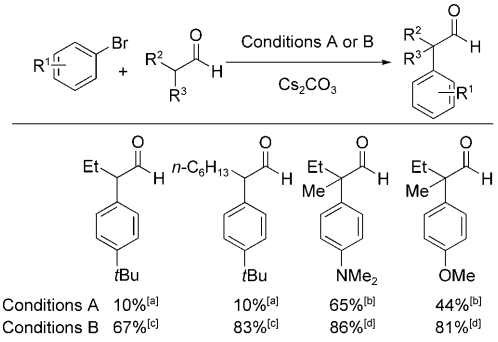
In a comparison study between their APC/phosphine and Buchwald's $Pd(OAc)_2$/phosphine catalyst systems, Hartwig and co-workers observed a remarkable difference in the yield of the α-arylated products of four chosen coupling partners (Scheme 33).[96] The APC/ligand method consistently per-



Scheme 31. α-Arylation of linear aldehydes.



Scheme 32. α-Arylation of branched aldehydes. [a] 0.5 mol% APC, 1 mol% Q-Phos (**32**), 80 °C. [b] 1 mol% APC, 2 mol% Q-Phos (**32**), 90 °C. [c] 1 mol% APC, 4 mol% DPPF in dioxane. TMS = trimethylsilyl.

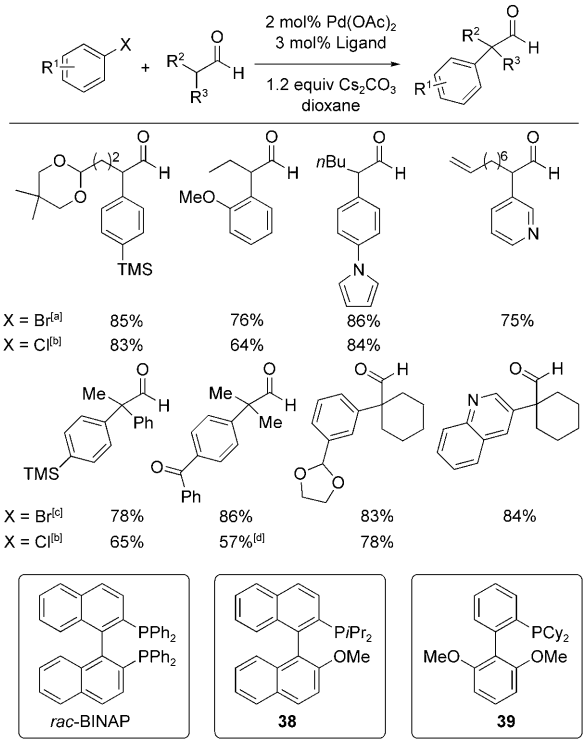


Scheme 33. Comparison study of the arylation of aldehydes. [a] 2 mol% $Pd(OAc)_2$, 3 mol% *rac*-binap (**2**), dioxane. [b] 2 mol% $Pd(OAc)_2$, 3 mol% S-Phos (**39**), dioxane. [c] 1 mol% APC, 4 mol% DPPF, dioxane. [d] 0.5 mol% APC, 1 mol% Q-Phos (**32**), THF.

formed better, with differences in the yields of up to 73%. The authors attribute this superior activity to a combined effect of both the palladium precursor APC and the ligands.

6.3. Electron-Rich Biaryl Phosphine Ligands

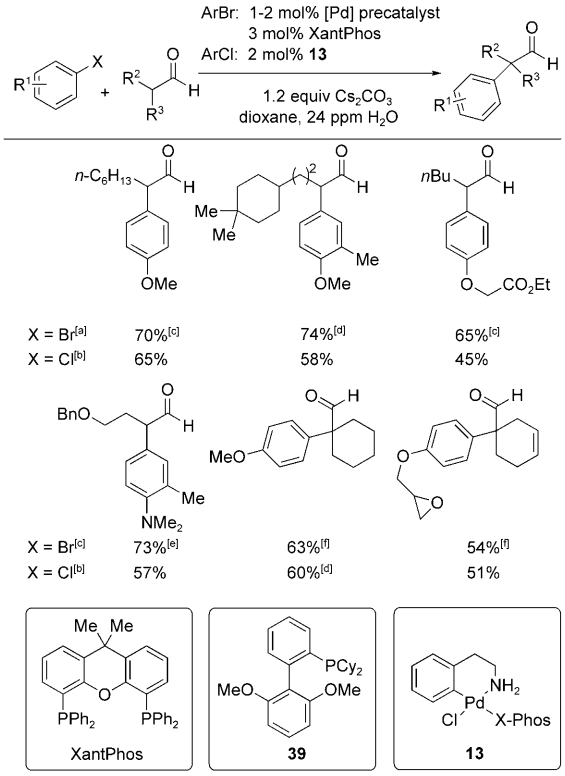
Martín and Buchwald reported a general method for the α-arylation of both linear and α-branched aldehydes through the use of catalysts generated from $Pd(OAc)_2$ and the biaryl phosphine ligands **2**, **38**, or **39** (Scheme 34).[98] Although the substrate scope for this transformation was broad, it did not encompass the coupling between electron-rich aryl halides and linear aldehydes.



Scheme 34. α-Arylation of aldehydes. Ligand and reaction temperature: [a] *rac*-Binap, 80 °C. [b] **38**, 100 °C. [c] **39**, 80 °C. [d] Two equivalents of the aldehydes were used at 80 °C.

To overcome this limitation and get a better understanding of the reaction, Martín and Buchwald studied the significance of water in the reaction mixture. They had already noted the influence of water during their initial studies on α-arylation.[98] The addition of molecular sieves, the use of vigorously anhydrous solvents, and flame-dried Cs_2CO_3 all resulted in very poor yields of the desired product, whereas the use of regular anhydrous solvents with a small amount of water notably increased the yield. It was, therefore, suggested that the presence of a small amount of water might promote the reduction of $Pd(OAc)_2$ to form the active $[L_nPd^0]$ species.[99] Having identified this, Martín and Buchwald were able to improve the yields of the α-arylation of linear aldehydes with aryl halides bearing electron-donating sub-

stituents (Scheme 35).[100] It was also hypothesized that employing a ligand with a wider bite angle might improve the yield, since bidentate phosphines with a larger bite angle



Scheme 35. Arylation of aldehydes using electron-rich aryl halides. [a] 80 °C. [b] 100 °C. [c] 1 mol% APC. [d] [{Pd(cinnamyl)Cl}$_2$]. [e] 2 mol% Pd(OAc)$_2$. [f] 2 mol% Pd(OAc)$_2$, 3 mol% S-Phos (**39**).

facilitate the reductive elimination step.[101] After optimization studies, it was found that [{Pd(allyl)Cl}$_2$] or [{Pd(cinnamyl)Cl}$_2$] in combination with XantPhos (**12**) serves as the optimal catalyst system for the α-arylation of aryl bromide substrates. The use of precatalyst **13** in the coupling of linear aldehydes with electron-rich aryl chlorides afforded the α-arylated products in excellent yields. However, no examples of sterically hindered electron-rich aryl halides were reported in this study.

6.4. Carbene Ligands

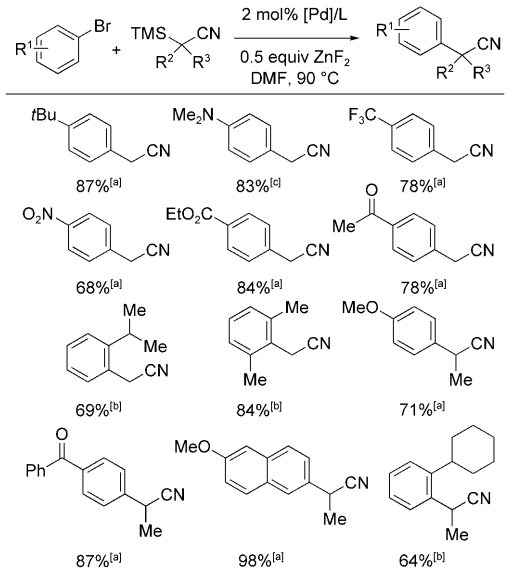
One single example of the α-arylation of isobutanal with 2-chlorotoluene was reported by Bertrand and co-workers, who employed their previously developed CAAC palladium complex **21** as a very effective catalyst.[36] The early success of Muratake et al.[94] and Bertrand and co-workers in effecting the difficult α-arylation reaction of aldehydes may have inspired other research groups to also investigate this field.

7. α-Arylation of Nitriles

The α-arylation of nitriles would provide a useful method to access some synthetically versatile intermediates and potential biologically active compounds.[102] An example of this is the synthesis of verapamil by Hartwig and co-workers,[108] which is a drug used in the treatment of hypertension and chest pain arising from a low supply of oxygen to the blood vessels.[103] However, the reactions of the aryl palladium cyanoalkyl intermediate that would be formed in the conventional catalytic cycle is not well known, and there are a number of possible bonding modes: The anions of nitriles can coordinate to a metal center through the α carbon atom[104] or through the cyano nitrogen atom.[105] Alternatively, the anion can bridge two metal centers to form a η^2-CN system.[106] Nitriles are also less acidic than ketones, but the cyano group is more electron withdrawing than a keto group, which could lead to unpredictable effects during catalysis, such as complications in the reductive elimination step.

7.1. Triaryl and Electron-Rich Alkyl Phosphine Ligands

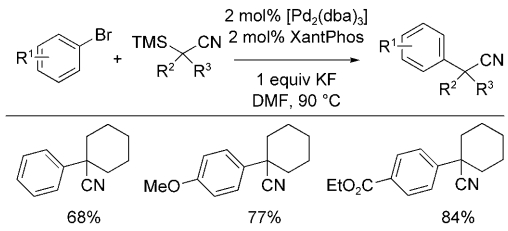
To gain some insight into cyanoalkyl complexes, Culkin and Hartwig prepared a number of these compounds that contained a variety of phosphine ligands.[107] It was observed that the preferred binding mode for the cyanoalkyl group was through the α-carbon atom. In the case of very sterically demanding ligands (for example, diisopropylphosphinoferrocene; D*i*PPF), the nitrile coordinated to the palladium center through the nitrogen atom. In addition, when a labile ligand was present, the phosphine was displaced by the nitrogen atom of the cyano group, and a bridging cyanoalkyl complex was formed. Investigation into the reductive elimination from the isolated cyanoalkylpalladium complexes identified binap (**2**) as the optimal ligand for this transformation. In isolated examples, better yields were obtained with a combination of [Pd$_2$(dba)$_3$]·CHCl$_3$ and P*t*Bu$_3$. By using this method, however, it was not possible to achieve monoarylation of the primary nitriles—diarylation was always observed. This was proposed to be due to the lower pK_a value of the arylated nitrile compared to that of the starting material. To address this problem, Wu and Hartwig investigated this transformation under milder conditions. On the basis of their previous experience on α-arylation, they attempted coupling reactions with cyanoalkylzinc and -silicon reagents.[108] The lower basicity of these reagents compared to cyanoalkyl–alkali metal species resulted in improving the functional-group tolerance greatly. It was demonstrated initially that the monoarylation of acetonitrile could be achieved by using trimethylsilylacetonitrile (Scheme 36). The catalyst systems vary, depending on the aryl bromide substrate. Catalytic systems such as [Pd$_2$(dba)$_3$]/Xantphos, [Pd$_2$(dba)$_3$]/P*t*Bu$_3$, and [Pd$_2$(dba)$_3$]/PPh*t*Bu$_2$ were used, while ZnF$_2$ was employed as a substoichiometric additive. In analogy with work carried out on the coupling of silyl enol ethers,[109] it was proposed that ZnF$_2$ seems to be strong enough to form a hypervalent silicon species that is more activated towards transmetalation. Interestingly, no reaction was observed in the absence of this additive. The reaction conditions developed could successfully be transferred to the arylation of α-TMS-propionitrile; however, for the arylation of α-silylcyclohex-



Scheme 36. α-Arylation of TMS nitriles under mild conditions according to Wu and Hartwig. [a] 2 mol% $[Pd_2(dba)_3]$, 2 mol% XantPhos (**12**), 0.5 equiv ZnF_2, DMF, 90 °C. [b] 2 mol% $[Pd_2(dba)_3]$, 4 mol% $PtBu_3$, 0.5 equiv ZnF_2, DMF, 90 °C. [c] 2 mol% $[Pd_2(dba)_3]$, 4 mol% $PhPtBu_2$, 0.5 equiv ZnF_2, DMF, 90 °C. DMF = *N*,*N*-dimethylformamide.

ylcarbonitrile the ZnF_2 had to be replaced with the stronger Lewis base KF (Scheme 37).

With the aim of further extending the substrate scope, Hartwig and co-workers investigated the use of zinc reagents

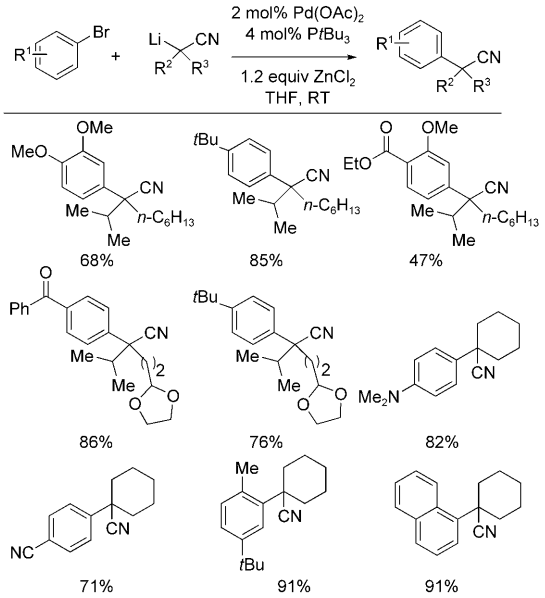


Scheme 37. α-Arylation of silyl derivatives of secondary nitriles.

in place of the silyl reagents. The zinc reagents were generated by treating the secondary nitrile with LDA, and removing the resulting diisopropylamine under vacuum before adding the $ZnCl_2$, palladium precursor, and ligand. If the amine was not removed from the reaction mixture prior to the coupling reaction, a significant amount of the the C–N coupling product was observed. By following this procedure they were able to improve dramatically the substrate scope for the arylation of secondary nitriles (Scheme 38).

7.2. Triaminophosphine Ligands

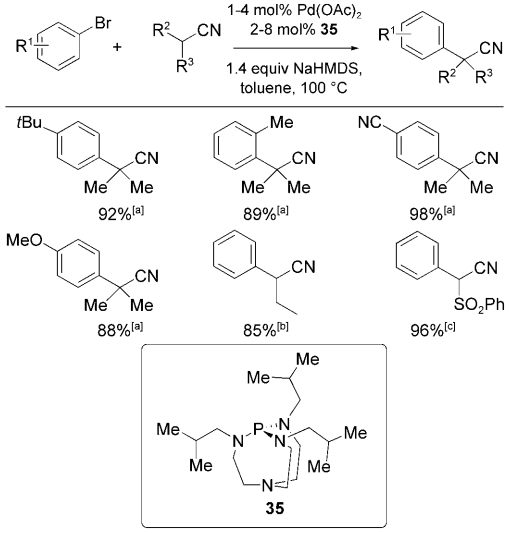
After successfully using their bicyclic proazaphosphatranes in palladium-catalyzed Suzuki cross-coupling reactions[72] and aryl aminations,[110] Verkade and co-workers also investigated their use in the arylation of nitriles, initially by



Scheme 38. α-Arylation of zinc nitriles.

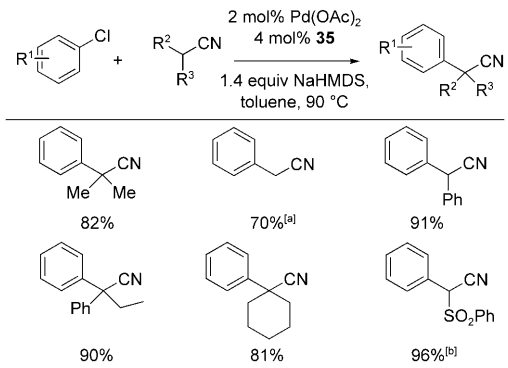
using aryl bromides.[73] The electronic and steric properties of the proazaphosphatranes can be adjusted by introducing the appropriate substituents at the PN_3 nitrogen atoms. The high stability of the metal complexes formed with this type of ligand is suggested to be due to the transannular interaction between the lone pair of electrons on the bridgehead nitrogen atom and the phosphorus atom.

The use of an in situ catalyst generated from $Pd(OAc)_2$ and phosphatrane **35** developed by Verkade and co-workers provided a very efficient system to arylate acetonitrile as well as primary and secondary nitriles (Scheme 39). The arylation of acetonitrile resulted exclusively in the diarylated product. Importantly, the $Pd(OAc)_2$/**35** catalyst system proved to be



Scheme 39. α-Arylation of nitriles using aryl bromides according to You and Verkade's. [a] 1 mol% $Pd(OAc)_2$, 2 mol% **35**. [b] 4 mol% $Pd(OAc)_2$, 8 mol% **35**, 90 °C. [c] 2 mol% $Pd(OAc)_2$, 4 mol% **35**, 90 °C.

very effective for the arylation of nitriles when employing less-expensive aryl chlorides as coupling partners (Scheme 40).[111] However, this arylation was only demonstrated for chlorobenzene with a number of primary and secondary nitriles. Notably, the monoarylation of acetonitrile was achieved in 70% yield by increasing the amount of acetonitrile.

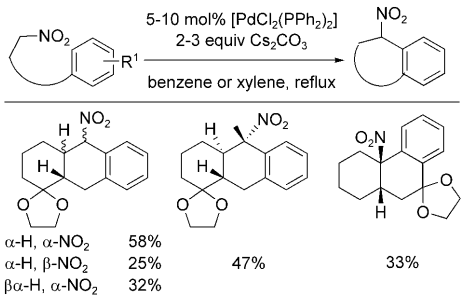


Scheme 40. α-Arylation using aryl chloride substrates according to You and Verkade.[111] [a] 10% of di-phenylated product observed. [b] Dioxane as the solvent, 1.4 equiv KO*t*Bu as a base.

8. Miscellaneous α-Arylations

8.1. Nitroalkanes

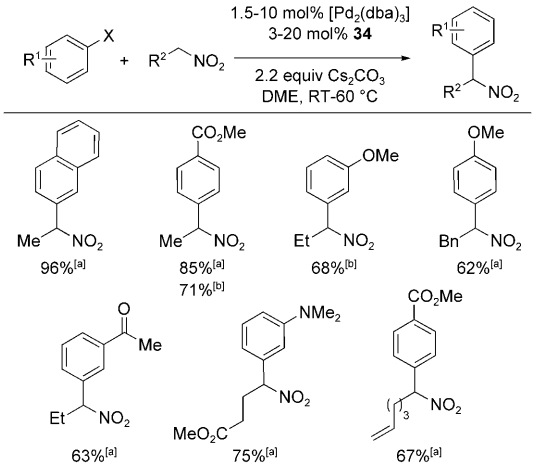
In addition to the functional groups already discussed, nitroalkanes are another plausible substrate class for α-arylation reactions. Muratake et al. demonstrated the first intramolecular version of this transformation to build up a number of tricyclic molecular structures (Scheme 41).[94] The



Scheme 41. Intramolecular α-arylation of nitroalkanes according to Muratake et al.

major side product was the corresponding ketones, formed by a Nef reaction from the secondary nitro group. In many cases, this was in fact the only product observed.

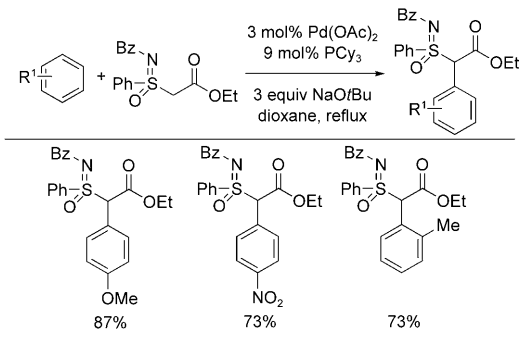
Buchwald and co-workers expanded the α-arylation reactions of ketones and esters to include nitroalkanes.[112] The use of $[Pd_2(dba)_3]$ in combination with monophosphine ligand **34** resulted in the intermolecular arylation of nitroalkanes in moderate to good yields (Scheme 42). Notably, the arylation could be carried out chemoselectively when carbonyl groups bearing α-hydrogen atoms were present in the substrates.



Scheme 42. α-Arylation of nitroalkanes according to Buchwald and co-workers. [a] Using aryl bromide. [b] Using aryl chloride. DME = 1,2-dimethoxyethane.

8.2. Sulfoximines

Inspired by the development of intramolecular α-arylation of sulfoximines to form heterocycles,[113] Bolm and co-workers investigated the intermolecular version of this palladium-catalyzed methodology to synthesize α-arylated sulfoximines, as this would offer a convenient route to substrates that were previously challenging to synthesize. Cho and Bolm achieved the α-arylation reaction in good yields by using a palladium catalyst generated from $Pd(OAc)_2$ or $[Pd_2(dba)_3]$ and PCy_3 (Scheme 43).[114] Subsequent hydrolysis effected decarboxylation to reveal the free sulfoximines.

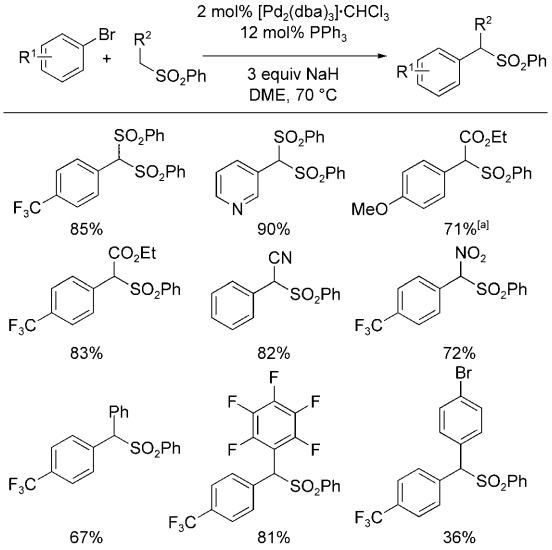


Scheme 43. α-Arylation of sulfoximines according to Cho and Bolm.

8.3. Sulfones

Beletskaya and co-workers were interested in using sulfones as auxiliaries for the more facile formation of carbanions and subsequent α-arylation.[115] The sulfones can later be easily removed by reductive desulfonylation.

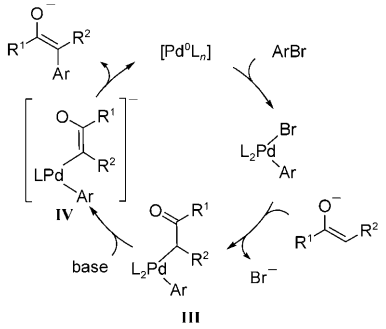
Beletskaya and co-workers demonstrated that a range of sulfones could be successfully arylated by using $[Pd_2(dba)_3]$/PPh_3 (Scheme 44). The substrate scope was, however, limited to the use of electron-neutral or electron-deficient aryl



Scheme 44. α-Arylation of sulfones according to Beletskaya and co-workers. [a] Using aryl iodide.

bromides, with only one example of an electron-rich aryl iodide. Interestingly, the use of bidentate and bulky electron-rich monophosphines as ligands did not lead to significant improvements over PPh_3. Furthermore, the use of excess base was also necessary to obtain the desired product. After mechanistic investigations, it was proposed that the base was not only involved in the formation of the enolate, but was also required to form the anionic palladium intermediate **IV**, which underwent a more-facile reductive elimination than the neutral transmetalated complex **III** (Scheme 45).[115]

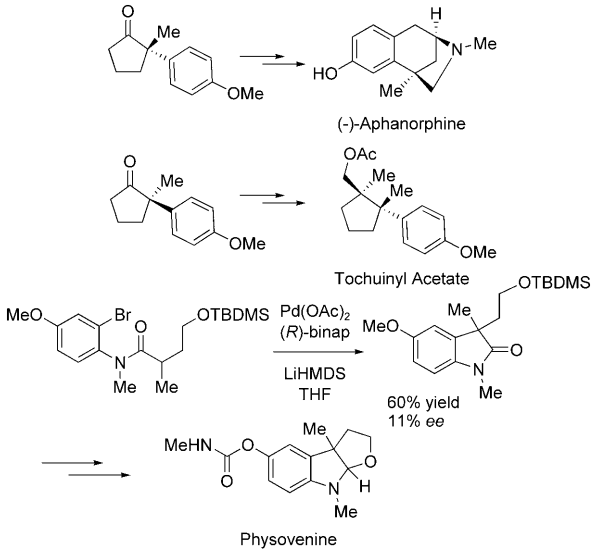
This hypothesis was supported by the fact that sulfones containing tertiary α-carbon atoms do not react to form the product, since the resulting aryl palladium intermediate cannot be deprotonated. This hypothesis could also explain why monoarylation of the sulfones was observed exclusively.



Scheme 45. Proposed mechanism by Beletskaya and co-workers for the arylation of sulfones.

9. Asymmetric α-Arylations

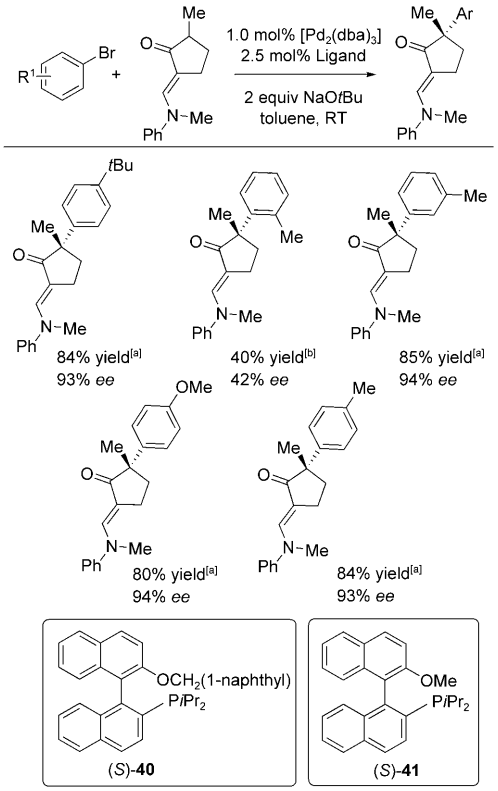
The asymmetric arylation of enolates would provide an effective method for constructing quaternary stereocenters. This structural motif is present in important intermediates in the syntheses of biologically active natural products, such as aphanorphine[116] and tochuinyl acetate (Scheme 46).[117] An early application of an enantioselective α-arylation reaction is illustrated by the formal total synthesis of physovenine by Zhang and Zhang (Scheme 46).[118] Physovenine belongs to a family of compounds that have been shown to be clinically useful for relieving symptoms of Alzheimer's disease.[119] In this section we will summarize the reported studies on ketones, esters, amides, and aldehydes.



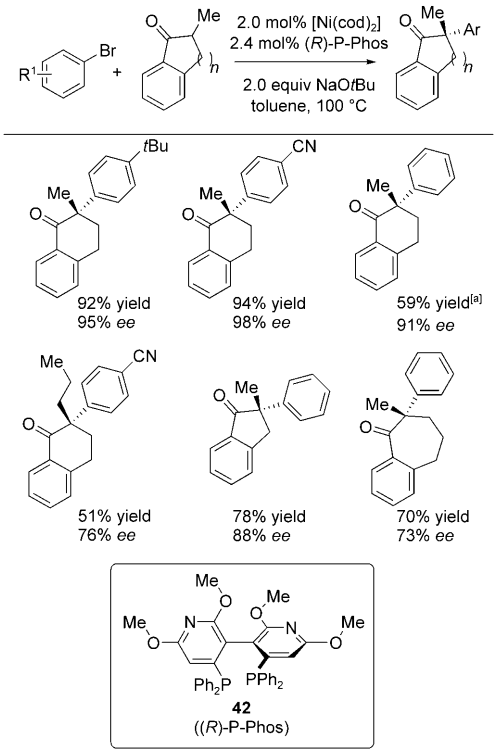
Scheme 46. α-Arylations in synthesis. TBDMS = *tert*-butyldimethylsilyl.

9.1. α-Arylation of Ketones

After development of an α-arylation protocol for the functionalization of ketones by employing *rac*-binap (**2**) as the ligand, Buchwald and co-workers reported an asymmetric variant in which Pd/(*S*)-binap was used as the catalyst system.[120] This process, however, suffered from high catalyst loadings (10 mol%) and forcing reaction conditions (100 °C). The same research group subsequently addressed these issues and reported an improved protocol for the asymmetric synthesis of 2-aryl-2-alkyl cyclopentanones.[121] A number of bidentate phosphine ligands that had previously been shown to be effective in the asymmetric vinylation of enolates[122] and Suzuki cross-coupling reactions[123] were investigated in the arylation reaction. Ligand (*S*)-**40** or (*S*)-**41** afforded the α-arylation products at room temperature with dramatically improved *ee* values over those obtained with the binap system (Scheme 47). In addition, the loading was reduced (to 1 mol% $[Pd_2(dba)_2]$). Importantly, the protecting group could be readily removed by treatment with aqueous HCl, followed by washing with aqueous sodium hydroxide to reveal the 2-alkyl-2-aryl cyclopentanone moiety.



Scheme 47. Improved method for the palladium-catalyzed asymmetric arylation of ketones according to Buchwald and co-workers. [a] (*S*)-**40**. [b] (*S*)-**41**.



Scheme 48. Nickel-catalyzed asymmetric α-arylation according to Chan and co-workers. [a] Using PhCl.

Inspired by the work of Buchwald and co-workers on the nickel-catalyzed asymmetric α-arylation of esters[39] (Section 9.2), Chan and co-workers extended the application to the arylation of ketones.[40] The atropisomeric ligand (*R*)-P-Phos (**42**) was employed in combination with $[Ni(cod)_2]$ to afford α-arylated products in moderate to good yields and *ee* values up to 98% (Scheme 48). The palladium-based catalytic systems had always been problematic with 2-methyl-1-indanone, in particular for *para*-substituted aryl bromides, where racemic mixtures of the product were obtained. Although Chan and co-workers solved this problem, they found that the nickel catalyst was limited to the asymmetric arylation of cyclic ketones.

Hartwig and co-workers subsequently reported a process where aryl triflates could be used as electrophiles in the presence of a palladium or nickel catalyst in combination with (*R*)-difluorphos (**43**; Scheme 49).[124] Notably, lower reaction temperatures could be used in the case of aryl triflates compared to the corresponding aryl bromides, which resulted in improved enantioselectivities (70–98%).

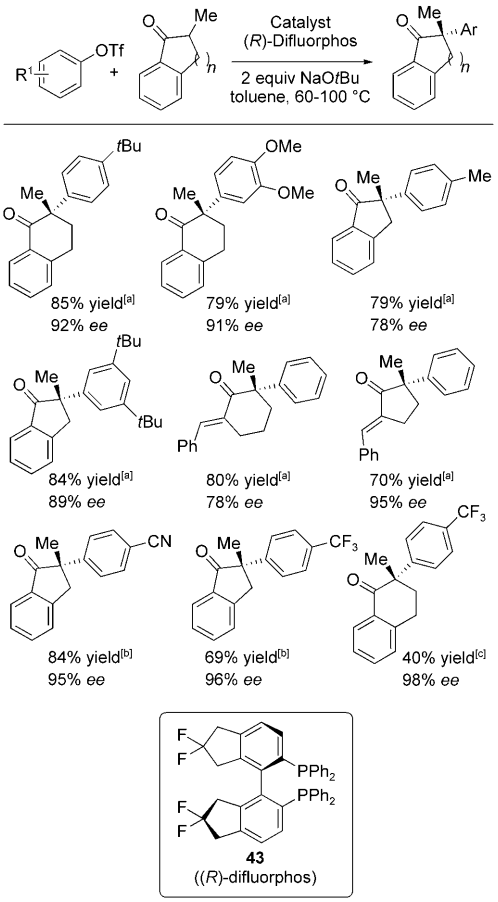
9.2. α-Arylation of Esters

The palladium/binap catalyst system proved unsuccessful in the asymmetric α-arylation of lactones. Buchwald and co-workers thus substituted the palladium catalyst with $[Ni(cod)_2]$, which provided the desired α-arylated products with excellent *ee* values (>90%; Scheme 50).[39] However the $[Ni(cod)_2]$ is not available in sufficient quantities for a commercial process. Interestingly, the addition of $ZnBr_2$ to the reaction mixture increased the yield. It was suggested that this additive acts as a Lewis acid to facilitate bromide abstraction from [(binap)Ni(Ar)(Br)] and generate the cationic species $[(binap)Ni(Ar)]^+$, which undergoes transmetalation more rapidly. This is the only report of the enantioselective α-arylation of ester substrates, although a couple of diastereoselective processes have been developed recently.

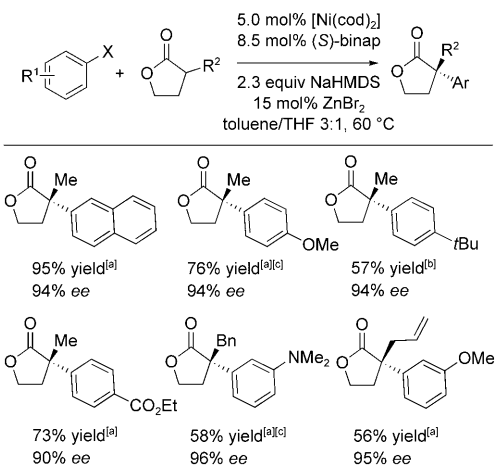
Researchers at Amgen reported a diastereoselective α-arylation of cyclic ester derivatives, where the use of palladium(I) dimer **33** resulted in a good yield and diastereomeric excess of the desired product.[125] Interestingly, the in situ catalyst system $[Pd_2(dba)_3]/PtBu_3$ gave products in significantly inferior yields to those obtained with the preformed catalyst (Scheme 51).

Jansat and co-workers subsequently developed a catalyst generated in situ from $Pd(OAc)_2$ and $PtBu_3{\cdot}HBF_4$ to effect the arylation of the dioxolane derivative of mandelic acid at room temperature to give the product in very good yields and diastereomeric excess (Scheme 52).[126]

The only examples of an asymmetric arylation of β-ketoesters were reported by Ma and co-workers, who employed copper catalysis to arylate 2-methylacetoacetate.[127]



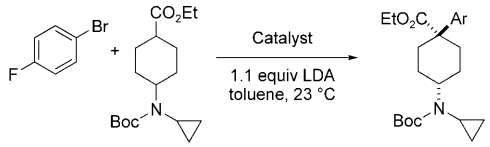
Scheme 49. Enantioselective α-arylation using aryl triflates according to Hartwig and co-workers. Tf = triflate. [a] 10 mol% $[Pd(dba)_2]$, 12 mol% **43**, 60 °C. [b] 5 mol% $[Ni(cod)_2]$, 6 mol% **43**, 80 °C. [c] 5 mol% $[Ni(cod)_2]$, 6 mol% **43**, 100 °C.



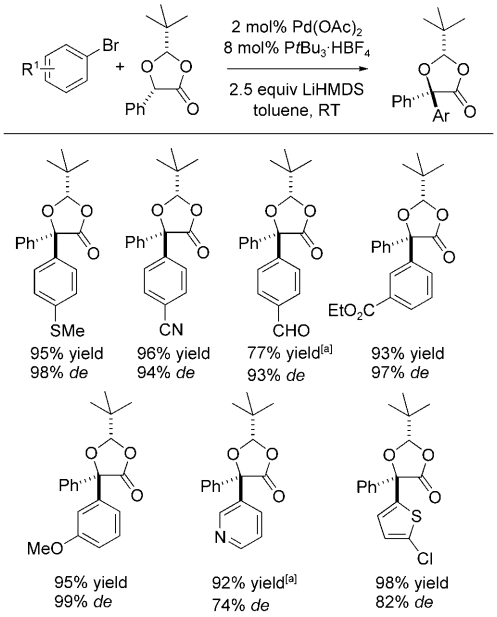
Scheme 50. Enantioselective α-arylation of esters according to Buchwald and co-workers. [a] From ArCl. [b] From ArBr. [c] 80 °C.

9.3. α-Arylation of Amides

Based on the poor enantioselectivities of commercially available chiral phosphine ligands, Lee and Hartwig decided



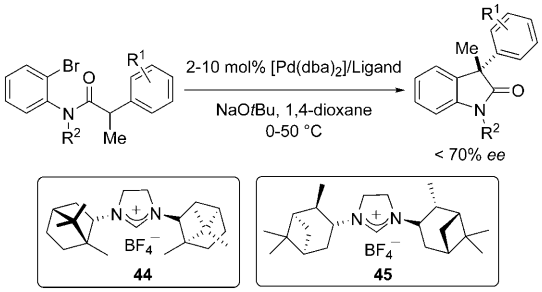
Scheme 51. Diastereselective α-arylation of esters according to Bercot et al.



Scheme 52. Diastereoselective arylation according to Jansat and co-workers. [a] 50 °C.

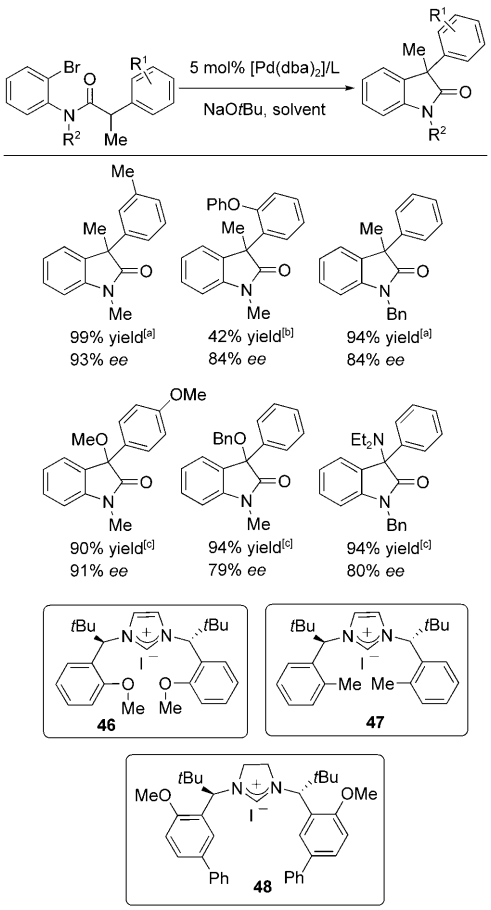
to investigate chiral carbenes in the palladium-catalyzed formation of oxindoles.[87] It was found that a catalyst generated in situ from $[Pd(dba)_2]$ and **44** or **45**, which contain chiral substituents on the nitrogen atom, provided the oxindole products in up to 70% *ee* (Scheme 53). Surprisingly, the two ligands (**44** and **45**) gave the products as opposite enantiomers.

Subsequent to the report by Lee and Hartwig, a number of other research groups disclosed their investigations of the enantioselective formation of oxindoles through the use of different carbene derivatives as ligands.[128] Kundig and co-workers reported the first excellent enantioselectivity



Scheme 53. Carbene-mediated enantioselective oxindole synthesis according to Lee and Hartwig.

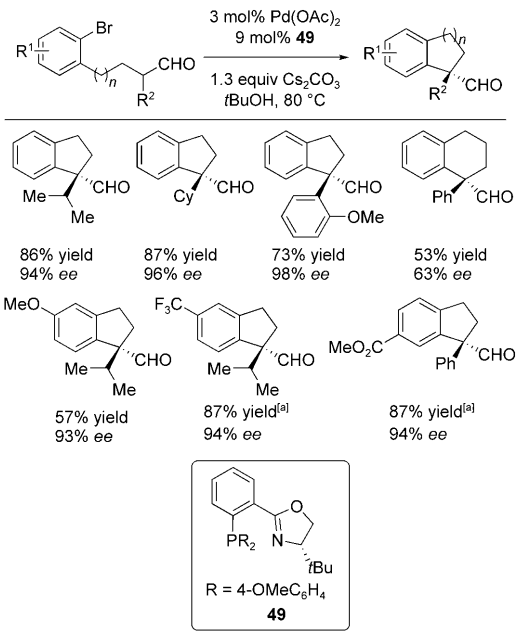
through the use of imidazolium iodide ligands **46**–**48** (Scheme 54).[129] The yields of the reaction were generally very high with *ee* values up to 90%.



Scheme 54. Improved asymmetric synthesis of oxindoles according to Kundig and co-workers. [a] Ligand **47**, DME, 23 °C. [b] Ligand **46**, DME, 23 °C. [c] Ligand **48**, toluene, 50 °C.

9.4. α-Arylation of Aldehydes

The only report in the literature that describes the enantioselective α-arylation of aldehydes is that by García-Fortanet and Buchwald.[130] They accomplished the intramolecular version of this transformation by employing ligand **49** to generate all-carbon tertiary stereocenters with excellent enantioselectivity. A number of ligands were screened for this reaction, including biaryl systems such as binap and SegPhos as well as chiral ferrocene ligands. However, all of them resulted in inferior enantioselectivity than the ligands from the phox family (Scheme 55).



Scheme 55. Enantioselective intramolecular arylation according to García-Fortanet and Buchwald. [a] Using 5 mol% $Pd(OAc)_2$ and 15 mol% **49**.

10. Summary and Outlook

Over the past ten years, great advances have been made in the field of α-arylation of carbonyl compounds catalyzed by transition-metal complexes. Today, a large number of carbonyl compounds—including ketones, esters, amides, nitriles, 1,3-dicarbonyl compounds, aldehydes, nitroalkanes, sulfoximines, and sulfones—can be coupled with electron-rich, electron-neutral, electron-poor, and sterically hindered aryl halides or pseudohalides. Until now, only a limited number of asymmetric versions of these reactions have been reported, and further studies are expected to be devoted towards improvements in this area. A number of commercial practical catalysts are available for this transformation. Palladium is still the metal of choice, although other metals such as copper and nickel have been used with some success. Some of these processes have been investigated by pharmaceutical companies on multi-kg scales for phase II and III trials of new drugs. Along with these developments, there is continual on-going research in industry and academia to develop more active and selective catalysts with higher turnover numbers. α-Arylation has some similarities with metal-catalyzed direct arylation chemistry, which also undergoes formation of a C–C bond by cleavage of a C–H bond, but has more in common with traditional cross-coupling reactions.

We thank Gerard Compagnoni (Director, Johnson Matthey Catalysis and Chiral Technologies, JMCCT) and Fred Hancock (Technical Director JMCCT) for their support in promoting new technologies relevant to the manufacture of catalysts for pharmaceutical, agrochemical, and fine chemicals applications.

Received: June 24, 2009

[1] a) H. Venkatesan, M. C. Davis, Y. Altas, J. P. Snyder, D. C. Liotta, *J. Org. Chem.* **2001**, *66*, 3653–3661; b) T. Y. Shen, *Angew. Chem.* **1972**, *84*, 512–526; *Angew. Chem. Int. Ed. Engl.*

1972, *11*, 460 – 472; c) W. B. Wright, J. B. Press, P. S. Chan, J. W. Marsico, M. F. Haug, J. Lucas, J. Tauber, A. S. Tomcufcik, *J. Med. Chem.* **1986**, *29*, 523 – 530; d) R. R. Goehring, Y. P. Sachdeva, J. S. Pisipati, M. C. Sleevi, J. F. Wolfe, *J. Am. Chem. Soc.* **1985**, *107*, 435 – 443; e) S. Edmondson, S. J. Danishefsky, L. Sepp-Lorenzino, N. Rosen, *J. Am. Chem. Soc.* **1999**, *121*, 2147 – 2155.

[2] R. K. Norris in *Comprehensive Organic Synthesis Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, New York, **1991**, chap. 2.2, and references therein.

[3] For selected references, see a) J. Morgan, J. T. Pinhey, B. A. Rowe, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1005 – 1008; b) J. H. Ryan, P. J. Stang, *Tetrahedron Lett.* **1997**, *38*, 5061 – 5064; c) T. Mino, T. Matsuda, K. Maruhashi, M. Yamashita, *Organometallics* **1997**, *16*, 3241 – 3242.

[4] D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 5816 – 5817.

[5] For reviews covering some of the areas discussed in this article, see a) M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 212 – 237; b) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234 – 235; c) G. C. Lloyd-Jones, *Angew. Chem.* **2002**, *114*, 995 – 998; *Angew. Chem. Int. Ed.* **2002**, *41*, 953 – 956. After submission and acceptance of this manuscript, a review overviewing developments in the same area was published: d) F. Bellina, R. Rossi, *Chem. Rev.* **2009**, DOI: 10.1021/cr9000836.

[6] a) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, L. D. Jones, *J. Am. Chem. Soc.* **1975**, *97*, 2507 – 2516; b) M. F. Semmelhack, R. D. Stauffer, T. D. Rogerson, *Tetrahedron Lett.* **1973**, *14*, 4519 – 4522.

[7] a) H. Muratake, A. Hayakawa, M. Natsume, *Tetrahedron Lett.* **1997**, *38*, 7577 – 7582; b) H. Muratake, A. Hayakawa, M. Natsume, *Chem. Pharm. Bull.* **2000**, *48*, 1558 – 1566; c) R. Mutter, E. M. Martin de La Neva, M. Wills, *Chem. Commun.* **2000**, 1675 – 1676; d) R. Mutter, I. B. Campbell, E. M. Martin de La Neva, A. T. Merritt, M. Wills, *J. Org. Chem.* **2001**, *66*, 3284 – 3290; e) F. Churruca, R. SanMartin, I. Tellitu, E. Dominguez, *Org. Lett.* **2002**, *4*, 1591 – 1594; f) F. Churruca, R. SanMartin, M. Carril, I. Tellitu, E. Dominguez, *Tetrahedron* **2004**, *60*, 2393 – 2408; g) F. Churruca, R. SanMartin, I. Tellitu, E. Dominguez, *Tetrahedron Lett.* **2003**, *44*, 5925 – 5929; h) D. Sole, L. Vallverdu, E. Peidro, J. Bonjoch, *Chem. Commun.* **2001**, 1888 – 1889; i) D. Sole, L. Vallverdu, X. Solans, M. Font-Bardia, J. Bonjoch, *J. Am. Chem. Soc.* **2003**, *125*, 1587 – 1594; j) D. Sole, L. Vallverdu, J. Bonjoch, *Adv. Synth. Catal.* **2001**, *343*, 439 – 442; k) T. Honda, Y. Sakamaki, *Tetrahedron Lett.* **2005**, *46*, 6823 – 6825.

[8] T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem.* **1997**, *109*, 1820 – 1822; *Angew. Chem. Int. Ed.* **1997**, *36*, 1740 – 1742.

[9] T. Satoh, J. Inoh, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239 – 2246. For a further extension of this method in which 1,2-dibromoarenes were applied, see Y. Terao, T. Satoh, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2345 – 2350.

[10] M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108 – 11109.

[11] B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 12382 – 12383.

[12] This ligand is not commercially available, but may be prepared by using a method reported by de Lang et al.: R.-J. de Lang, J. van Soolingen, H. D. Verkruijsse, L. Brandsma, *Synth. Commun.* **1995**, *25*, 2989 – 2991.

[13] For representative examples, see a) C. Carfagna, A. Musco, G. Sallese, R. Santi, T. Fiorani, *J. Org. Chem.* **1991**, *56*, 261 – 263; b) N. De Kimpe, Y. Zi-Peng, N. Schamp, *Bull. Soc. Chim. Belg.* **1989**, *98*, 481; c) M. Durandetti, J.-Y. Nedelec, J. Perichon, *J. Org. Chem.* **1996**, *61*, 1748 – 1755; d) J. F. Fauvarque, A. Jutand, *J. Organomet. Chem.* **1979**, *177*, 273 – 281; e) M. Kosugi, M. Suzuki, I. Hagiwara, K. Goto, K. Saitoh, T. Migita, *Chem. Lett.* **1982**, 939 – 940; f) I. Kuwajima, H. Urabe, *J. Am. Chem. Soc.* **1982**, *104*, 6831 – 6833; g) I. Kuwajima, E. Nakamura, *Acc. Chem. Res.* **1985**, *18*, 181 – 187; h) A. A. Millard, M. W. Rathke, *J. Org. Chem.* **1978**, *43*, 1834 – 1835; i) J. D. Stewart, S. C. Fields, K. S. Kochkar, H. W. Pinnick, *J. Org. Chem.* **1987**, *52*, 2110 – 2113; j) I. Shibata, A. Baba, *Org. Prep. Proced. Int.* **1994**, *26*, 85 – 100.

[14] a) D. H. R. Barton, J. P. Finet, J. Khamsi, C. Pichon, *Tetrahedron Lett.* **1986**, *27*, 3619 – 3622; b) D. H. R. Barton, D. M. X. Donnelly, J. P. Finet, P. J. Guiry, *J. Chem. Soc. Perkin Trans. 1* **1992**, 1365 – 1375.

[15] a) H. Muratake, M. Natsume, *Tetrahedron Lett.* **1997**, *38*, 7581 – 7582; b) H. Muratake, M. Natsume, H. Nakai, *Tetrahedron* **2004**, *60*, 11783 – 11803.

[16] a) T. Satoh, Y. Kametani, Y. Terao, M. Miura, M. Nomura, *Tetrahedron Lett.* **1999**, *40*, 5345 – 5348; b) Y. Terao, Y. Kametani, H. Wakui, T. Satoh, M. Miura, M. Nomura, *Tetrahedron* **2001**, *57*, 5967 – 5974.

[17] M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473 – 1478.

[18] G. A. Grasa, T. J. Colacot, *Org. Lett.* **2007**, *9*, 5489 – 5492.

[19] T. J. Colacot, H. A. Shea, *Org. Lett.* **2004**, *6*, 3731 – 3734.

[20] L. M. Klingensmith, E. R. Strieter, T. E Barder, S. L. Buchwald, *Organometallics* **2006**, *25*, 82 – 91.

[21] G. A. Grasa, and T. J. Colacot, *Org. Process Res. Dev.* **2008**, *12*, 522 – 529.

[22] A. Ehrentraut, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 209 – 217.

[23] D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722 – 9723.

[24] J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360 – 1370.

[25] L. A. van der Veen, P. H. Keeven, G. C. Schoemaker, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, M. Lutz, A. L. Spek, *Organometallics* **2000**, *19*, 872 – 883.

[26] J. L. Rutherford, M. P. Rainka, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 15168 – 15169.

[27] M. R. Biscoe, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 1773 – 1775.

[28] H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818 – 11819.

[29] G. Adjabeng, T. Brenstrum, C. S. Frampton, A. J. Robertson, J. Hillhouse, J. McNulty, A. Capretta, *J. Org. Chem.* **2004**, *69*, 5082 – 5086.

[30] a) M. S. Viciu, R. F. Germaneau, S. P. Nolan, *Org. Lett.* **2002**, *4*, 4053 – 4056; b) M. S. Viciu, R. F. Germaneau, O. Navarro-Fernandez, E. D. Stevens, S. P. Nolan, *Organometallics* **2002**, *21*, 5470 – 5472.

[31] S. A. Stanton, S. W. Felman, C. S. Parkurst, S. A. Godleski, *J. Am. Chem. Soc.* **1983**, *105*, 1964 – 1969.

[32] M. S. Viciu, R. A. Kelly III, E. D. Stevens, F. Naud, M. Studer, S. P. Nolan, *Org. Lett.* **2003**, *5*, 1479 – 1482.

[33] N. Marion, E. C. Ecarnot, O. Navarro, D. Amoroso, A. Bell, S. P. Nolan, *J. Org. Chem.* **2006**, *71*, 3816 – 3821.

[34] K. Matsubara, H. Okazaki, M. Senju, *J. Organomet. Chem.* **2006**, *691*, 3693 – 3699.

[35] a) D. Wang, Z. Wu, *Chem. Commun.* **1999**, 529; b) D. Wang, P. Wei, Z. Wu, *Macromolecules* **2000**, *33*, 6896 – 6898.

[36] V. Lavallo, Y. Canac, C. Prasang, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2005**, *117*, 5851 – 5855; *Angew. Chem. Int. Ed.* **2005**, *44*, 5705 – 5709.

[37] Glorius and co-workers introduced the concept of flexible steric bulk when developing NHC ligands bearing cyclohexyl substituents: a) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195 – 15201; b) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew.*

Chem. **2003**, *115*, 3818 – 3821; *Angew. Chem. Int. Ed.* **2003**, *42*, 3690 – 3693.
[38] a) L. Ackermann, R. Born, *Angew. Chem.* **2005**, *117*, 2497 – 2500; *Angew. Chem. Int. Ed.* **2005**, *44*, 2444 – 2447; b) L. Ackermann, J. H. Spatz, C. J. Gschrei, R. Born, A. Althammer, *Angew. Chem.* **2006**, *118*, 7789 – 7792; *Angew. Chem. Int. Ed.* **2006**, *45*, 7627 – 7630.
[39] a) D. J. Spielvogel, W. M. Davis, S. L. Buchwald, *Organometallics* **2002**, *21*, 3833 – 3836; b) D. J. Spielvogel, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 3500 – 3501.
[40] G. Chen, F. Y. Kwong, H. O. Chan, W.-Y. Yu, A. S. C. Chan, *Chem. Commun.* **2006**, 1413 – 1415.
[41] K. Matsubara, K. Ueno, Y. Koga, K. Hara, *J. Org. Chem.* **2007**, *72*, 5069 – 5076.
[42] M. Scholl, S. Ding, C. Woo Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953 – 956.
[43] L. J. Goossen, *Chem. Commun.* **2001**, *669–670*.
[44] T. Satoh, J. Inoh, Y. Kawamura, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239 – 2246.
[45] D. Solé, O. Serrano, *J. Org. Chem.* **2008**, *73*, 2476 – 2479.
[46] W. A. Moradi, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7996 – 8002.
[47] K. G. Hampton, T. M. Harris, C. R. Hauser, *J. Org. Chem.* **1963**, *28*, 1946 – 1948.
[48] M. Schlosser in *Organometallics in Synthesis: A Manual* (Ed.: M. Schlosser), Wiley, New York, **1994**, chap. 1.
[49] a) M. A. Ciufolini, M. E. Browne, *Tetrahedron Lett.* **1987**, *28*, 171 – 174; b) M. A. Ciufolini, H.-B. Qi, M. E. Browne, *J. Org. Chem.* **1988**, *53*, 4149 – 4151.
[50] F. A. Khan, R. Czerwonka, H.-U. Reissig, *Eur. J. Org. Chem.* **2000**, 3607 – 3617.
[51] O. Gaertzen, S. L. Buchwald, *J. Org. Chem.* **2002**, *67*, 465 – 475.
[52] a) M. Jørgensen, S. Lee, X. Liu, J. P. Wolkowski, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 12557 – 12565; b) S. Lee, N. A. Beare, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 8410 – 8411.
[53] X. Liu, J. F. Hartwig, *Org. Lett.* **2003**, *5*, 1915 – 1918.
[54] B. M. Trost, A. J. Xavier, *J. Am. Chem. Soc.* **1999**, *121*, 10727 – 10737.
[55] T. Hama, X. Liu, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 11176 – 11177.
[56] For examples of zinc enolate cross coupling reactions, see a) F. Orsini, F. Pelizzoni, *Synth. Commun.* **1987**, *17*, 1389 – 1402; b) F. Orsini, F. Pelizzoni, L. M. Vallarino, *J. Organomet. Chem.* **1989**, *367*, 375 – 382; c) J. F. Fauvarque, A. Jutand, *J. Organomet. Chem.* **1979**, *177*, 273 – 281; d) J. F. Fauvarque, A. Jutand, *J. Organomet. Chem.* **1977**, *132*, C17 – C19; e) P. Knochel, P. Jones in *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, Oxford, **1999**; f) E.-I. Negishi in *Metal catalyzed Cross-coupling Reactions* (Ed.: P. J. Stang), Wiley-VCH, Weinheim, **1998**, chap. 1.
[57] a) T. J. Colacot in *Encyclopedia of Reagents for Organic Synthesis* [Online], Wiley, **2009**, www.mrw.interscience.wiley.com/eros DOI: 10.1002/047084289X.rn01103; b) T. J. Colacot, *Platinum Metals Rev.* **2009**, *53*, 183 – 185.
[58] T. Hama, J. F. Hartwig, *Org. Lett.* **2008**, *10*, 1545 – 1548.
[59] T. Hama, J. F. Hartwig, *Org. Lett.* **2008**, *10*, 1549 – 1552.
[60] E. Bentz, M. G. Moloney, S. M. Westaway, *Tetrahedron Lett.* **2004**, *45*, 7395 – 7397.
[61] a) A. Osuka, S. Kobayashi, H. Suzuki, *Synthesis* **1983**, 67 – 68; b) J.-I. Setsune, K. Matsukawa, H. Wakemoto, T. Kitao, *Chem. Lett.* **1981**, 367 – 370; c) K. Okuro, M. Furuune, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 7606 – 7607; d) A. Bruggink, A. McKillop, *Tetrahedron* **1975**, *31*, 2607 – 2619; e) A. McKillop, D. P. Rao, *Synthesis* **1977**, 759 – 760.
[62] J. A. MacKay, R. L. Bishop, V. H. Rawal, *Org. Lett.* **2005**, *7*, 3421 – 3424.
[63] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467 – 4470; b) S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627 – 630.
[64] M. Uno, K. Seto, S. Takahashi, *J. Chem. Soc. Chem. Commun.* **1984**, 932 – 933.
[65] M. Uno, K. Seto, W. Ueda, M. Masuda, S. Takahashi, *Synthesis* **1985**, 506 – 508.
[66] T. Sakamoto, E. Katoh, Y. Kondo, H. Yamanaka, *Chem. Pharm. Bull.* **1988**, *36*, 1664 – 1668.
[67] Y. Kondo, K. Inamoto, M. Uchiyama, T. Sakamoto, *Chem. Commun.* **2001**, 2704 – 2705.
[68] N. A. Beare, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 541 – 555.
[69] S. R. Stauffer, N. A. Beare, J. P. Stambuli, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 4641 – 4642.
[70] J. G. Zeevaart, C. J. Parkinson, C. B. de Koning, *Tetrahedron Lett.* **2004**, *45*, 4261 – 4264.
[71] M. A. Aramendia, V. Borau, C. Jimenez, J. M. Marinas, J. R. Ruiz, F. J. Urbano, *Tetrahedron Lett.* **2002**, *43*, 2847 – 2849.
[72] S. Urgaonkar, M. Nagarajan, J. G. Verkade, *Tetrahedron Lett.* **2002**, *43*, 8921 – 8924.
[73] J. You, J. G. Verkade, *J. Org. Chem.* **2003**, *68*, 8003 – 8007.
[74] a) W. R. H. Hurtley, *J. Chem. Soc.* **1929**, 1870 – 1873; b) for a representative procedure, see A. Bruggink, S. J. Ray, A. McKillop, *Org. Synth.* **1978**, *58*, 52 – 55.
[75] a) J. Setsune, K. Matsukawa, H. Wakemoto, T. Kaito, *Chem. Lett.* **1981**, 367 – 370; b) J. Setsune, K. Matsukawa, T. Kaito, *Tetrahedron Lett.* **1982**, *23*, 663 – 666; c) H. Suzuki, T. Kobayashi, Y. Yoshida, A. Osuka, *Chem. Lett.* **1983**, 193 – 194; d) H. Suzuki, Q. Yi, J. Inoue, K. Kusume, T. Ogawa, *Chem. Lett.* **1987**, 887 – 890.
[76] K. Okuro, M. Furuune, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 7606 – 7607.
[77] E. J. Hennessy, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 269 – 272.
[78] X. Xie, G. Cai, D. Ma, *Org. Lett.* **2005**, *7*, 4693 – 4695.
[79] S. F. Yip, H. Y. Cheung, Z. Zhou, F. Y. Kwong, *Org. Lett.* **2007**, *9*, 3469 – 3472.
[80] H. J. Cristau, R. Vogel, M. Taillefer, A. Gadras, *Tetrahedron Lett.* **2000**, *41*, 8457 – 8460.
[81] R. Freund, W. W. K. R. Mederski, *Helv. Chim. Acta* **2000**, *83*, 1247 – 1255.
[82] S. K. Shah, J. J. Hale, H. Qi, D. J. Miller, P. Dorn, Jr., S. G. Mills, S. J. Sadowski, M. A. Cascieri, J. M. Metzger, G. J. Eiermann, M. J. Forrest, D. E. MacIntyre, M. MacCoss, Abstracts of Papers, 211th Am. Chem. Soc., National Meeting (New Orleans), March 24 – 29, **1996**, MEDI 136.
[83] B. Evans, J. L. Leighton, K. E. Rittle, K. F. Gilbert, G. F. Lundell, N. P. Gould, D. W. Hobbs, R. M. DiPardo, D. F. Veber, D. J. Pettibone, B. V. Clineschmidt, P. S. Anderson, R. M. Freidinger, *J. Med. Chem.* **1992**, *35*, 3919 – 3927.
[84] S. M. N. Efange, A. P. Kamath, A. B. Khare, M.-P. Kung, R. H. Mach, S. M. Parsons, *J. Med. Chem.* **1997**, *40*, 3905 – 3914.
[85] T. Honda, H. Namiki, F. Satoh, *Org. Lett.* **2001**, *3*, 631 – 633.
[86] K. H. Shaughnessy, B. C. Hamann, J. F. Hartwig, *J. Org. Chem.* **1998**, *63*, 6546 – 6553.
[87] S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, *66*, 3402 – 3415.
[88] T. Hama, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 4976 – 4985.
[89] a) A. de Filippis, D. G. Pardo, J. Cossy, *Tetrahedron* **2004**, *60*, 9757 – 9767; b) A. de Filippis, D. G. Pardo, J. Cossy, *Synthesis* **2004**, 2930 – 2933; c) J. Cossy, A. de Filippis, D. G. Pardo, *Org. Lett.* **2003**, *5*, 3037 – 3039; d) J. Cossy, A. de Filippis, D. G. Pardo, *Synlett* **2003**, 2171 – 2174.
[90] M. J. Durbin, M. C. Willis, *Org. Lett.* **2008**, *10*, 1413 – 1415.
[91] T. Y. Zhang, H. Zhang, *Tetrahedron Lett.* **2002**, *43*, 193 – 195.
[92] C. Zhang, J. Huang, M. L. Trudell, S. P. Nolan, *J. Org. Chem.* **1999**, *64*, 3804 – 3805.

[93] a) H. Muratake, M. Natsume, *Angew. Chem.* **2004**, *116*, 4746 – 4749; *Angew. Chem. Int. Ed.* **2004**, *43*, 4646 – 4649; b) H. Muratake, M. Natsume, *Tetrahedron Lett.* **2002**, *43*, 2913 – 2917.
[94] a) H. Muratake, M. Natsume, H. Nakai, *Tetrahedron* **2004**, *60*, 11783 – 11803; b) H. Muratake, H. Nakai, *Tetrahedron Lett.* **1999**, *40*, 2355 – 2358.
[95] Y. Terao, Y. Fukuoka, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **2002**, *43*, 101 – 104.
[96] G. D. Vo, J. F. Hartwig, *Angew. Chem.* **2008**, *120*, 2157 – 2160; *Angew. Chem. Int. Ed.* **2008**, *47*, 2127 – 2130.
[97] For evidence of the facile generation of [L_nPd^0] species from APC, see N. Marion, O Navarro, J. Mei, E. P. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101 – 4111.
[98] R. Martín, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 7374 – 7377; *Angew. Chem. Int. Ed.* **2007**, *46*, 7236 – 7239.
[99] a) B. P. Fors, P. Krattiger, E. Strieter, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 3505 – 3508; b) F. Ozawa, A. Kubo, T. Hayashi, *Chem. Lett.* **1992**, 2177 – 2180.
[100] R. Martín, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 4546 – 4564.
[101] J. M. Brown, P. J. Guiry, *Inorg. Chim. Acta* **1994**, *220*, 249 – 259.
[102] For examples of biological activity, see S. Caron, E. Vazquez, J. M. Wojcik, *J. Am. Chem. Soc.* **2000**, *122*, 712 – 713.
[103] K. Midtboe, O. Hals, O. Lauve, J. van der Meer, L. Storstein, *Br. J. Clin. Pharmacol.* **1986**, *21*, 165S – 171S.
[104] For example, see P. R. Alburquerque, A. R. Pinhas, J. A. K. Bauer, *Inorg. Chim. Acta* **2000**, *298*, 239 – 244, and references therein.
[105] For example, see T. Naota, A. Tanna, S.-I. Murahashi, *Chem. Commun.* **2001**, 63 – 64, and references therein.
[106] J. Ruiz, V. Rodriguez, G. Lopez, J. Casabo, E. Molins, C. Miravitlles, *Organometallics* **1999**, *18*, 1177 – 1184.
[107] D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 9330 – 9331.
[108] L. Wu, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 15824 – 15832.
[109] W. Su, S. Raders, J. G. Verkade, X. Liao, J. F. Hartwig, *Angew. Chem.* **2006**, *118*, 5984 – 5987; *Angew. Chem. Int. Ed.* **2006**, *45*, 5852 – 5855.
[110] a) S. Urgaonkar, M. Nagarajan, J. G. Verkade, *J. Org. Chem.* **2003**, *68*, 452 – 459; b) S. Urgaonkar, M. Nagarajan, J. G. Verkade, *Org. Lett.* **2003**, *5*, 815 – 818.
[111] J. You, J. G. Verkade, *Angew. Chem.* **2003**, *115*, 5205 – 5207; *Angew. Chem. Int. Ed.* **2003**, *42*, 5051 – 5053.
[112] a) E. M. Vogl, S. L. Buchwald, *J. Org. Chem.* **2002**, *67*, 106 – 111; b) J. M. Fox, X. H. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360 – 1370.
[113] a) C. Bolm, H. Okamura, M. Verrucci, *J. Organomet. Chem.* **2003**, *687*, 444 – 450; b) C. Bolm, M. Martin, L. Gibson, *Synlett* **2002**, 832 – 834.
[114] G. Y. Cho, C. Bolm, *Org. Lett.* **2005**, *7*, 1351 – 1354.
[115] a) A. V. Mitin, A. N. Kashin, I. P. Beletskaya, *J. Organomet. Chem.* **2004**, *689*, 1085 – 1090; b) A. N. Kashin, A. V. Mitin, I. P. Beletskaya, R. Wife, *Tetrahedron Lett.* **2002**, *43*, 2539 – 2542.
[116] S. Takano, K. Inomata, T, Sato, M, Takahashi, *J. Chem. Soc. Chem. Commun.* **1990**, 290 – 292.
[117] A. Srikrishna, T. J. Reddy, *Tetrahedron* **1998**, *54*, 8133 – 8140.
[118] T. Y. Zhang, H. Zhang, *Tetrahedron Lett.* **2002**, *43*, 1363 – 1365.
[119] For a review of the biological activities of the compounds, see D. J. Triggle, J. M. Mitchell, R. Filler, *CNS Drug Rev.* **1998**, *4*, 87 – 136.
[120] J. Åhman, J. P. Wolfe, M. V. Troutman, M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 1918 – 1919.
[121] T. Hamada, A. Chieffi, J. Ahman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1261 – 1268.
[122] A. Chieffi, K. Kamikawa, J. Ahman, J. M. Fox, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1897 – 1900.
[123] J. Yin, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12051 – 12052.
[124] X. Liao, Z. Weng, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 195 – 200.
[125] E. A. Bercot, S. Caille, T. M. Bostick, K. Ranganathan, R. Jensen, M. M. Faul, *Org. Lett.* **2008**, *10*, 5251 – 5254.
[126] L. Jiang, S. Weist, S. Jansat, *Org. Lett.* **2009**, *11*, 1543 – 1546.
[127] X. Xie, Y. Chen, D. Ma, *J. Am. Chem. Soc.* **2006**, *128*, 16050 – 16051.
[128] a) T. Arao, K. Kondo, T. Aoyama, *Tetrahedron Lett.* **2006**, *47*, 1417 – 1420; b) T. Arao, K. Sato, K. Kondo, T. Aoyama, *Chem. Pharm. Bull.* **2006**, *54*, 1576 – 1581; c) F. Glorius, G. Altenhoff, R. Goddard, C. Lehmann, *Chem. Commun.* **2002**, 2704 – 2705.
[129] a) Y.-X. Jia, M. Hillgren, E. L. Watson, S. P. Marsden, E. P. Kundig, *Chem. Commun.* **2008**, 4040 – 4042; b) E. P. Kündig, T. M. Seidel, Y.-X. Jia, G. Bernardinelli, *Angew. Chem.* **2007**, *119*, 8636 – 8639; *Angew. Chem. Int. Ed.* **2007**, *46*, 8484 – 8487.
[130] J. García-Fortanet, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 8228 – 8231; *Angew. Chem. Int. Ed.* **2008**, *47*, 8108 – 8111.