Palladium-catalyzed direct arylation of simple arenes in synthesis of biaryl molecules

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Significant progress has been made in the direct arylation of simple arenes. A number of catalyst systems have been developed which enable the intramolecular direct arylation of aryl chlorides, bromides and iodides in high yield as well as conditions capable of achieving intermolecular direct arylation with simple arenes. This account describes recent progress by our group and others in the development of these reactions.

Introduction

The history of synthetic chemistry directed at the efficient preparation of biaryl molecules is long and rich.[1] From the first reports of the Ullmann coupling over a century ago,[2] to the modern transition metal-catalyzed cross-coupling reactions of today,[3] there has been a revolution in our ability to create these once challenging bonds. Presently, biaryl molecules can be prepared in high yield under mild conditions with catalysts that exhibit broad functional group tolerance. Given this situation, one is right to question whether the synthesis of these molecules really warrants continued methodological attention from the synthetic community. Is there any work left to be done?

When evaluating the true efficiency of a chemical process, one must consider not only the final yield, but also the availability of the starting materials and any steps involved in their synthesis with particular emphasis on the need to install functional groups that do not appear in the final products. In this light, a common limitation and inefficiency in all modern transition metal-catalyzed cross coupling reactions is the requirement for activating groups on both of the arene coupling partners. This pre-activation of both partners is inherently wasteful since several steps can be required for the installation of these activating groups. This may also be problematic from a synthetic perspective since not all regioisomers of the organometallic or aryl halide may be readily available or easily synthesized. Thus, even though chemists have clearly made major advances in the formation of biaryl molecules, there still remains significant work to be done, particularly in the development of new reactions that do not rely on wasteful substrate pre-activation.

In recent years, reactions that can substitute one of the pre-activated species with a simple arene have begun to appear.[4] These processes have been described in several ways including C–H (bond) activation, C–H (bond) functionalization, and others. Since this terminology can be problematic when inconsistently applied,[5] we opt to use the term ''catalytic direct arylation'' to describe these reactions. This puts the focus on the arene being functionalized and not the bond that is being transformed which, we feel, is more in-line with common convention in organic synthesis.[6] Furthermore, it does not convey any mechanistic information which may not be known and/or may change from one substrate class to another.

While examples of direct arylation have appeared where the aryl halide is replaced with a simple arene,[7] a more attractive alternative involves the replacement of the organometallic species since it is frequently the component that is less stable and more challenging to prepare (Scheme 1). If such direct arlyation reactions could be achieved with a wide range of aromatic coupling partners under conditions amenable to the synthesis of complex biaryl molecules, then this would constitute a true advance in the preparation of this class of compound.[8] While this goal is still a long way off, important steps towards this objective have already been made. This feature article will outline recent advances in this field with a focus on the contributions that our research group has made at the University of Ottawa.

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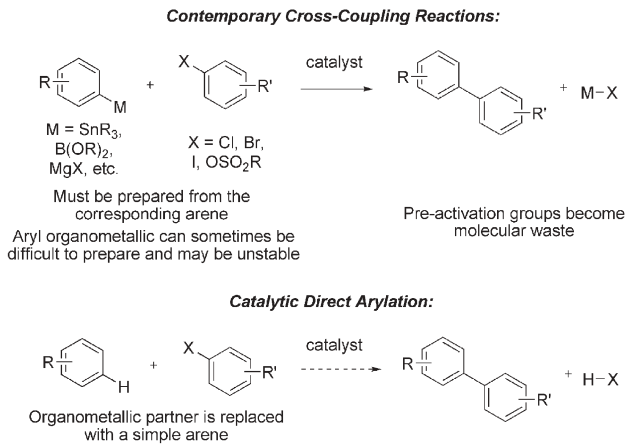
Keith Fagnou was born in Saskatoon, Saskatchewan, Canada. He received a Bachelor of Education (BEd) degree from the University of Saskatchewan in 1995 and, after teaching at the high school level for a short period, continued his studies in chemistry at the University of Toronto. In 2000 he received his MSc degree and in 2002 completed a PhD. Since joining the faculty at the University of Ottawa in December 2002, he has been the recipient of a Cottrell Research Scholar Award, the Boehringer Ingelheim Young Investigator Award, a Premier's Research Excellence Award and the John C. Polanyi Award for Chemistry.



Scheme 1 Modern methods for the formation of biaryl compounds.

Background

Direct arylation of heterocyclic arenes

Since the organometallic compound typically reacts as a nucleophile in cross-coupling reactions, it is logical to assume that when this coupling partner is substituted, more electron-rich nucleophilic arenes will exhibit enhanced reactivity. In this context, the use of π-electron-rich heteroaromatics have featured prominently in these transformations. While the heteroatoms in the aromatic ring may also be acting as directing groups, the benefit of enhanced nucleophilicity has been clearly demonstrated.[9] One of the first examples of these reactions was reported in 1989 when Ohta and co-workers demonstrated that *N*-substituted indoles could be arylated selectively at the 2-position using 2-chloro-3,6-dialkylpyrazines (eqn (1)).[10] This result set the stage for numerous examples of such coupling reactions using other aryl halides, and many arylation reactions of heteroaromatic substrates have since appeared.[11] Fig. 1 shows a variety of heteroaromatic compounds that have been shown to undergo direct arylation. Noteable contributions in recent years dealing with the use of electron-rich heterocyclic arenes have been made by the Sames research group at Columbia University.[11a,f] Given the utility of these compounds in medicinal chemistry, many more important advances can be anticipated.

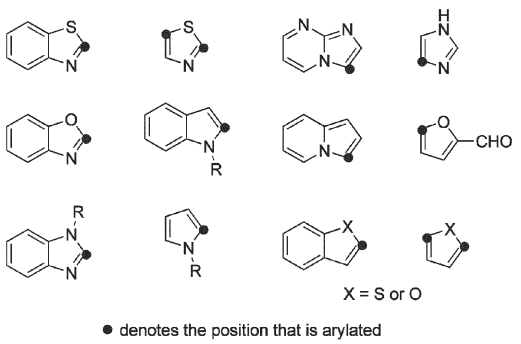
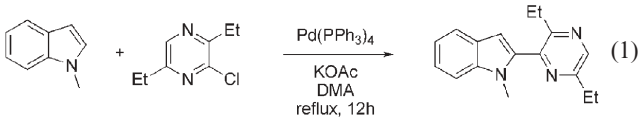
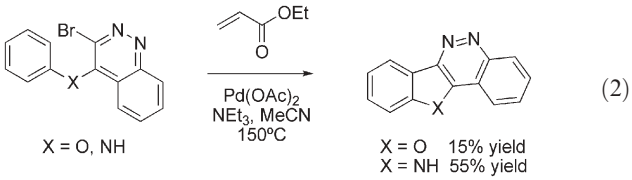


Fig. 1 Examples of heteroaromatic compounds used in direct arylation.



Direct arylation of simple arenes

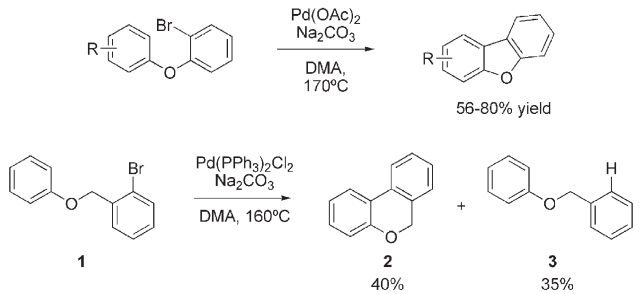
Simple arenes are much less reactive than the heteroaromatic counterparts in direct arylation reactions – an observation likely attributable to diminished nucleophilicity. Nonetheless, significant advances in both intra- and intermolecular direct arylation reactions have appeared. An early example appeared in 1982 when Ames and co-workers described an interesting side reaction observed while attempting a Heck reaction with bromocinnolines.[12] Instead of the Heck-product, they observed direct arylation of the pendant phenyl ring affording the five-membered ring direct arylation product (eqn (2)).



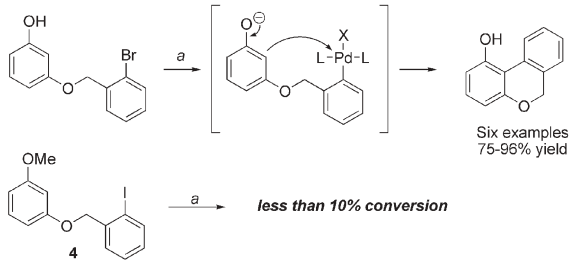
This discovery prompted additional investigations. Although the formation of a variety of five-membered benzofurans was feasible with 10% palladium catalyst,[13] the formation of six-membered ring benzopyrans proved problematic resulting in only 40% yield of **2** along with 35% of the hydrodebromination byproduct **3** (Scheme 2).[14]

To circumvent the lower nucleophilicity of simple arenes in these reactions, Rawal and co-workers employed substrates bearing a phenol functionality which becomes deprotonated under the reaction conditions to generate a more reactive coupling partner.[15] Under optimal conditions (Scheme 3), direct arylation occurs in high yield with complete selectivity for the *ortho*-position relative to the hydroxyl group. Evidence for enhanced reactivity of the phenolate anion was obtained from the reaction with methoxy-substituted **4**. In this case, less than 10% conversion is observed.

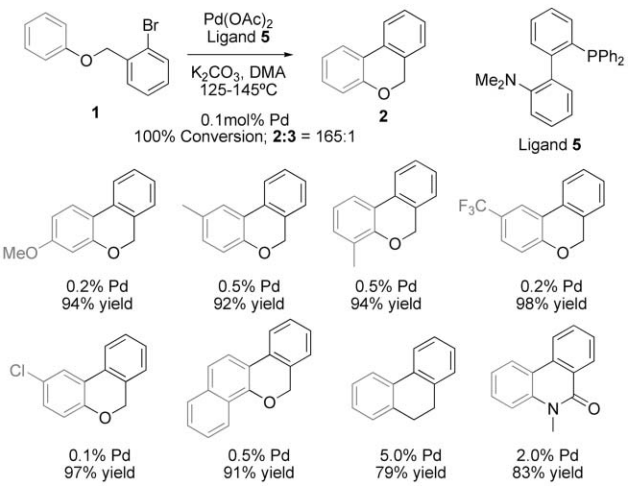
Intramolecular direct arylation as the terminating event of a migratory cascade has recently been examined by Campo and Larock based on their[16] and Gallagher's work[17] on palladium-catalyzed migrations in Heck reactions. For example, reaction with $Pd(OAc)_2$, dppm and caesium pivalate in DMF at 100 °C



Scheme 2 Ames' first examples with simple arenes.

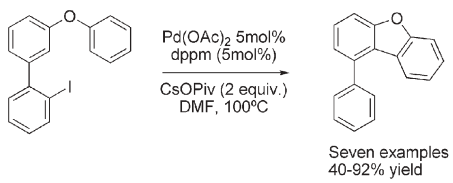


Scheme 3 Rawal's anion-accelerated intramolecular direct arylation. *Reagents and conditions*: (a) $Pd(OAc)_2$ 5 mol%, (*o*-tolyl)$_3$P 5 mol%, Cs_2CO_3 (3 equiv.) in DMA, 85–115 °C.



Scheme 4 Scope of biaryl formation.

results in the formation of the five-membered ring product (eqn (3)).[18]



(3)

Intermolecular direct arylation reactions with simple arenes have also appeared. In each case, the presence of an *ortho*-directing group is essential. Since arene–transition metal interactions are typically very weak, these groups facilitate the direct arylation step by holding the arene within the coordination sphere of the metal. Phenols,[19] amides,[20] ketones,[7a,b] imines[21] and pyridines[22] are commonly used directing groups (Fig. 2). Different strategies have been developed and exploited to achieve these successes. For example, the Sanford group has pioneered the use of palladium(II) catalysis in conjunction with phenyliodonium salts in the direct arylation of simple arenes.[22c] Daugulis has achieved similar success with aryl iodides in conjunction with silver salts and a palladium(0) catalyst.[20a] Another interesting strategy based on rhodium catalysis and the use of phosphite co-catalysts has also been devised by Bedford and co-workers for the direct arylation of phenols.[19b]

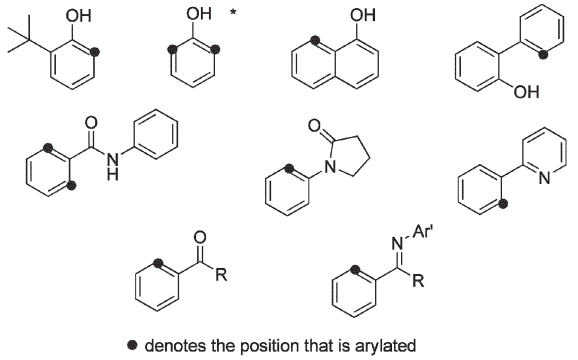


Fig. 2 Substrates used in intermolecular direct arylation; *mixtures of polyarylated product obtained

Results and discussion

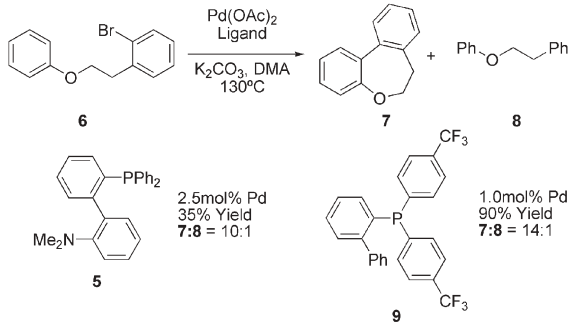
Our research group was interested in the use of a Pd^0/Pd^{II} catalytic cycle since it could potentially allow for cheap aryl chlorides and bromides to be cross coupled with simple and inexpensive aromatic compounds. As a stepping stone to more challenging reactions, we chose to first study the more precedented intramolecular variants. An initial goal was to advance the use of intramolecular direct arlyation as a synthetic tool in the construction of tricyclic biaryl molecules with a wide range of substrates and to apply these advances to the synthesis of natural and synthetic target molecules. A secondary goal was to apply newly gained knowledge to the development of new intermolecular direct arylation reactions.

First-generation catalyst

Aware of the lack of general methods to achieve intramolecular direct arylation and the limitations including unacceptably high catalyst loadings and hydrodehalogenation to arylation ratios, initial efforts were aimed at overcoming these obstacles.[23] Catalyst and reaction condition screens were performed with the simple aryl bromide **1** as the model substrate.[24]

As anticipated, poor reactivity and significant dehalogenation were obtained under previously reported conditions. In contrast, excellent results could be achieved with a catalyst generated from $Pd(OAc)_2$ and 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl **5** (Scheme 4).[25] A base and solvent screen revealed that K_2CO_3 in *N*,*N*-dimethylacetamide (DMA) gives near quantitative yields of the arylated product with as little as 0.1 mol% catalyst loading and with only trace hydrodehalogenation. Such high turnover numbers were unprecedented at the time in this class of reaction. An initial scope investigation revealed that the reaction could be carried out with a range of substituents including electron-withdrawing groups on the arene being functionalized.

The formation of seven-membered rings *via* intramolecular direct arylation is scarce.[26] Unfortunately, application of the optimal conditions for the formation of six-membered rings resulted in poor outcomes with **6**. A reinvestigation of the ligand parameters lead to the preparation and examination of sterically encumbered, electron-deficient ligand **9**. With ligand **9**, direct arylation of **6** to close the seven-membered ring could be achieved in 90% yield with 1.0 mol% palladium (Scheme 5).



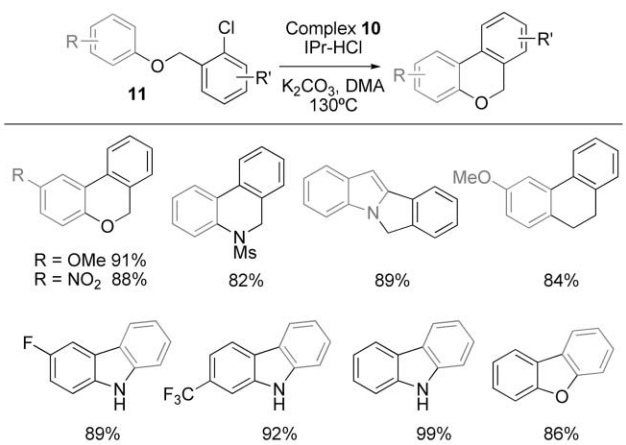
Scheme 5 Ligand effect on seven-membered ring formation.

This might be due to the facile dissociation of the bulky electron-poor ligand from the palladium metal allowing for more facile coordination of the arene. Since most ligand development efforts are directed at the preparation of bulky electron-rich systems, these observations that the use of bulky electron-deficient ligands can lead to excellent results should prompt their investigation in other challenging direct arylation reactions.

Although both of these catalyst systems proved extremely effective in the direct arylation of aryl bromides, they were both inefficient and low yielding with not only aryl chloride substrates, but also (surprisingly) with aryl iodides. These observations prompted a re-exploration of the reaction landscape with other aryl halides.

Second-generation catalyst

NHC ligands have become increasingly used in transition metal catalysis.[27] Their strong electron-donating ability has made them valuable tools for use with aryl chlorides in palladium-catalyzed cross-coupling reactions.[28] Since it had been demonstrated in other reactions that 1:1 NHC–palladium complexes are superior to 2:1 complexes,[29] both *in situ* generated catalysts and pre-formed 1:1 complexes were evaluated (Scheme 6).[30] Best results were achieved with complex **10** (Fig. 3), which gave a turnover number (TON) of 70 in the reaction of aryl chloride **11**.[31] An *in situ* generated catalyst prepared by mixing $Pd(OAc)_2$ and IPr–HCl (1:1) also



Scheme 6 Direct arylation of aryl chlorides with **15**/IPr–HCl.

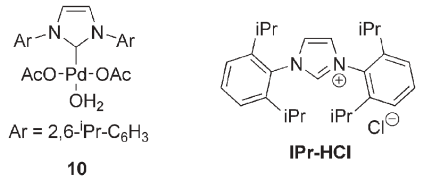


Fig. 3 *N*-Heterocyclic carbene catalysts for direct arylation.

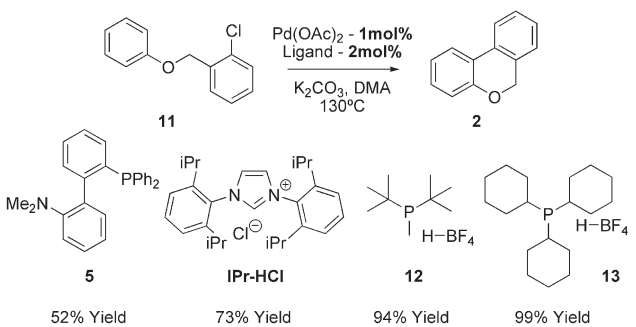
showed promise, albeit with a slightly reduced TON of 50. Intriguingly, the TON could be increased to 73 by generating the catalyst *in situ* with two equivalents IPr–HCl per palladium atom.

These observations prompted investigations into the use of IPr–HCl as an additive in reactions with catalyst **10**. The superior reactivity of mono-NHC palladium catalysts would appear to make this deliberate addition of NHC–HCl salts (pre-NHC ligands) to mono-NHC complexes counterproductive since bis-NHC complexes would be produced. Nonetheless, when complex **10** is used in conjunction with IPr–HCl (1 equivalent per **10**), an improvement from 70 to 116 TON can be achieved.[32] While the reason for this enhancement is not clear, preliminary experiments suggest that the reactivity of **10**, once reduced to palladium(0), is not negatively influenced by the presence of a slight excess of IPr, and that the free NHC ligand may recapture Pd(0) subsequent to catalyst decomposition to reform an active species.

The scope of this second-generation catalyst system is broad for a wide range of aryl chlorides (Scheme 6). An exception to the typically high yields is when more sterically encumbered arenes are employed. In these cases, low reactivity and incomplete conversion ($\sim$45%) is often obtained.

Third-generation catalyst – a general catalyst for the direct arylation of aryl chlorides, bromides and iodides

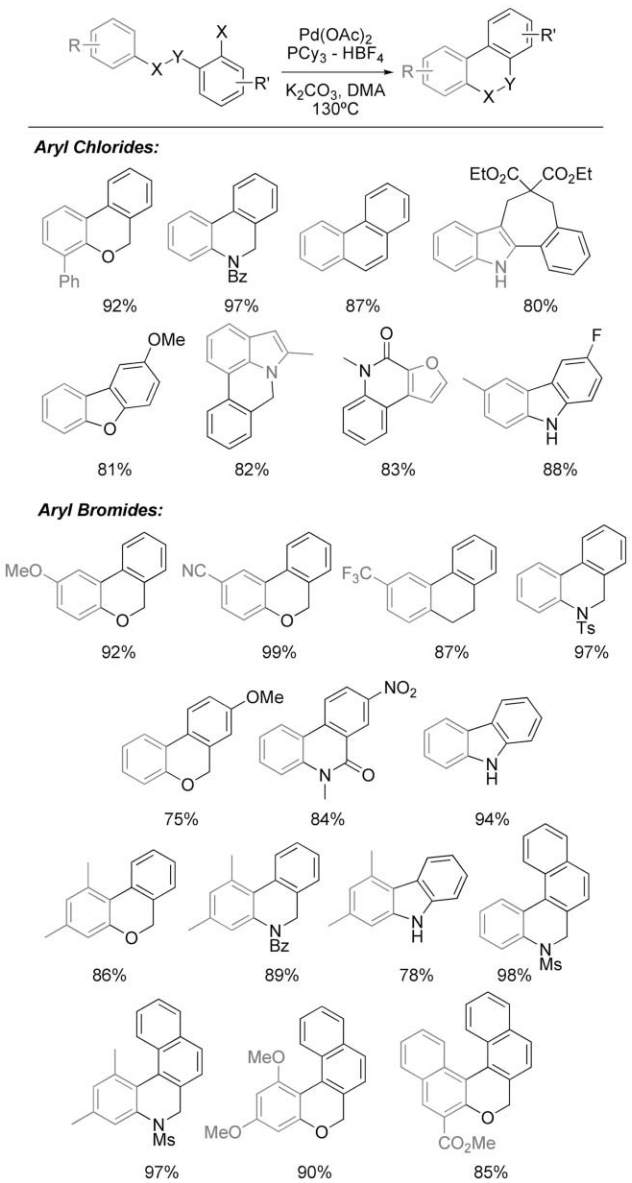
With the goal of achieving a single catalyst that would enable the direct arylation of a broad range of aryl halides, including chlorides, bromides and iodides, with the minimum of synthetic limitations, catalyst development efforts were continued. These led to the discovery that two phosphorous donor atom ligands, tricyclohexylphosphine and di-*tert*-butylmethylphosphine, added as their HBF_4 salt in combination with $Pd(OAc)_2$, lead to excellent reaction outcomes. Results from reactions performed with aryl chloride **11** are informative. Reactions with phosphine **5** or IPr–HCl give **2** in only 52 and 73% yield, respectively (Scheme 7). On the other hand, both



Scheme 7 Catalyst screen for direct arylation of aryl chlorides.

tricyclohexylphosphine and di-*tert*-butylmethylphosphine HBF_4 salts **12** and **13** provide essentially complete conversion.[33,34] While the use of the HBF_4 salts is not essential, their use enables all reagents to be weighed out in the open air with no special precautions or inert atmosphere until the solvent is added in the presence of a base. We also note that superior reaction outcomes are regularly obtained with salts **12** and **13** compared to their free bases even when all precautions are taken.

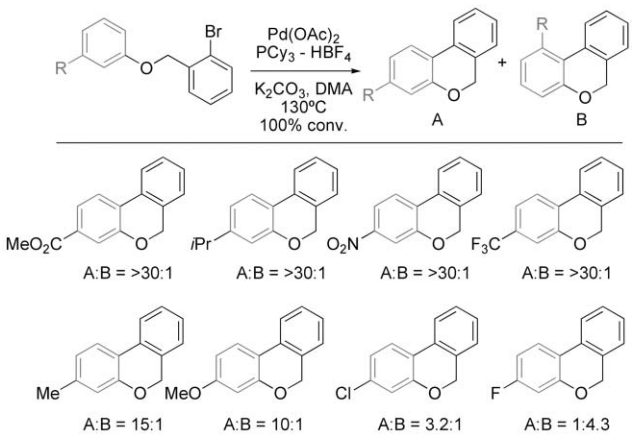
Because the use of pre-ligand **13** typically provided slightly higher yields and TONs than pre-ligand **12** in preliminary screens, it was selected to investigate the reaction scope (Scheme 8). This catalyst is very general, leading to clean conversion to the desired biaryl product for a variety of substrates with no change in the conditions required for aryl chloride and bromide substrates. Many substitution patterns and functional groups can be employed. Recent developments in biaryl synthesis have been directed at the synthesis of hindered tri- and tetra-ortho substituted biaryls.[35] This catalyst system can achieve direct arylation reactions with more sterically demanding substrates such as tetra-*ortho*-substituted substrates. In the case of *meta*-substituted arenes, very good selectivity is obtained in most cases although some substrates lead to modest selectivity (Scheme 9).



Scheme 8 Selected examples of direct arylation of aryl chlorides.

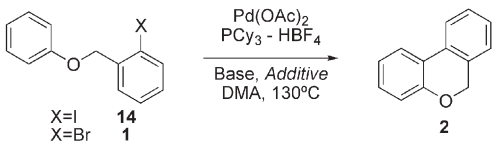
There is strong literature precedent for the use of aryl iodides in transition metal catalyzed cross coupling reactions.[3] In the development of new direct arylation reactions, aryl iodides are commonly used with far less focus on aryl bromides and chlorides. Since it is well precedented that oxidative insertion into a C–X bond is most facile for aryl iodides,[36] it might be anticipated that catalytic demand could be reduced by choosing an aryl iodide, thus allowing attention to be paid to the challenging ''arylation'' step of the catalytic cycle.

Given the common use of aryl iodides in direct arylation processes,[37] we were surprised to find that when aryl iodide **14** was reacted in the presence of $Pd(OAc)_2$ and $Cy_3P{\cdot}HBF_4$, a maximum TON of 64 could be achieved (Table 1) (in contrast, a TON of greater than 100 was observed when aryl bromide **1** is used). By following the reaction profile for the direct



Scheme 9 Catalyst selectivity in direct arylation.

Table 1 Halide effect in direct arylation reactions[a]



Entry	Halide	Base	Additive	Yield[b] (%)
1	Br	K_2CO_3	None	99
2	I	K_2CO_3	None	64[c]
3	Br	K_2CO_3	KI[d]	>5
4	I	Cs_2CO_3	None	89[e]
5	I	K_2CO_3	AgOTf[d]	99
6	I	K_2CO_3	Ag_2CO_3[f]	99

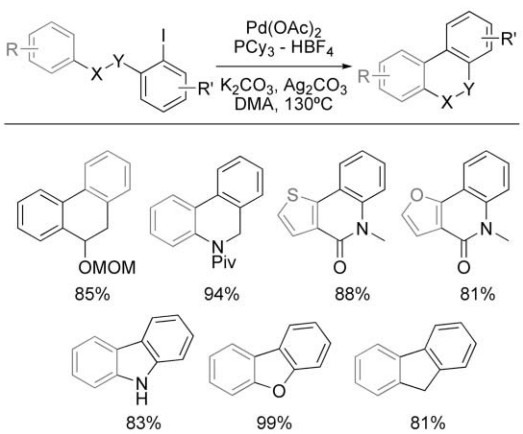
[a] *Conditions*: Substrate, $Pd(OAc)_2$ (1 mol%), PCy_3–HBF_4 (2 mol%), K_2CO_3 (2 equiv.) are dissolved in DMA (0.2 M) and heated to 130 °C. [b] GC-MS Yields. [c] **2**:**3** = 8:1. [d] 1 equivalent. [e] **2**:**3** = 8.5:1. [f] 0.5 equivalent.

arylation of iodide **14**, it was noted that a very fast initial reaction occurs which begins to slow at approximately 40% conversion, and plateaus at approximately 60% conversion.

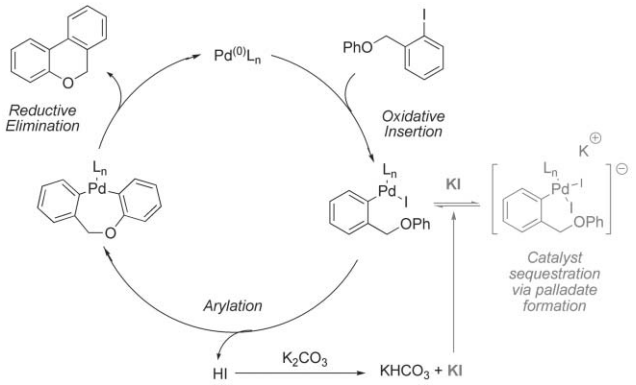
Since the only byproduct of the reaction is an accumulation of iodide anions, experiments were performed to determine if these salts were poisoning the catalyst. In an informative reaction, one equivalent of potassium iodide was added to a reaction with aryl bromide **1**. When this is done, essentially no reaction is observed (Table 1, entry 3), strongly supporting the notion that it is the iodide anions generated over the course of the reaction that prevent the direct arylation reaction from occuring.

To remedy this problem, the use of various silver salts and bases was explored. It has previously been noted that the use of caesium carbonate can improve the reactivity of aryl iodides in direct arylation reactions.[37a] Unfortunately, when Cs_2CO_3 is used, the ratio of arylation to hydrodehalogenation drops from >99:1 to 8.5:1. The use of silver salt additives was more effective. Both AgOTf and Ag_2CO_3 lead to high conversions and excellent arylation to hydrodehalogenation ratios (Table 1, entries 5 and 6). Ag_2CO_3 was used to examine the scope due to its ease of handling and lower cost. Selected examples are included in Scheme 10.

How are the iodide ions inhibiting the direct arylation reaction? Since the use of aryl iodides is well precedented in standard cross coupling methodology, it is not plausible that the accumulation of iodide in the reaction media is inhibiting the oxidative addition or the reductive elimination steps. In contrast, the arylation step of the catalytic cycle will rely on the ability of the palladium catalyst to interact with the aryl ring that is to undergo functionalization. Since this interaction is likely to be very weak, it is plausible that the iodide is inhibiting this step of the catalytic cycle. It is well documented that halides can interact with palladium(II) complexes to generate palladate species.[38] It is also known that the stability of these complexes is greatest with iodide compared to bromide and chloride.[39] The binding of an iodide to form such a species would block an additional coordination site and deter the arene–palladium interactions (Scheme 11). These observations warn against the presumption of the increased reactivity of aryl iodides in catalyst/reaction development efforts in direct arylation processes and indicate that catalyst



Scheme 10 Selected examples of direct arylation of aryl iodides.

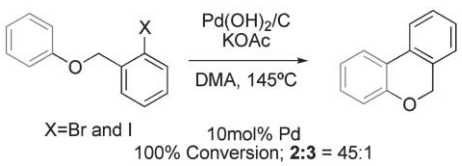


Scheme 11 Plausible influence of iodide ions on the catalytic cycle.

and substrate screens in the search for new reactions may best be performed with aryl bromides and/or chlorides, and not with aryl iodides as is commonly the case.

Direct arylation with Pearlman's catalyst

In early catalyst development efforts, we observed that some successful reactions turned black in early stages of substrate conversion. This observation led us to wonder whether palladium colloids or nanoparticles, generated under the reaction conditions, could behave as catalyst. Aware of the fact that reactions employing "heterogeneous" solid supported catalysts can actually occur *via* leaching of a homogeneous catalyst species such as soluble metal colloids,[40,41] we assayed several commercially available heterogeneous palladium sources in the intramolecular direct arylation of bromo and iodo arenes. From these studies, $Pd(OH)_2/C$, or Pearlman's catalyst, emerged as an active catalyst, generating **2** in 89% yield with a **2**:**3** ratio of 45:1.[42] Further catalyst optimization lead to the optimal conditions: $Pd(OH)_2/C$ (10 mol%), KOAc (2 equiv.), DMA (0.2 M) at 145 °C (eqn (4)). This catalyst does not suffer from iodide poisoning associated with the palladium/phosphine catalysts when used with aryl iodide substrates.



(4)

This catalyst can also be used in intramolecular direct arylation of various aryl iodide and bromide substrates. Intermolecular direct arylation of a variety of π-electron-rich heteroaromatic substrates which were known to react in intermolecular direct arylation reactions (Fig. 4).[11e,i]

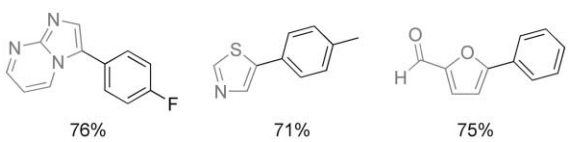


Fig. 4 Direct arylation of heteroaromatic substrate with Pearlman's catalyst.

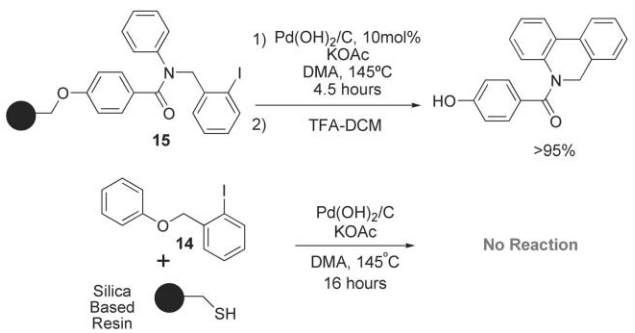
To determine the nature of the active catalyst two approaches based on the three-phase test were used (Scheme 12).[43] In one test, a solid supported substrate **15** was reacted with the $Pd(OH)_2/C$ catalyst which upon cleavage gave greater than 95% conversion. Since interaction between two solid phases is not possible, this result indicates that a soluble catalyst species had leached into solution. In a second test, homogeneous aryl iodide **14** was reacted in the presence of a solid phase thiol scavenger resin. This resin would be able to remove any homogeneous catalyst, but would not prevent the reaction from occuring at an active heterogenous catalyst anchored to the carbon matrix. In this case no reaction was observed indicating that the only active catalyst is a homogeneous species.

Tandem catalysis: heck, arylation and hydrogenation with a single catalyst

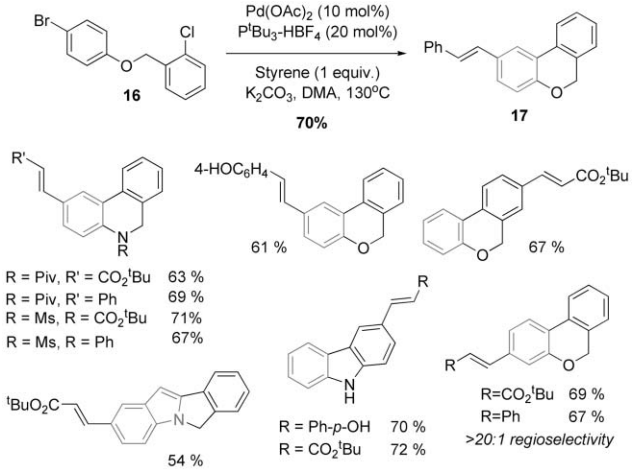
An emerging area of study in transition metal catalysis involves the use of a single catalyst to perform multiple one-pot transformations, or so-called tandem catalysis.[44] A growing number of processes involving two tandem reactions have appeared,[45] but examples where a single catalyst is able to perform three mechanistically distinct tandem catalytic reactions are rare.[44b] While direct arylation reactions have appeared as the terminating event of a catalytic cascade,[46] little is known about the compatibility of these reactions in the context of sequential, distinct tandem catalytic processes.[47] With this in mind, the application of direct arylation in tandem with Heck and hydrogenation reactions was investigated.[48]

Initial reaction screens revealed that the order of the reaction sequence was crucial for the tandem reaction to occur. Under no circumstances were acceptable results obtained when the direct arylation occurred first in the catalytic sequence. On the other hand, acceptable outcomes were achieved with substrate **16** requiring the Heck reaction to occur first. Optimized reaction conditions (**16**, styrene (1 equivalent), $Pd(OAc)_2$ (10 mol%), P^tBu_3-HBF_4 (20 mol%), K_2CO_3 (4 equivalents) in DMA at 130 °C), give a 70% isolated yield of the desired product **17** with less than 5% of other side products being formed. These conditions were employed to investigate the scope of the tandem Heck–direct arylation reaction (Scheme 13).

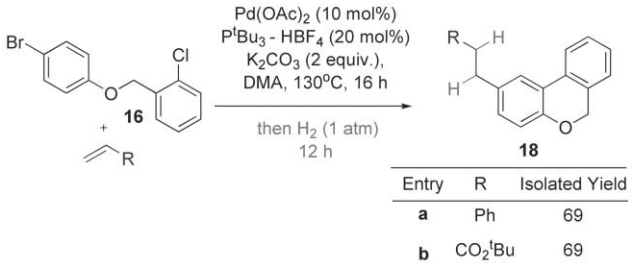
Whereas palladium catalysts are commonly employed in hydrogenation reactions, palladium/phosphine based catalysts



Scheme 12 Three-phase test performed on direct arylation with Pearlman's catalyst.



Scheme 13 Scope of tandem Heck/direct arylation.



Scheme 14 Double tandem multifunctional catalysis.

are rarely used. Indeed, control experiments focusing on the hydrogenation of **17** under the tandem reaction conditions produced no detectable reaction. Nonetheless, good yields could be achieved when the reactions are run in tandem, despite the fact that the catalyst used at the outset is incompatible with the third reaction of the series. For example, treatment of **16** with one equivalent of either styrene or *tert*-butyl acrylate under the standard conditions followed by replacement of the nitrogen atmosphere with hydrogen and reaction at 100 °C for an additional 12 h provides **18a** and **18b** in good yield (Scheme 14). This implies that the catalyst is being transformed under the reaction conditions to one that is capable of performing alkene hydrogenation.[49]

Application in the synthesis of biologically active compounds

Despite the significant potential of direct arylation in the synthesis of biaryl natural products, its use with unactivated arenes has been rarely adopted compared to traditional cross-coupling processes. When the preparation of tricyclic biaryls is called for, this strategy may be of particular utility. The molecules in Fig. 5 have all been prepared employing direct arylation.[23b,d,h,26b,50] The complexity of several of these molecules clearly illustrates the synthetic utility of this approach. In particular, a recent synthesis of rhazinilam by Trauner employed direct arylation to not only form the biaryl linkage but also a challenging nine-membered ring.[51] We have applied this strategy in the synthesis of three natural product classes, the carbazole, aporphine and allocolchicine alkaloids.

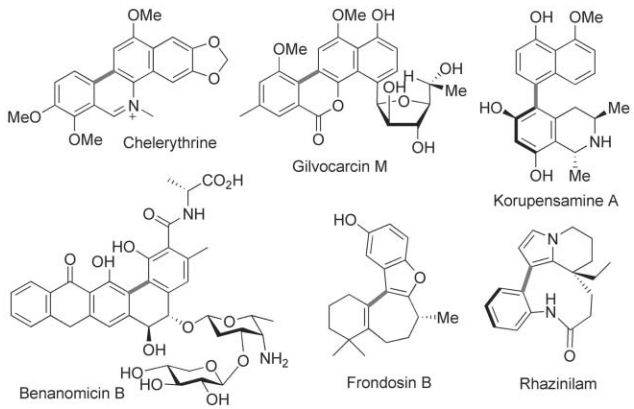
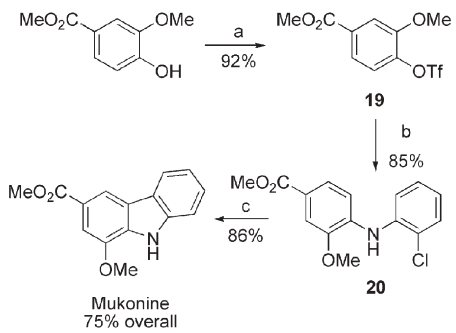


Fig. 5 Direct arylation in natural product synthesis.

Carbazole alkaloids have attracted significant attention due to their structural features and biological activities.[52] The carbazole nucleus can be formed easily *via* direct arylation, making this approach ideally suited for the synthesis of such compounds. This is illustrated by a rapid synthesis of mukonine (Scheme 15).[33] Starting from commercially available methyl vanillate, triflation of the free hydroxyl group provided aryl triflate **19** in 92% yield. Selective Buchwald–Hartwig amination with 2-chloroaniline provides diaryl amine **20** in 85% yield. Finally direct arylation using $Pd(OAc)_2$ (3 mol%), PCy_3–HBF_4 (6 mol%), K_2CO_3 (2 equiv.) in DMA (0.2 M) at 130 °C provides mukonine in 86% isolated yield.

Aporphine alkaloids have enjoyed increased synthetic attention in recent years.[53] Despite the continued synthetic work aimed at their preparation, the biaryl bond remains a consistent synthetic challenge.[54] In this context we[55] and Cuny[56] envisioned that direct arylation could be used in their preparation. Cuny applied a direct arylation strategy based on the Rawal precedent (see Scheme 3) involving a phenol activating group, to achieve useful yields of direct arylation and access several members of the aporphine family.[56] Our approach targeted the aporphine core *via* direct arylation in the absence of a phenol activating group. The direct arylation precursors were synthesized in a straightforward manner in high yields. A five-step sequence was developed for the synthesis of five direct arylation precursors (**21**) with overall yields in the range 50–80% (Scheme 16). Conditions derived from our initial report[24] were used to study the direct arylation. Under optimal conditions, reaction with only 3 mol% $Pd(OAc)_2$, 6 mol% ligand **5**, KOAc (2 equiv.) in DMA at 130 °C provides the aporphine core (**22**) in 76–99% yield. From **22**, a variety of aporphines and analogues can be synthesized by simple manipulations.



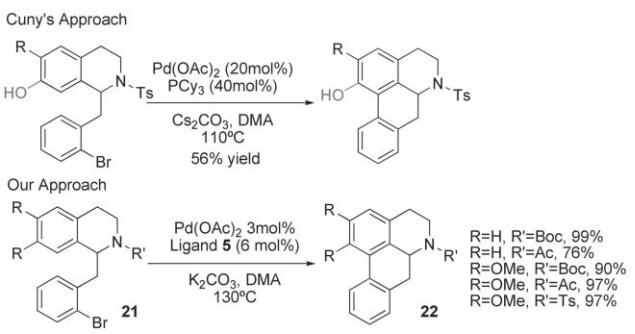
Scheme 15 Synthesis of mukonine. *Reagents and conditions*: (a) Tf_2O (1.1 equiv.), DIPEA (2 equiv.), THF −78 °C to 0 °C; (b) Pd_2dba_3 (2.5 mol%), 2-(di-*tert*-butylphophino)-2′-methylbiphenyl (10 mol%), K_3PO_4 (1.4 equiv.), 2-chloroaniline (1.2 equiv.), DME 80 °C; (c) $Pd(OAc)_2$ (3 mol%), PCy_3–HBF_4 (6 mol%), K_2CO_3 (2 equiv.), DMA 130 °C.

The allocolchicines, which are seven-membered ring biaryl analogues of naturally occuring colchicine, show promise in the development of new antitumor agents.[57] For example, the tricyclic biaryl core of allocolchicine presents several synthetic challenges in the context of direct arylation methodology. Direct arlyation has scarcely been investigated in the context of seven-membered ring formation. Furthermore, the availablility of starting materials required the use of an aryl chloride arylation precursor, for which there were limited examples when this target was selected.[58,59]

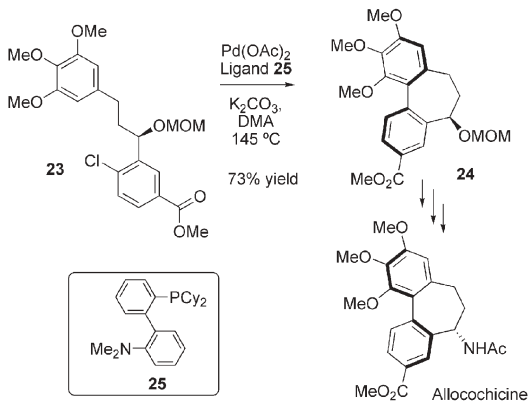
Precursor **23** was prepared in five steps in an overall yield of 54%. Investigations of the key direct arylation step revealed that up to 92% conversion could be obtained with the first-generation palladium/phosphine catalyst, but this was accompanied with an unacceptable 4:1 ratio of arylation to dehalogenation. Optimization studies uncovered a crucial link between the molar ratio of palladium to ligand and the ratio of arylation to dehalogenation. For example, with ligand **5**, the ratio could be improved by using a 1:1 Pd:ligand ratio. Unfortunately, this improvement came at the expense of severely diminished conversion. Continued studies revealed that when ligand **5** is replaced with electron-rich **25**,[60] increased conversion can be achieved while maintaining a synthetically acceptable arylation to dehalogenation ratio (Scheme 17). Under optimal conditions, $Pd(OAc)_2$ (10 mol%), **25** (10 mol%), K_2CO_3 (2 equiv.) in DMA at 145 °C, 94% conversion is obtained with a product to dehalogenation ratio of 14:1. The enantioselective formal synthesis was completed in four additional steps. The synthesis of an allocolchicine ring-C analogue was also completed employing the same route.

Mechanistic investigations

Several mechanistic scenarios have been proposed for direct arylation reactions including electrophilic palladation,[61,62] C–H oxidative insertion,[18] Heck-like processes[63] and others.[64] To probe the reaction mechanism, competition experiments



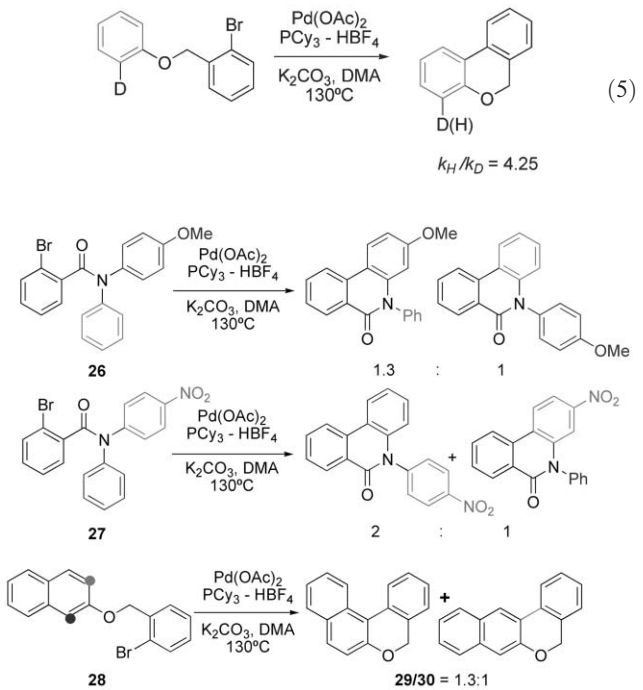
Scheme 16 Synthesis of aporphine alkaloids *via* direct arylation.



Scheme 17 Allocolchicine synthesis *via* direct arylation.

were devised to determine if the catalyst would react with the more electron-poor or electron-rich arene. Two amide substrates were synthesized where in one case (**26**) the catalyst can chose between electron-neutral (Ph) and electron-rich (*p*-$MeOC_6H_4$) aromatic rings and in the other (**27**) between electron-neutral (Ph) and electron-poor (*p*-$O_2NC_6H_4$) aromatic rings (Scheme 18). In both cases, very small selectivity is obtained for the more electron-rich arene. We also studied regioselectivity with 2-naphthol derived **28**. It is well documented that electrophilic additions to naphthalene systems occur preferentially at the 1-position.[65] The reaction of **28** under standard direct arylation reactions is essentially non-selective giving a 1.3:1 ratio of **29**:**30**.

The presence of a kinetic isotope effect (KIE) can also provide valuable information in mechanism elucidation. In our first report using ligand **5** we reported a KIE of 3.5.[24] When we repeated the experiment under the third-generation conditions with PCy_3–HBF_4, a KIE of 4.25 was obtained (eqn (5)).[33]

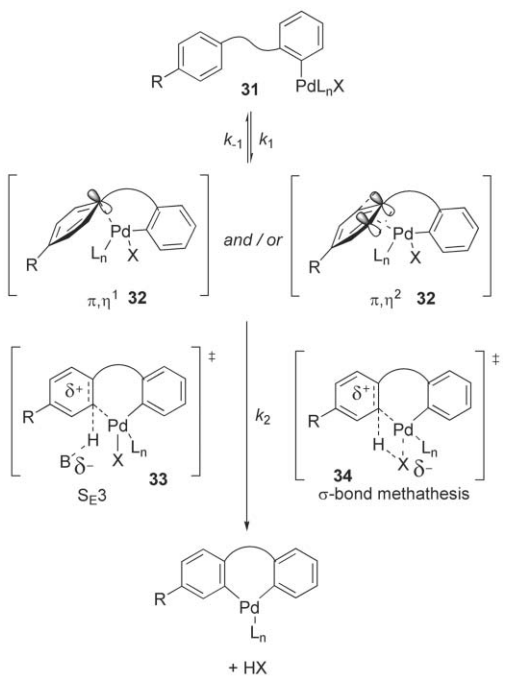


(5)

Scheme 18 Electronic bias in direct arylation.

Plausible mechanisms are illustrated in Scheme 19 that take into account these results and literature precedent. An electrophilic aromatic substitution pathway has significant mechanistic support in the direct arylation of other classes of arenes. Most electrophilic aromatic substitution reactions do not exhibit KIEs, however, because deprotonation is fast relative to the formation of the arenium σ-complex. In some cases, significant KIEs are observed as exemplified by electrophilic mercurations for which KIEs of up to six have been reported.[66] The presence of a primary kinetic isotope effect in direct arylation can be rationalized by considering the relative rates of coordination of the arene to give π,η^2-**32** and/or π,η^1-**32** from the palladium(II) arene intermediate **31** (k_1 and k_{-1}) and comparing them to the deprotonation step (k_2). The presence of a primary KIE implies that k_2 is kinetically significant. For this to occur k_1 and k_{-1} would have to be fast and reversible compared to k_2. Two scenarios are possible when considering these factors: a concerted S_E3 process,[67] where an external base deprotonates the arene as the Pd–C bond is forming, or a σ-bond metathesis mechanism where an anionic ligand on the palladium removes the proton. Recent computational studies support the σ-bond metathesis pathway,[68] but more work is required to definitively elucidate the mechanism.

It is reasonable to anticipate that the electronic properties of the arene ring will influence k_1 and k_{-1}. The competition experiments as well as reactions with 2-naphthol derived substrates (Scheme 18) reveal a very small but reproducible bias for more electron-rich arene (or site). The small electronic bias may point to a lack of cationic arenium character at the rate determining step which may be anticipated in a concerted palladium–carbon/carbon–hydrogen bond formation/cleavage process.



Scheme 19 Proposed mechanism for direct arylation.

Application in the development of new intermolecular direct arylation reactions

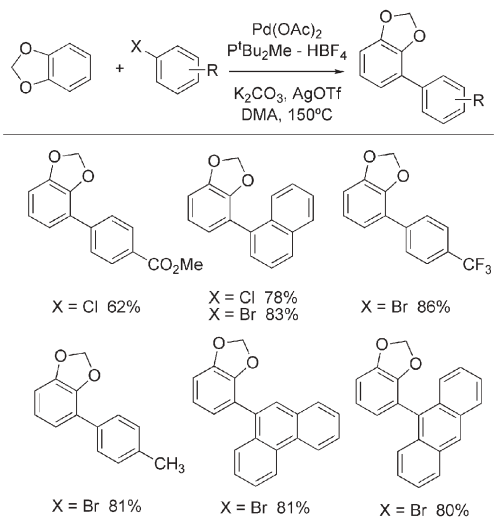
In addition to the development of catalysts for efficient intramolecular direct arylation, our studies were conducted with the desire to gain a better understanding of direct arylation processes in the hope of developing new intermolecular reactions. This goal is beginning to be realized. For example, using the conditions developed for the intramolecular reactions as a starting point, a new direct arylation reaction of 1,3-benzodioxole was achieved.[33] The regiochemistry obtained in these reactions provides biaryl products that are complimentary to those accessible *via* common cross-coupling methodology with readily available starting materials.

Under optimized conditions, the aryl bromide or chloride is treated with benzodioxole (10 equivalents), $Pd(OAc)_2$ (10 mol%), $P^tBu_2Me{\cdot}HBF_4$ (30 mol%), AgOTf (1 equivalent), K_2CO_3 (2 equivalents) in DMA (0.8 M) at 150 °C to give the direct arylation product in very good yield as exclusively one regioisomer (Scheme 20). The arylation occurs at the 4-position perhaps due to a directing effect of the dioxole group. These reaction conditions enable the intermolecular direct arylation of benzodioxole with a range of aryl chlorides and bromides. Both activated and non-activated aryl chlorides can be employed as well as more sterically encumbered aryl halides.

Interestingly, no cross-coupled direct arylation product is obtained when these reactions are run with iodobenzene. In this case, the major product is biphenyl arising from homocoupling of the iodobenzene. This result underlines the importance of the findings that aryl iodides can frequently exhibit inferior reactivity in direct arylation reactions with simple arenes and that they should not be used exclusively as model substrates in the development of new direct arylation processes.

Conclusions

In recent years, significant progess has been made in the direct arylation of simple arenes. A number of catalyst systems have been developed which now enable the intramolecular direct arylation of aryl chlorides, bromides and iodides in high yield. The lessons learned along the way have set the stage for new *intermolecular* reactions such as those described in the introduction and those with 1,3-benzodioxole. As more examples of such coupling appear, chemists will be able to gain a better insight into the catalyst and substrate requirements for efficient and synthetically useful direct arylation reactions which might allow for lower temperatures and catalyst loadings to be used, and new substrates to be employed. As catalytic direct arylation reactions become viable alternatives to traditional cross-coupling methodology, their use in organic synthesis will undoubtedly lead to shorter and more efficient syntheses of biaryl molecules.



Scheme 20 Direct arylation of 1,3-benzodioxole.

Note added in proof: After submission of this manuscript Maseras and Echavarren[69] published studies that strongly support a proton abstraction mechanism for these transformations.

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References

1 J. Hassan, M. Sevignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359.
2 F. Ullmann and J. Bielecki, *Chem. Ber.*, 1901, **34**, 2174.
3 For reviews on this topic, see: *Metal-catalyzed Cross-coupling Reactions*, ed. F. Diederich and P. J. Stang, Wiley-VCH, New York, 1998.
4 For recent reviews, see: (*a*) F. Kakiuchi and S. Murai, *Acc. Chem. Res.*, 2002, **35**, 826; (*b*) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731; (*c*) M. Miura and M. Nomura, *Top. Curr. Chem.*, 2002, **219**, 211; (*d*) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077.
5 For a discussion on this topic, see: "What is C–H Bond Activation?", B. Sezen and D. Sames, in *Handbook of C–H Transformations*, ed. G. Dyker, Wiley-VCH, Weinheim, 2005.
6 For example, an organic chemist would never refer to a Friedel–Crafts alkylation or a Fischer indole synthesis as functionalizations of the C–H bond. While these reactions do not involve metal catalysts, the reaction outcomes are the same – the arene ring becomes functionalized by the transformation.
7 (*a*) F. Kakiuchi, S. Kan, K. Igi, N. Chatani and S. Murai, *J. Am. Chem. Soc.*, 2003, **125**, 1698; (*b*) F. Kakiuchi, Y. Matsuura, S. Kan and N. Chatani, *J. Am. Chem. Soc.*, 2005, **127**, 5936, and references therein; (*c*) S. Oi, S. Fukita and Y. Inoue, *Chem. Commun.*, 1998, 2439.
8 I. J. S. Fairlamb, *Tetrahedron*, 2005, **41**, 9661.
9 B. S. Lane, M. A. Brown and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 8050.
10 Y. Akita, Y. Itagaki, S. Takizawa and A. Ohta, *Chem. Pharm. Bull.*, 1989, **37**, 1477.

11 (*a*) X. Wang, B. S. Lane and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 4996; (*b*) B. S. Lane and D. Sames, *Org. Lett.*, 2004, **6**, 2897; (*c*) J. C. Lewis, S. H. Wiedemann, R. G. Bergmann and J. A. Ellman, *Org. Lett.*, 2004, **6**, 35; (*d*) C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek and V. Gevorgyan, *Org. Lett.*, 2004, **6**, 1159; (*e*) W. Li, D. P. Nelson, M. S. Jensen, R. S. Hoerrner, G. J. Javadi, D. Cai and R. D. Larsen, *Org. Lett.*, 2003, **5**, 4835; (*f*) B. Sezen and D. Sames, *J. Am. Chem. Soc.*, 2003, **125**, 5274; (*g*) T. Okazawa, T. Satoh, M. Miura and M. Nomura, *J. Am. Chem. Soc.*, 2002, **124**, 5286; (*h*) F. Kakiuchi, S. Kan, K. Igi, N. Chatani and S. Murai, *J. Am. Chem. Soc.*, 2003, **125**, 1698; (*i*) M. S. McClure, B. Glover, E. McSorley, A. Millar, M. H. Osterhout and F. Roschangar, *Org. Lett.*, 2001, **3**, 1677; (*j*) Y. Aoyagi, A. Inoue, I. Koizumi, R. Hashimoto, K. Tokunaga, K. Gohma, J. Komatsu, K. Sekine, A. Miyafuji, J. Kunoh, R. Honma, Y. Akita and A. Ohta, *Heterocycles*, 1992, **33**, 257; (*k*) J. F. D. Chabert, L. Joucla, E. David and M. Lemaire, *Tetrahedron*, 2004, **60**, 3221; (*l*) A. Yokooji, T. Okazawa, T. Satoh, M. Miura and M. Nomura, *Tetrahedron*, 2003, **59**, 5685.

12 D. E. Ames and B. Bull, *Tetrahedron*, 1982, **38**, 383.

13 D. E. Ames and A. Opalko, *Synthesis*, 1983, **39**, 234.

14 D. E. Ames and A. Opalko, *Tetrahedron*, 1984, **40**, 1919.

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

16 M. A. Campo and R. C. Larock, *J. Am. Chem. Soc.*, 2002, **124**, 14326.

17 G. Karig, M.-T. Moon, N. Thasana and T. Gallagher, *Org. Lett.*, 2002, **4**, 3115.

18 M. A. Campo, Q. Huang, T. Yao, Q. Tian and R. C. Larock, *J. Am. Chem. Soc.*, 2003, **125**, 11506.

19 (*a*) T. Satoh, Y. Kawamura, M. Miura and M. Nomura, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1740; (*b*) R. B. Bedford, S. J. Coles, M. B. Hursthouse and M. E. Limmert, *Angew. Chem., Int. Ed.*, 2003, **42**, 112; (*c*) Y. Kawamura, T. Satoh, M. Miura and M. Nomura, *Chem. Lett.*, 1998, 961.

20 (*a*) O. Daugulis and V. G. Zaitsev, *Angew. Chem., Int. Ed.*, 2005, **44**, 4046; (*b*) Y. Kametani, T. Satoh, M. Miura and M. Nomura, *Tetrahedron Lett.*, 2000, **41**, 2655.

21 S. Oi, Y. Ogino, S. Fukita and Y. Inoue, *Org. Lett.*, 2002, **4**, 1783.

22 (*a*) Ref. 7*c*; (*b*) S. Oi, S. Fukita, N. Hirata, N. Watanuki, S. Miyano and Y. Inoue, *Org. Lett.*, 2001, **3**, 2579; (*c*) D. Kalyani, N. R. Deprez, L. V. Desai and M. S. Sanford, *J. Am. Chem. Soc.*, 2005, **127**, 7330; (*d*) L. Ackermann, *Org. Lett.*, 2005, **14**, 3123.

23 With 30 mol% catalyst: (*a*) M. Kitamura, K. Ohmori, T. Kawase and K. Suzuki, *Angew. Chem., Int. Ed.*, 1999, **38**, 1229; (*b*) J. E. Rice, Z.-W. Cai, Z.-M. He and E. J. LaVaoie, *J. Org. Chem.*, 1995, **60**, 8101; with 26 mol% catalyst: (*c*) T. Hosoya, E. Takashiro, T. Matsumoto and K. Suzuki, *J. Am. Chem. Soc.*, 1994, **116**, 1004; with 25 mol% catalyst: (*d*) T. Matsumoto, T. Hosoya and K. Suzuki, *J. Am. Chem. Soc.*, 1992, **114**, 3568; with 20–25 mol% catalyst: (*e*) G. D. Cuny, *Tetrahedron Lett.*, 2003, **44**, 8149; (*f*) G. Qabaja and G. B. Jones, *J. Org. Chem.*, 2000, **65**, 7187; with as low as 10 mol% catalyst: (*g*) G. Bringmann, M. Heubes, M. Breuning, L. Gobel, M. Ochse, B. Schoner and O. Schupp, *J. Org. Chem.*, 2000, **65**, 722; (*h*) G. Bringmann, M. Ochse and R. Gotz, *J. Org. Chem.*, 2000, **65**, 2069; (*i*) T. Harayama and H. Yasuda, *Heterocycles*, 1997, **46**, 61.

24 L.-C. Campeau, M. Parisien, M. Leblanc and K. Fagnou, *J. Am. Chem. Soc.*, 2004, **126**, 9186.

25 M. C. Harris, O. Geis and S. L. Buchwald, *J. Org. Chem.*, 1999, **64**, 6019; this ligand is commercially available from Strem Chemicals.

26 For examples using heterocyclic arenes, see: (*a*) A. P. Kozikowski and D. Ma, *Tetrahedron Lett.*, 1991, **32**, 3317; (*b*) C. C. Hughes and D. Trauner, *Angew. Chem., Int. Ed.*, 2002, **41**, 1569.

27 For a review, see: W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1290.

28 For a review of palladium-catalyzed cross-coupling reactions of aryl chlorides, see: A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176.

29 For example, see: (*a*) A. C. Hillier, G. A. Grasa, M. S. Viciu, H. M. Lee, C. Yang and S. P. Nolan, *J. Organomet. Chem.*, 2002, **653**, 69; (*b*) J. Huang and S. P. Nolan, *J. Am. Chem. Soc.*, 1999, **121**, 9889; (*c*) J. Huang, G. A. Grasa and S. P. Nolan, *Org. Lett.*, 1999, **1**, 1307; (*d*) H. M. Lee and S. P. Nolan, *Org. Lett.*, 2000, **2**, 119; (*e*) G. A. Grasa, M. S. Viciu, J. Huang and S. P. Nolan, *J. Org. Chem.*, 2001, **66**, 7729; (*f*) G. A. Grasa, M. S. Viciu, J. Huang, C. Zhang, M. L. Trudell and S. P. Nolan, *Organometallics*, 2002, **21**, 2866; (*g*) M. S. Viciu, R. M. Kissling, E. D. Stevens and S. P. Nolan, *Org. Lett.*, 2002, **4**, 2229; (*h*) M. S. Viciu, R. F. Germaneau, O. Navarro-Fernandez, E. D. Stevens and S. P. Nolan, *Organometallics*, 2002, **21**, 5740.

30 (*a*) M. S. Viciu, O. Navarro, R. F. Germaneau, R. A. Kelly, III, W. Sommer, N. Marion, E. D. Stevens, L. Caballo and S. P. Nolan, *Organometallics*, 2004, **23**, 1629; (*b*) D. R. Jensen, M. J. Schultz, J. A. Mueller and M. S. Sigman, *Angew. Chem., Int. Ed.*, 2003, **42**, 3810; (*c*) A. C. Frisch, F. Rataboul, A. Zapf and M. Beller, *J. Organomet. Chem.*, 2003, **687**, 403; (*d*) M. S. Viciu, E. D. Stevens, J. L. Petersen and S. P. Nolan, *Organometallics*, 2004, **23**, 3752.

31 L.-C. Campeau, P. Thansandote and K. Fagnou, *Org. Lett.*, 2005, **7**, 1857.

32 This kind of TON increase upon NHC–HCl addition was also observed in telomerisation of dienes with alcohols but increased reaction rates were observed with higher imidazolium salt additive concentrations which is not the case here: R. Jackstell, S. Harkal, H. Jiao, A. Spannenberg, C. Borgmann, D. Röttger, F. Nierlich, M. Elliot, S. Niven, K. Cavell, O. Navarro, M. S. Viciu, S. P. Nolan and M. Beller, *Chem.–Eur. J.*, 2004, **10**, 3891.

33 L.-C. Campeau, M. Parisien, A. Jean and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 581.

34 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295.

35 For recent advances, see: (*a*) J. E. Milne and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **126**, 13028; (*b*) S. D. Walker, T. E. Barder, J. R. Martinelli and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2004, **43**, 1871.

36 For a discussion, see: (*a*) V. V. Grushin and H. Alper, in *Activation of Unreactive Bonds and Organic Synthesis*, ed. S. Murai, Springer, Berlin, 1999, pp. 193–226; (*b*) V. V. Grushin and H. Alper, *Chem. Rev.*, 1994, **94**, 1047.

37 (*a*) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura and M. Nomura, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 467; also see refs. 42, 18, 11*a* and 15.

38 C. Amatore and A. Jutand, *Acc. Chem. Res.*, 2000, **33**, 314.

39 For a review on halide effects in transition metal catalysis, see: K. Fagnou and M. Lautens, *Angew. Chem., Int. Ed.*, 2002, **41**, 26.

40 For a review: (*a*) B. M. Bhanage and M. Arai, *Catal. Rev. Sci. Eng.*, 2001, **43**, 315; for example: (*b*) W.-C. Shieh, R. Shekhar, T. Blacklock and A. Todesco, *Synth. Commun.*, 2002, **32**, 1059; (*c*) R. L. Augustine and S. T. O'Leary, *J. Mol. Catal.*, 1992, **72**, 229; (*d*) S. Iyer and V. V. Thakur, *J. Mol. Catal. A: Chem.*, 2000, **157**, 275.

41 For release and capture mechanisms, see: (*a*) H. L. Davies, A. M. Walji and T. Nagashima, *J. Am. Chem. Soc.*, 2004, **126**, 4271; (*b*) ref. 40*c*.

42 M. Parisien, D. Valette and K. Fagnou, *J. Org. Chem.*, 2005, **70**, 7578.

43 (*a*) I. W. Davies, L. Matty, D. L. Hughes and P. J. Reider, *J. Am. Chem. Soc.*, 2001, **123**, 10139; (*b*) J. Rebek and F. Gavina, *J. Am. Chem. Soc.*, 1974, **96**, 7112; (*c*) J. Rebek, D. Brown and S. Zimmerman, *J. Am. Chem. Soc.*, 1975, **97**, 454; (*d*) J. Rebek, *Tetrahedron*, 1979, **35**, 723.

44 (*a*) H.-B. Yu, Q.-S. Hu and L. Pu, *J. Am. Chem. Soc.*, 2000, **122**, 6500; (*b*) C. W. Bielawski, J. Louie and R. H. Grubbs, *J. Am. Chem. Soc.*, 2000, **122**, 12872; (*c*) P. A. Evans and J. E. Robinson, *J. Am. Chem. Soc.*, 2001, **123**, 4609; (*d*) J. Louie, C. W. Bielawski and R. H. Grubbs, *J. Am. Chem. Soc.*, 2001, **123**, 11312; (*e*) P. Zezschwitz, F. Petry and A. de Meijere, *Chem.–Eur. J.*, 2001, 4035; (*f*) S. D. Drouin, F. Zamanian and D. E. Fogg, *Organometallics*, 2001, 5495; (*g*) B. M. Choudary, N. S. Chowdari, K. Jyothi, N. S. Kumar and M. L. Kantam, *Chem. Commun.*, 2002, 586; (*h*) E. Teoh, E. A. Campi, W. R. Jackson and A. J. Robinson, *Chem. Commun.*, 2002, 978; (*i*) B. A. C. van As, J. V. Buijtenen, A. Heise, Q. B. Broxterman, G. K. M. Verzijl, A. R. A. Palmans and E. W. Meijer, *J. Am. Chem. Soc.*, 2005, **127**, 9964; (*j*) A. N. Thadani and V. H. Rawal, *Org. Lett.*, 2002, **4**, 4317; (*k*) A. N. Thadani and V. H. Rawal, *Org. Lett.*, 2002, **4**, 4321.

45 For recent reviews of domino reactions, see: (*a*) S. Ikeda, *Acc. Chem. Res.*, 2000, **33**, 511; (*b*) G. Poli, G. Giambastiani and A. Heumann, *Tetrahedron*, 2000, **56**, 5959; (*c*) A. de Meijere and S. Brase, *J. Organomet. Chem.*, 1999, **576**, 88; (*d*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*e*) P. J. Parsons, C. S. Penkett and

A. J. Shell, *Chem. Rev.*, 1996, **96**, 195; (*f*) M. Malacria, *Chem. Rev.*, 1996, **96**, 289; (*g*) A. Heumann and M. Reglier, *Tetrahedron*, 1996, **52**, 9289; (*h*) J.-C. Wasilke, S. J. Obrey, T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001; (*i*) D. E. Foff and E. N. dos Santos, *Coord. Chem. Rev.*, 2004, **248**, 2365.
46 (*a*) For example, see ref. 18; (*b*) H. Ohno, K. Miyamura, T. Mizutani, Y. Kadoh, Y. Takeoka, H. Hamaguchi and T. Tanaka, *Chem.–Eur. J.*, 2005, **11**, 3728; (*c*) F. Faccini, E. Motti and M. Catellani, *J. Am. Chem. Soc.*, 2004, **126**, 78; (*d*) G. Cuny, M. Bois-Choussy and J. Zhu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4774; (*e*) P. Mauleon, A. A. Nunez, I. Alonzo and J. C. Carretero, *Chem.–Eur. J.*, 2003, **9**, 1511; (*f*) C. Bressy, D. Alberico and M. Lautens, *J. Am. Chem. Soc.*, 2005, **127**, 13148.
47 For a seminal example, see: R. B. Bedford and C. S. J. Cazin, *Chem. Commun.*, 2002, 2310.
48 J.-P. Leclerc, M. André and K. Fagnou, *J. Org. Chem.,* ASAP Article.
49 We observe the formation of insoluble palladium black after the completion of the Heck and arylation steps. It may be that palladium colloids are responsible for the hydrogenation chemistry observed. This is under study.
50 T. Harayama, T. Akiyama, H. Akamatsu, K. Kawano, H. Abe and Y. Takeuchi, *Synthesis*, 2001, **3**, 444.
51 A. L. Bowie, Jr., C. C. Hughes and D. Trauner, *Org. Lett.*, 2005, **7**, 5207.
52 For a review on biologically active carbazole alkaloids, see: H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303.
53 (*a*) T. Linnanen, M. Brisander, N. Mohell and A. M. Johansson, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 367; (*b*) Y.-C. Chia, K.-S. Chen, Y.-L. Chang, C.-M. Teng and T.-C. Wu, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3295; (*c*) Y.-C. Wu, F.-R. Chang, Y.-C. Chao and C.-M. Teng, *Phytother. Res.*, 1998, **12**, S39.
54 (*a*) F. Roblot, R. Hocquemiller and A. Cavé, *Bull. Soc. Chim. Fr.*, 1990, **127**, 258; (*b*) Y. Landais and J. P. Robin, *Tetrahedron*, 1992, **48**, 7185.
55 M. Lafrance, N. Blaquiere and K. Fagnou, *Chem. Commun.*, 2004, 2874.
56 (*a*) Ref. 23*e*; (*b*) G. D. Cuny, *Tetrahedron Lett.*, 2004, **45**, 5167.
57 (*a*) E. Hamel, *Med. Res. Rev.*, 1996, **16**, 207; (*b*) Q. Shi, S. L. Morris-Natschke and K.-H. Lee, *Curr. Pharmaceut. Des.*, 1998, **4**, 219; (*c*) K.-H. Lee, *J. Biomed. Sci.*, 1999, **6**, 236; (*d*) L. M. Leoni, E. Hamel, D. Genini, H. Shih, C. J. Carrera, H. B. Cottam and D. A. Carson, *J. Natl. Cancer Inst.*, 2000, **92**, 217; (*e*) T. Graening and H.-G. Schmalz, *Angew. Chem., Int. Ed.*, 2004, **43**, 3230.
58 Successful reaction with aryl chlorides has been achieved in intermolecular reactions with electron rich zinc pyrroles, and intramolecularly in the formation of five-membered rings in moderate to good yield. See: (*a*) R. D. Rieth, N. P. Mankad, E. Calimano and J. P. Sadighi, *Org. Lett.*, 2004, **6**, 3981; (*b*) ref. 47.
59 M. Leblanc and K. Fagnou, *Org. Lett.*, 2005, **7**, 2849.
60 H. Tomori, J. M. Fox and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 5334; this ligand is commercially available from Strem Chemicals.
61 With simple arenes: (*a*) B. Martin-Matute, C. Matea, D. J. Cardenas and A. M. Echavarren, *Chem.–Eur. J.*, 2001, **7**, 234; (*b*) A. M. Echavarren, B. Gòmez-Lor, J. J. Gonzàlez and O. de Fruto, *Synlett*, 2003, **5**, 585; (*c*) J. J. Gonzalez, N. Garcia, B. Gomez-Lor and A. M. Echavarren, *J. Org. Chem.*, 1997, **62**, 1286; (*d*) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries and P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.*, 2002, **124**, 1586; (*e*) R. S. Shue, *J. Am. Chem. Soc.*, 1971, **93**, 7116; (*f*) G. W. Parshall, *Acc. Chem. Res.*, 1970, **3**, 139.
62 With heteroaromatics: (*a*) B. S. Lane, M. A. Brown and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 8050, and references therein; (*b*) ref. 26*b*; (*c*) B. Glover, K. A. Harvey, B. Liu, M. J. Sharp and M. F. Tymoschenko, *Org. Lett.*, 2003, **5**, 301.
63 This pathway has been proposed as a possibility before: (*a*) M. Toyata, A. Ilangovan, R. Okamoto, T. Masaki, M. Arakawa and M. Ihara, *Org. Lett.*, 2002, **4**, 4293; (*b*) ref. 62. Proposed but dismissed: ref. 26*b*.
64 E. J. Hennessy and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 12084, and references therein.
65 For a discussion on the preferred site of attack of many ring systems, see: P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution Nitration and Halogenation*, Academic Press, NY, 1959, p. 169.
66 A. J. Kresge and J. F. Brennan, *J. Org. Chem.*, 1967, **32**, 752.
67 H. Zollinger, *Adv. Phys. Org. Chem.*, 1964, **2**, 162–200.
68 This alternative has recently been shown to be lower in energy than oxidative insertion of a C–H bond *via* computational calculations, see: (*a*) A. J. Mota, A. Dedieu, C. Bour and J. Suffert, *J. Am. Chem. Soc.*, 2005, **127**, 7171. It has also been shown computationally to be a viable mechanism in cyclopalladation, see: (*b*) D. L. Davies, S. A. Donald and S. A. Macgregor, *J. Am. Chem. Soc.*, 2005, **127**, 13754.
69 D. García-Cuadrado, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2006, ASAP Article.

