REVIEW

DOI: 10.1002/adsc.200900059

Transition Metal-Catalysed, Direct and Site-Selective N1-, C2- or C3-Arylation of the Indole Nucleus: 20 Years of Improvements

Lionel Joucla[a] and Laurent Djakovitch[a,*]

[a] Université de Lyon, CNRS, UMR 5256, IRCELYON, Institut de recherches sur la catalyse et l'environnement de Lyon, 2 avenue Albert Einstein, F-69626 Villeurbanne, France
Fax: (+33)-472-445-399; phone: (+33)-472-445-381; e-mail: laurent.djakovitch@ircelyon.univ-lyon1.fr

Received: January 27, 2009; Revised: March 6, 2009; Published online: March 20, 2009

Abstract: The direct and site-selective transition metal-catalysed N1-, C2- or C3-arylations of indoles have been the subject of almost continuous improvements since their discovery in early 1980s. This research area is mainly motivated by the biological relevance of this class of compounds in order to propose catalytic alternative syntheses to the well known methodologies involving the formation of the indole ring like the Fischer, Larock, Cacchi, Lautens etc. reactions. Since the late 1990s it has experienced new impulses related to the intensive development of catalytic C–H activation. Today, through the intensive studies of Buchwald and Hartwig, the N1-arylation of indoles has reached sufficient maturity for both academic and industrial applications. On the other hand, the selective C2- or C3-arylation of indoles, initiated by Ohta in the middle 1980s, has become a hot research area these last years following the reports of Sames. Surprisingly, only few reports concern the use of heterogeneous catalysts; however, the application of these emerging methodologies seems to be related to the discovery of industrially attractive systems.

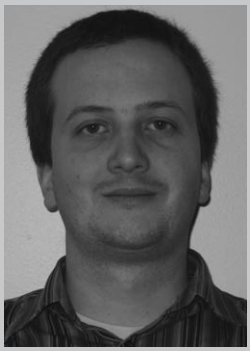
Keywords: arylindoles; Buchwald–Hartwig amination; C–H activation; oxidative coupling; site-selective arylation

1 Introduction

Arylindoles are ubiquitous in biochemical, biological and medicinal structures and functions.[1,2] N1-Arylindoles are of interest as antigiotensin II-1 antagonists,[3] MT_1 melatonin receptor partial agonists,[4] antipsychotic agents,[5] etc., and synthetic intermediates used in the preparation of other biologically active heterocycles.[6] Similarly, C2- and C3-arylindoles exhibit also important biological responses,[7] for example, as antimicrobial compounds active against fungi and Gram-positive bacteria, antiprotozoal agents,[8] gonodotropin releasing hormone antagonists,[9] h5-HT_{2A} receptor antagonist,[10] etc. Others are cell proliferative inhibitors or botulinum neurotoxin inhibitors. To underline the diversity of these bioactive molecules, the World Drug Index contains forty-six referenced 2-arylindoles and thirty-eight 3-arylindoles.[11]

In the light of the importance of these bioactive molecules, several synthetic protocols have been reported. Concerning the N1-arylindoles, traditionally, these compounds have been synthesised by S_NAr of NH-containing π-electron-rich nitrogen heterocycles with electron-deficient aryl halides[12–14] or *via* stoichiometric Ullmann-type[15] or Goldberg-type[16] coupling methodologies. Alternatively, some authors re-

After a sixteen-month research period at the University of Cambridge with Dr. S. Warren (1992), *Laurent Djakovitch* received his PhD from the University of Bordeaux in 1995 under the direction of Prof. D. Astruc. In the following years, he joined the Technical University of Munich for 4 years working as a Alexander von Humboldt post-doc fellow with Prof. W. A. Herrmann (1995) and as a Marie-Curie fellow with Prof. K. Köhler (1997). In 1999 he returned at the University of Lyon in France, first as a research assistant in the group of Prof. J.-M. Basset before joining the CNRS at the *Institut de Recherches sur la Catalyse et l'Environnement de Lyon*. His current research interests include the use of heterogeneous catalysts for fine chemical syntheses from cross-coupling reactions to the one-pot synthesis of bioactive molecules.



Lionel Joucla was born in Toulouse, France, in 1980. After undergraduate studies at the Institute of Technology of Castres, he moved to Lyon and graduated as a chemical engineer in 2003 from Ecole Supérieure de Chimie Physique Electronique de Lyon. He received his Ph.D. degree from University of Lyon in 2007 for studies focussing on palladium-catalysed aryl cross-couplings with application in the syntheses of biologically active azepinones. After a six-month research period devoted to the transformation of vegetable oils in the group of Prof. M. Lemaire, he joined the *Institut de Recherches sur la Catalyse et l'Environnement de Lyon* as a CNRS post-doctoral fellow, working on the development of heterogeneous catalysts for one-pot syntheses.

ported the activation of aryl halides, mainly fluoride, by π-complexation with either chromium tricarbonyl or analogues.[17–20] However, all these methods are not considered as catalytic routes and will not be further developed in this review. Recent reports involved the N1-arylation of indole without transition metal catalysts under microwave heating conditions.[21] Nevertheless, these methods generally concern only few examples and do not constitute a general approach for the preparation of N1-arylindoles.[22]

Generally, C2- and C3-arylated indoles are synthesised by coupling preactivated arenes with indoles or by intermolecular cyclisations that produce the azole ring. Among the methods reported, the Fisher[23] and Larock indole syntheses[24] that belong to the first class of reaction, are probably the most known as they cover as well these two substitution positions. Today's popular alternative methods to produce either C2- or C3-arylindoles through intramolecular cyclisations, known as Cacchi[7] and Lautens[25–27] syntheses, have been described. All these methods have been the subject of specific research works that are almost out of the scope of this review article and we do not intend to give more details here. The reader interested in these fields can refer to the corresponding more authoritative articles.[7,23–27]

This review covers rather an emerging area that has been under development for two decades. It concerns the direct arylation of the indole nucleus catalysed by transition metals (mainly Cu and Pd), through either a *Buchwald–Hartwig* amination[28,29] reaction for N1-arylindoles or *C–H activation* for C2- and C3-arylindoles (Figure 1). These methods appeared to be very powerful for producing these important classes of molecules. This review article provides a survey of the relevant literature on the N1-, C2- and C3-arylation of indoles according to the substitution position since this makes the organisation easier. It also contains a mechanistic outlook before the concluding remarks.

2 Selective N1-Arylation

2.1 Copper-Catalysed Methodologies

2.1.1 Ligand-Free Procedures

One of the first catalytic procedures, based on the Ullmann reaction, was reported by Unangst and co-workers in 1987. Using either copper oxide (30 mol%) or a mixture of cuprous bromide (10 mol%) and cuprous oxide (10 mol%) as catalyst in refluxing DMF, the authors reported the arylation of 2-carboxy-5-methoxy-1*H*-indole methyl ester by bromobenzene.[30] This catalytic system was also applied to indole-2-carboxylic acid by Olgen and co-workers.[31] The method was further adapted by Perregard and co-workers for the synthesis of 5-HT_2 antagonists.[32,33] Working in NMP and using copper iodide as catalyst (25 mol%) in the presence of K_2CO_3 as base and ZnO as co-catalyst, variously substituted indoles were N1-arylated using aryl iodide derivatives (Scheme 1). This method was further applied by Tarzia and co-workers[34] and Espejo-González and

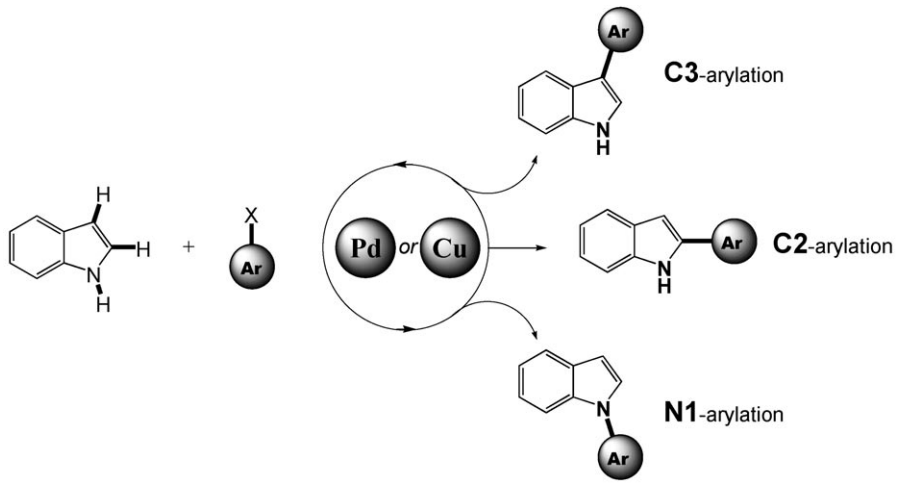
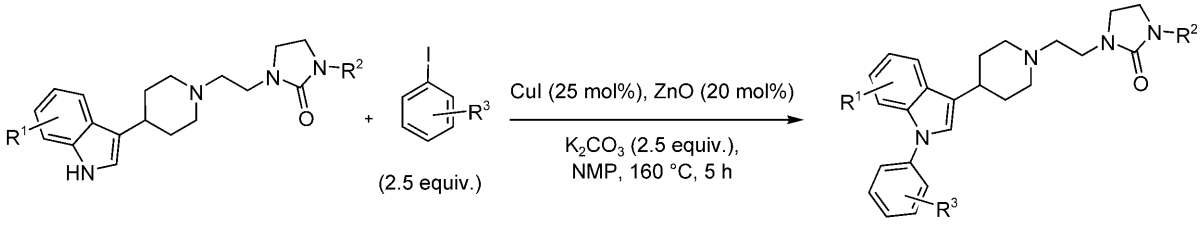


Figure 1. Overview of selective N1-, C2- or C3-arylation of the indole core.



R^1 = 6-Cl, 6-CH_3, 6-CF_3, 6-F, 6-$CH(CH_3)_2$
R^2 = H, $CH(CH_3)_2$
R^3 = H, 2-F, 3-F, 3-CF_3, 4-Cl,4-F

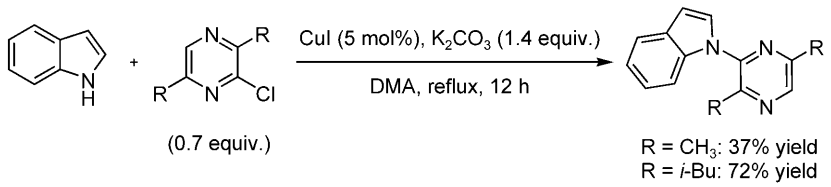
Scheme 1. Synthesis of 5-HT_2 antagonists by copper-catalysed N1-arylation of the corresponding indole derivatives.

co-workers[35] for the synthesis of novel indole melatonin analogues, by Andersen and co-workers for the synthesis of a new class of selective α_1-adrenoreceptor antagonists,[36] and by Vaz and co-workers for the preparation of Sertindole analogues (antipsychotic drugs).[37]

Alternatively, Barton and co-workers reported in 1988 a copper-catalysed methodology based on the use of $Cu(OAc)_2$ in the presence of triphenylbismuth(IV) diacetate as arylating agent. The reaction was performed in dichloromethane at room temperature using 10 mol% copper catalyst. Applied to indole, moderate yields were achieved; other 2,3-disubstituted indoles (i.e., 2,3,4,9-tetrahydro-1*H*-carbazole or 9*H*-carbazole) gave moderate to good yields of the expected N-phenyl compounds.[38]

Similarly, Ohta and co-workers reported the N1-arylation of indole by 2-chloro-3,6-dialkylpyrazine in the presence of copper iodide (5 mol%) using potassium carbonate as base in dimethylacetamide (DMA). Depending on the substituents present on the heteroaryl halide moderate to good yields were achieved (Scheme 2).[39]

Chen and co-workers reported an alternative, ligand-free procedure using diaryliodonium salts (Figure 2). Good isolated yields were achieved in relatively short reaction times; however, the N1-arylation must be performed at high reaction temperatures (140–150 °C).[40] Interestingly, using this method full



Scheme 2. N1-Arylation of indole by 2-chloro-3,6-dialkylpyrazine.

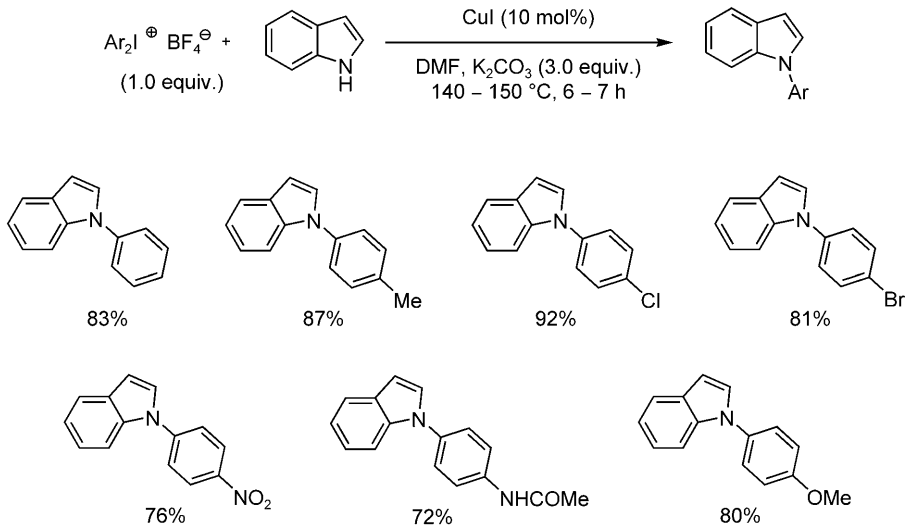


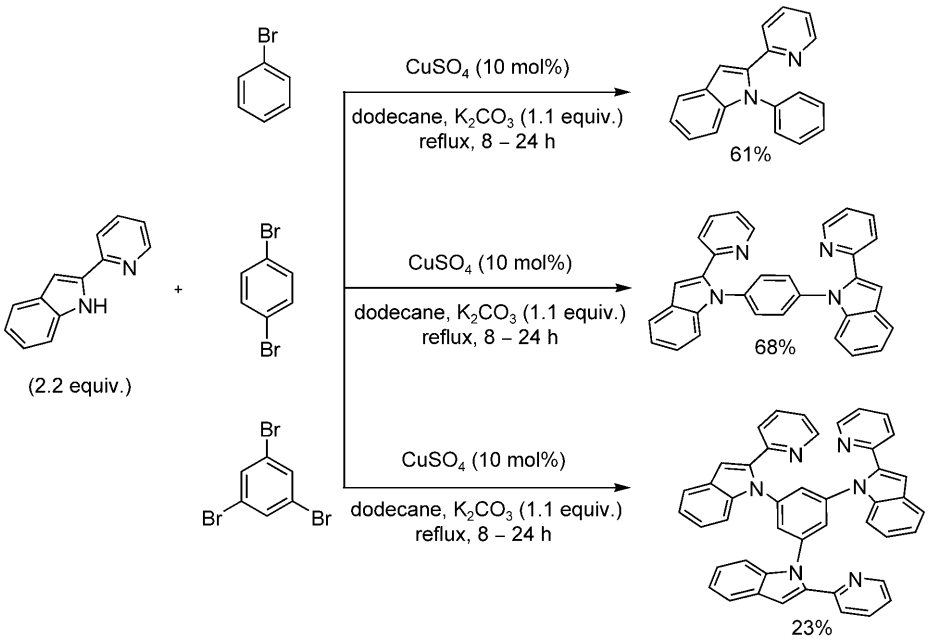
Figure 2. Copper-catalysed N1-arylation of indoles with diaryliodonium salts.

selectivities in the coupling reaction of indole with aryl iodide derivatives substituted by either a bromine or a chlorine atom were achieved.

A variation of this ligand-free procedure was reported by Fukayama and co-workers. Using a stoichiometric amount of CuI with CsOAc (2.5 equiv.) as base in DMF at 90 °C, the N1-arylation of indole by 4-iodonitrobenzene gave a 73% yield in 24 h.[41]

Interestingly, the synthesis of luminescent atropoisomeric N,N-chelating ligands by a copper-catalysed one-pot C–N and C–C coupling reactions starting from indole was recently described by Wang and co-workers. Using $CuSO_4$, the authors described the preparation of a series of "*monomeric*" compounds (Scheme 3).[42] Remarkably, using this simple procedure they achieved either the mono-, di- or trisubstitution with respectively mono-, di- or tribromoaromatic compounds in reasonable to high yields. Noticeably, under these reaction conditions, the authors observed the formation of a "*dimeric*" structure resulting from concomitant C–N and C–C coupling at the C3-position in 5–15% yield.

Correa and Bolm reported a ligand-free procedure for the N1-arylation of heterocycles catalysed by



Scheme 3. One-pot consecutive C–N coupling reactions of 2-(pyridin-2-yl)-1*H*-indole with mono-, di or tri-bromobenzene catalysed by $CuSO_4$.

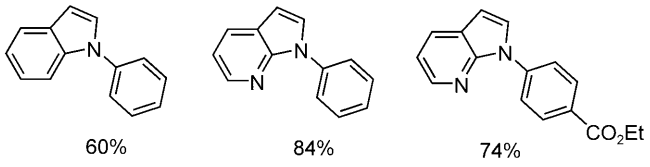


Figure 3. Iron-catalysed N1-arylation of indole derivatives.

copper oxide. However, only one example concerned the N1-arylation of indole with iodobenzene in 95% yield [Cu_2O (10 mol%), Cs_2CO_3 (2.0 equiv.), DMF, 100 °C, 18 h].[43]

Pursuing their investigation they reported a procedure catalysed by iron chloride in the presence of DMEDA (*N*,*N*′-dimethylethylenediamine) affording moderate to good yields towards the expected N1-arylindoles under relatively common reaction conditions [indole (1.0 mmol), aryl iodide (1.5 equiv.), K_3PO_4 (2.0 equiv.), $FeCl_3$ (10 mol%), DMEDA (20 mol%), toluene, 135 °C, 24 h] (Figure 3).[44]

Another ligand-free procedure was recently reported by Chan and co-workers. Using a mixture of copper iodide and *n*-Bu_4NBr, the authors described the N1-arylation of indole by iodobenzene and *p*-iodotoluene giving respectively 80% and 64% isolated yields [CuI (5 mol%), NaOH (2.0 equiv.), toluene, reflux, 2 h].[45] While the authors call this procedure "ligand and additive free", we do consider the extra added *n*-Bu_4NBr as an additive, following the generally accepted definition in the literature.

Recently, Taillefer and co-workers reported an improved iron/copper co-catalysed procedure. Using CuO (10 mol%) and [$Fe(acac)_2$] (30 mol%) the authors reported a 93% yield in the N1-arylation of indole with iodobenzene at 90 °C after 30 h in DMF using Cs_2CO_3 as base.[46] However, regarding the other reported procedures in this area, the use of an extra 30 mol% iron salt did not contribute to a strong improvement.

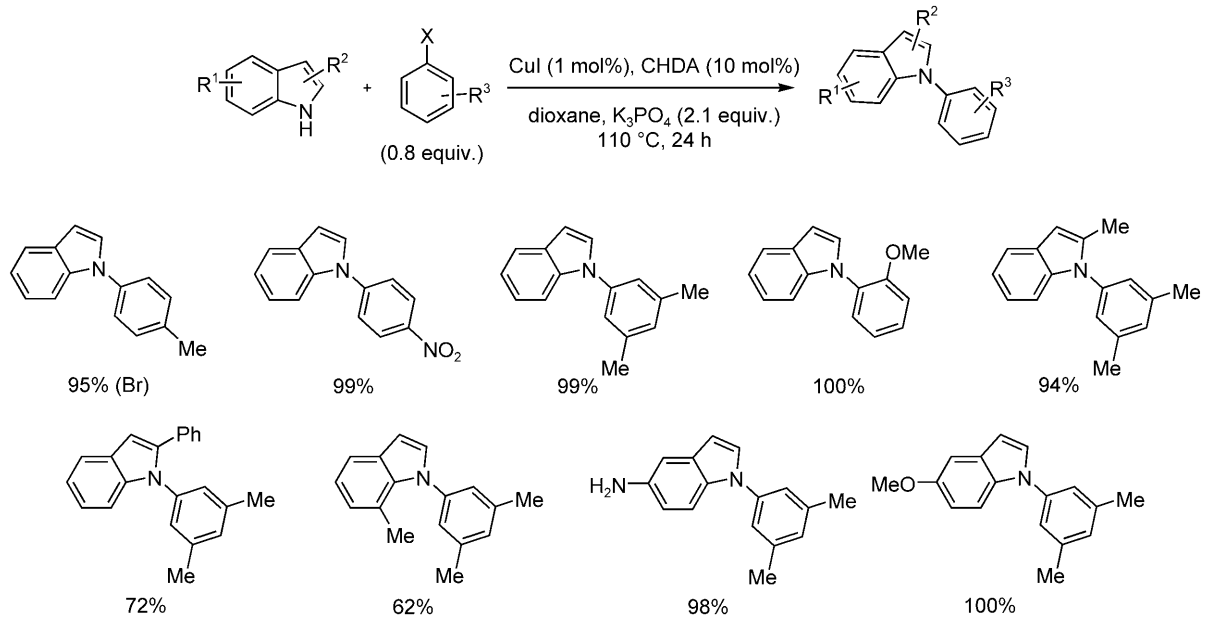
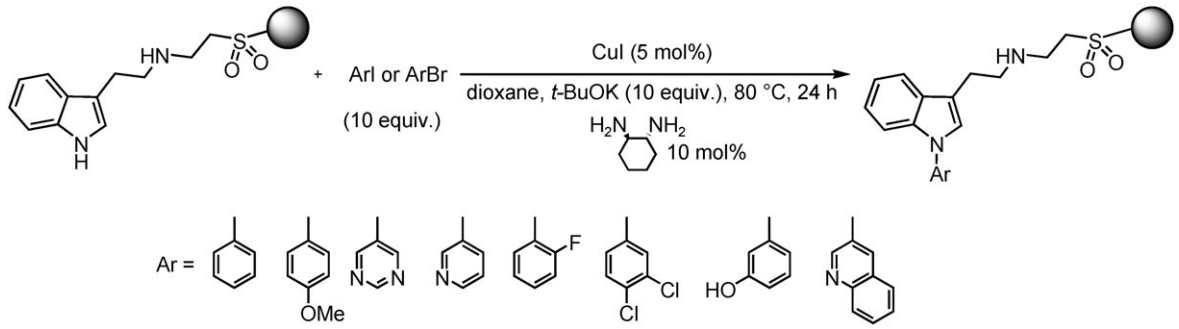


Figure 4. Copper-catalysed N1-arylation of indoles in presence of *trans*-1,2-cyclohexanediamine (CHDA).



Scheme 4. N1-Arylation of tryptamine on a solid phase.

2.1.2 Diamine and Related Dinitrogen Ligands

Following their achievement in the amination of aryl halides, Buchwald and co-workers reported a procedure based on the use of a copper catalyst (CuI) for the N1-arylation of various indoles using *trans*-1,2-cyclohexanediamine (CHDA) as ligand (Figure 4). High isolated yields were achieved; however the low catalyst loading (1 mol%) remain linked to the use of aryl iodides, otherwise the sole example reported with 4-bromotoluene as aryl halide required a catalyst loading of 5 mol%.[47] This method was successfully applied by Wu and Schultz to the N1-arylation of tryptamine on a solid-phase affording a compound with >80% purity and 10–20% purified yields (Scheme 4).[48] Zhang and co-workers applied this

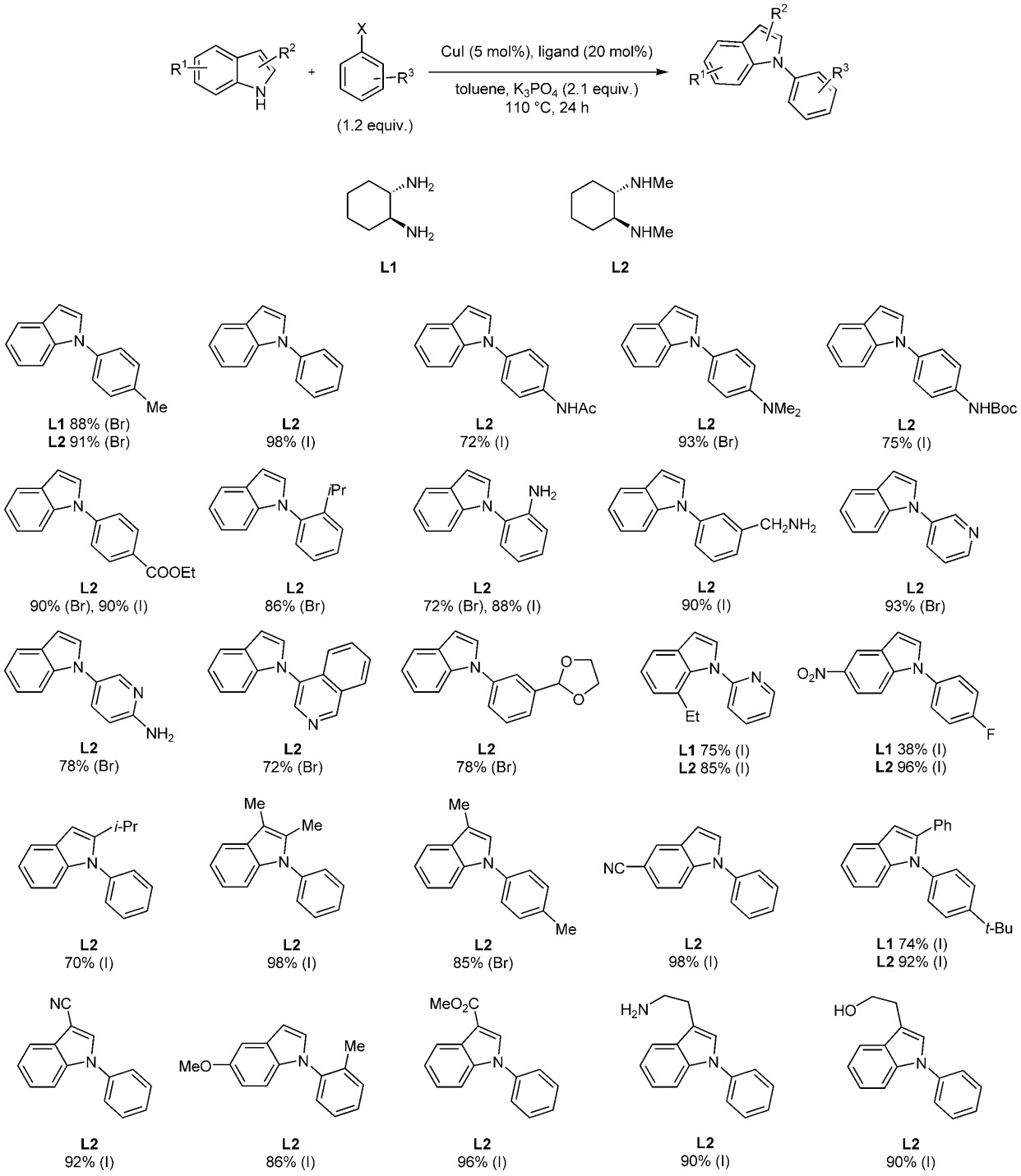


Figure 5. Copper-catalysed N1-arylation of indoles in presence of diamine ligands.

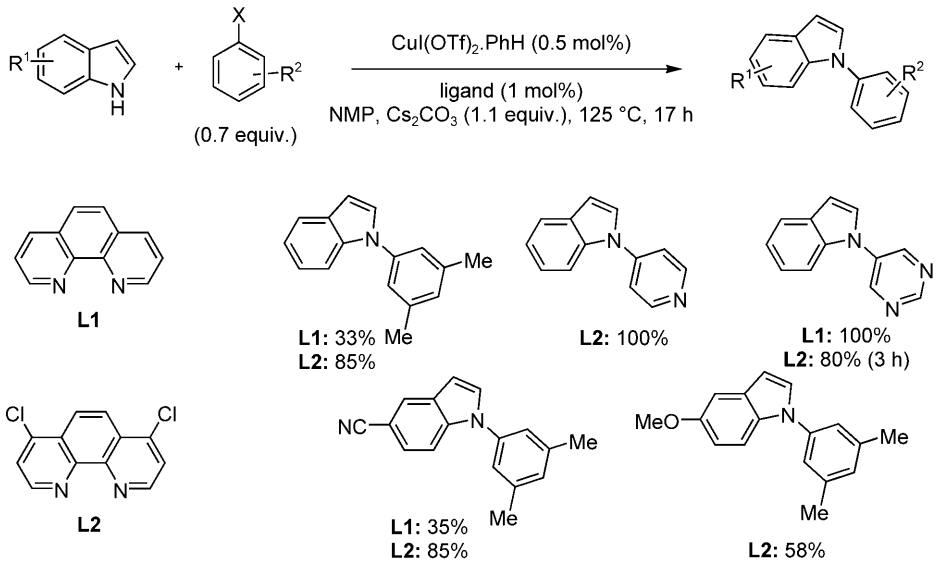


Figure 6. N1-Arylation of indoles using phenanthroline ligands.

methodology using ethylenediamine as ligand to prepare 1-(2-bromophenyl)-1*H*-indoles as intermediates in the synthesis of indolo[1.2-*f*]phenanthridines.[49]

Developing further the reaction conditions, Buchwald and co-workers screened various diamine ligands, the best results being achieved with either *trans*-1,2-cyclohexanediamine or *trans*-*N,N′*-dimethyl-1,2-cyclohexanediamine (Figure 5).[50] Alternatively, the authors reported a solvent-free variation: using *N,N*-diethylsalicylamide as ligand, the N1-arylation of indole by 3,5-dimethylbromobenzene gave an 89% isolated yield in 18–22 h.[51]

Kang and co-workers reported a general procedure for the N1-arylation of various nitrogen heterocycles including indoles catalysed by copper iodide in the presence of ethylenediamine as ligand and Cs_2CO_3 as base. Working in dioxane at 100 °C, the coupling reaction of indole with 3,5-dimethyliodobenzene afforded a 96% isolated yield of the target compound.[52]

Strijdonck and co-workers reported a copper-catalysed procedure using $CuI(OTf)_2{\cdot}PhH$ for the N1-arylation of indoles by aryl bromides using 1,10-phenanthroline or 4,7-dichloro-1,10-phenanthroline as ligands. Good to high conversions were achieved in NMP with a low catalyst loading (0.5 mol%) in relatively short reaction time (17 h) when using Cs_2CO_3 as base (Figure 6).[53]

Alternatively, Chandrasekhar and co-workers reported a procedure that uses ethylenediamine as ligand following the ones described by Buchwald. The authors worked in PEG-400 as solvent that allows recycling of the catalyst (CuI/Ligand) for up to 6 runs; however a gradual deactivation (i.e., 79% yield for the run of the fresh catalyst, 60% yield for the 6th cycle) was observed. For the evaluated reactions, good yields were achieved under standard conditions

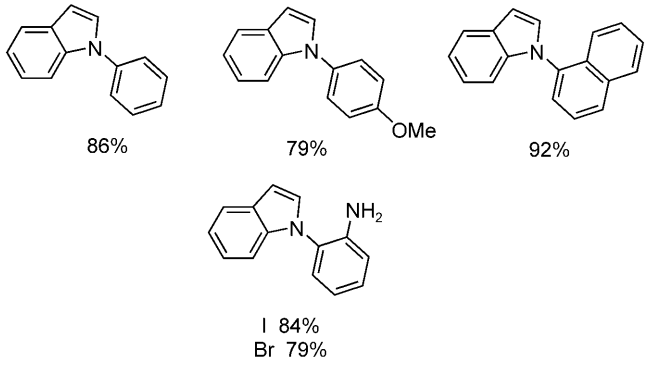


Figure 7. N1-Arylation of indoles in PEG-400 media.

[indole (1.0 mmol), aryl halide (1.2 equiv.), K_2CO_3 (2.0 equiv.), CuI (5 mol%), ethylenediamine (10 mol%), PEG-400, 80 °C, 24 h] (Figure 7).[54]

Wong and co-workers reported the synthesis of 9-azajulodinine as a dinitrogen ligand in the copper iodide-catalysed Ullmann N-arylation of heterocycles. Under classical reaction conditions [N-heterocycle (1.2 equiv.), aryl iodide (1.0 equiv.), NaO-*t*-Bu (2 equiv.), CuI (5 mol%), ligand (10 mol%), toluene, 110 °C, 40 h] the N1-arylation of indole with 4-iodotoluene afforded the expected compound in 99% yield.[55]

Similarly, the use of the commercially available DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) associated with $Cu(OAc)_2$ was reported by Liu and co-workers in a ligand-free N1-arylation of indole by both iodobenzene or bromobenzene affording, respectively, 92% and 95% yield in 10 min under microwave irradiation.[56] However, one should note that DBU while acting as a base is also considered as a dinitrogen ligand in related reactions.

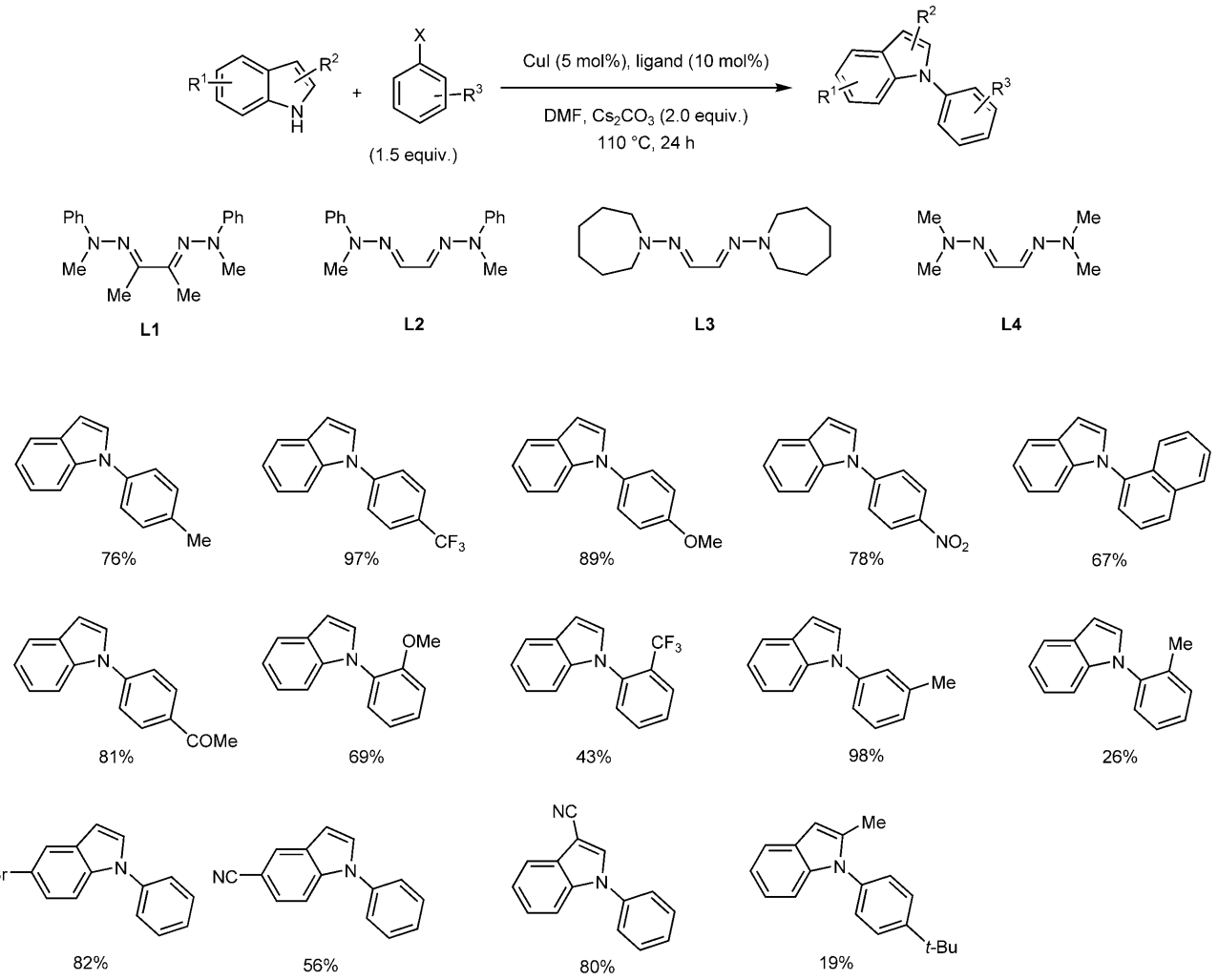


Figure 8. N1-Arylation of indoles catalysed by copper/hydrazone systems.

In the same direction, a CuI-catalysed procedure was reported by Mino and co-workers using hydrazones as ligands. The authors particularly studied the reaction conditions (base, solvent, ligand) in the phenylation of indole finding that ligand **L3** was the most suitable for this reaction. The optimum conditions [indole (1.0 mmol), aryl iodide (1.5 equiv.), Cs_2CO_3 (2 equiv.), CuI (5 mol%), ligand (10 mol%), DMF, 110 °C, 24 h] were then applied to a wide range of derivatives (Figure 8).[57]

Periasamy and co-workers revisited the Buchwald N1-arylation of indoles using piperazine-based ligands (Figure 9) associated to copper(I) salts in toluene. The authors evaluated the reactivity of the catalytic system (±)-*trans*-2,3-diarylpiperazine/copper(I) halide in the phenylation of indole [reaction conditions: indole (1 mmol), iodobenzene (1.5 equiv.), base (2 equiv.), CuI (10 mol%), ligand (10 mol%), toluene, reflux, 24 h]. Varying the base [K_2CO_3 or K_3PO_4] they showed that little difference in terms of yield exists when CuI was used as the catalyst precusor; however slightly better yields were achieved with K_3PO_4 (i.e., generally +5–8%). The best results were achieved with ligands **L5** and **L6**. Varying the nature of the copper salt (CuI, CuBr, CuCl) they found that the iodide gave the highest yields with both ligands (respectively, 94% and 96%). The best conditions [indole (1 mmol), aryl halide (1.5 equiv.), K_3PO_4 (2 equiv.), CuI (10 mol%), **L6** (10 mol%), solvent, reflux, 24 h] were applied to other aryl halides, that is, bromonaphthalene and 4-bromotoluene. In these cases, the authors noticed that toluene was not suitable as solvent and DMF should be used to give, respectively, 82% and 95% yields. This was attributed to the low polarity of the C–Br bond in aryl bromides compared to aryl iodides. Interestingly, during the course of this study the authors observed the formation of copper diimine complexes (**C1**–**6**) that gave almost the same results when used as catalysts under the optimised conditions. Alternatively, a mixture of CuI and the corresponding diimine ligands could be used.[58] The results achieved here are really compara-

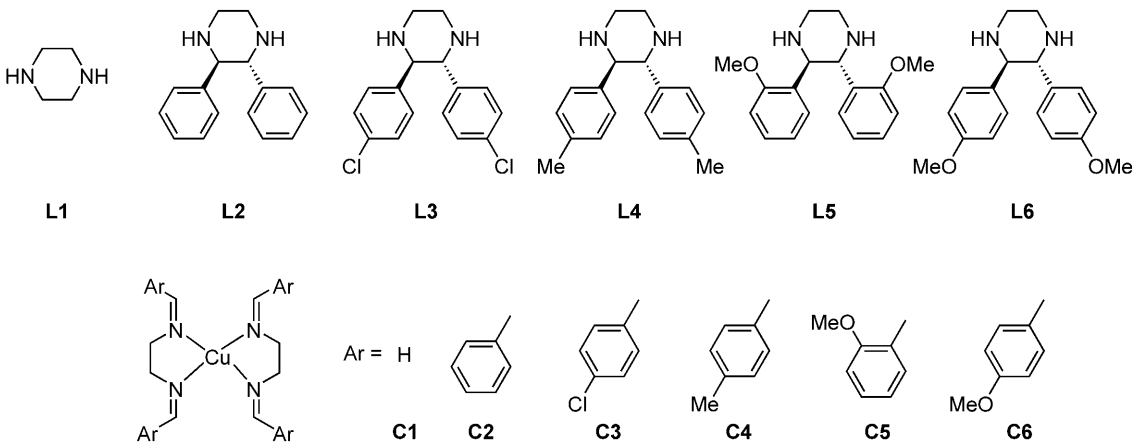


Figure 9. Piperazine-based ligands and associated copper-diimine complexes observed by Periasamy et al.

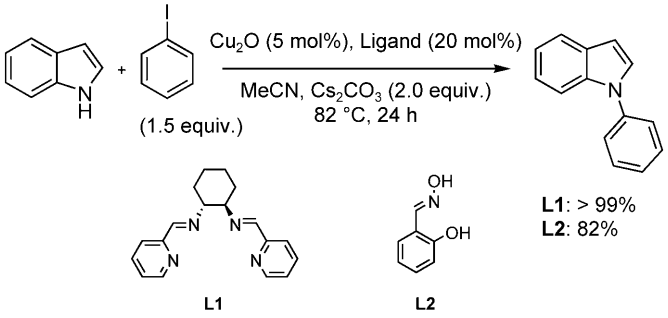
ble to those obtained by Buchwald and co-workers when using diamine ligands.[50]

2.1.3 Schiff Base and Related Oxime Ligands

Cristau, Taillefer and co-workers reported an important study on the N1-arylation of heterocycles developing the original method of Unangst and co-workers[30] using *Schiff base* **L1** or salicyladoxime **L2** as ligands. Optimising the reaction conditions, the authors reached a lower catalyst loading (5 mol% *versus* 30 mol%) under milder conditions; however using aryl iodides instead of bromides (Scheme 5).[59]

Attempting to improve this procedure, Wan and co-workers reported the N1-arylation of indole by iodobenzene catalysed by a system made from Cu_2O (5 mol%) and [2-(diphenylphosphine oxide)benzaldehyde oxime] as ligand (10 mol%).[60] However, the procedure was more successful when applied to other N-heterocyles as a moderate 64% yield was achieved with indoles when working in acetonitrile with Cs_2CO_3 as base.

Jiang and co-workers developed a simple, efficient, and inexpensive catalytic system for the N1-arylation of indoles with aryl iodides and bromides by applying



Scheme 5. N1-Arylation of indole catalysed by Cu_2O and Schiff base or oxime ligands.

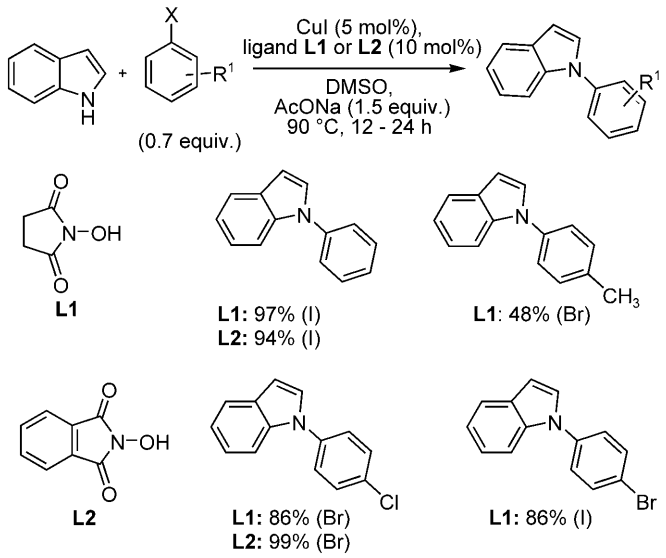


Figure 10. N1-Arylation of indole using oxime ligands.

CuI as catalyst and either *N*-hydroxysuccinimide **L1** or *N*-hydroxyphthalimide **L2** as ligand (Figure 10).[61] For the examples reported, the methodology described here gave comparable results to palladium-catalysed procedures.

2.1.4 α-Amino Acids as Ligands

Ma and Cai reported a procedure, similar to that of Buchwald,[50] in which the diamine ligand is replaced by amino acids, the best results being achieved with L-proline. Thus, the N1-arylation of various indoles was achieved using copper iodide as catalyst and K_2CO_3 as base under mild reaction conditions (75–90 °C, 22-40 h) in DMSO (Figure 11).[62–64]

Similarly, Guo and co-workers reported a procedure using the catalytic system CuI/L-proline for the N1-arylation of indole with K_3PO_4 as base. Under

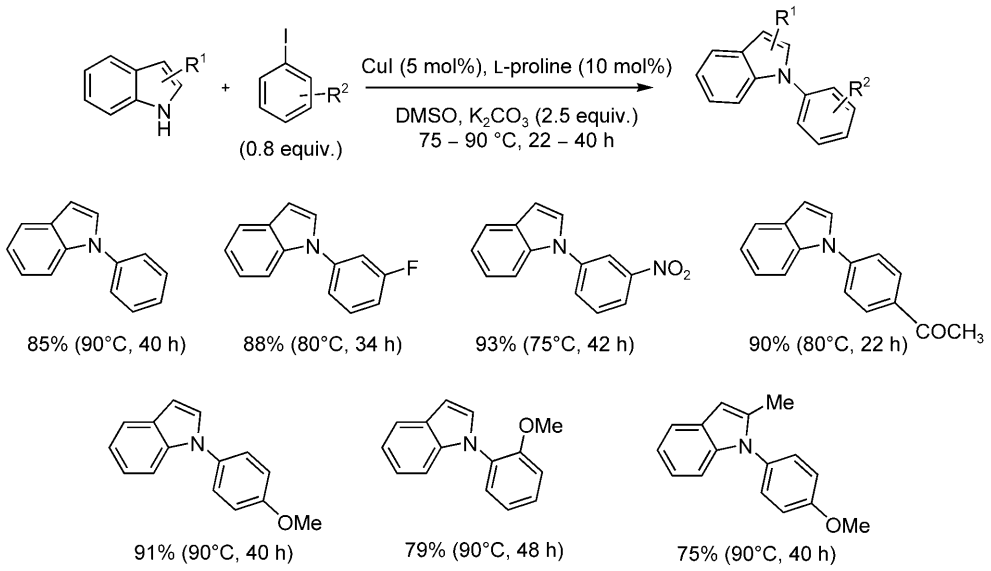


Figure 11. Copper-catalysed N1-arylation of indoles using L-proline as ligand.

these conditions, the reaction could be performed in 1,4-dioxane as solvent instead of the generally used DMSO, or alternatively in DMF. Furthermore, aryl bromides reacted quite similarly as the corresponding aryl iodides (Figure 12).[65]

The use of the commercially available pipecolinic acid as ligand in the copper iodide-catalysed N1-arylation of indole was reported by Fu and co-workers. Using a mixture of 10 mol% CuI and 20 mol% pipecolinic acid in the presence of K_2CO_3 as base (2 equiv.) in DMF, high yields of the target compounds (i.e., 91% when using bromobenzene; 95% when using iodobenzene) were achieved. Interestingly, the authors observed a full selectivity when coupling 4-bromoiodobenzene towards the *N*-(4-bromophenyl)indole with high yield (94%).[66] These authors reported also an alternative procedure giving comparable isolated yields using an easily available bidentate ligand (pyrrolidine-2-phosphonic acid phenyl monoester) to perform the same transformations with very similar reaction conditions (K_3PO_4 was used as base).[67]

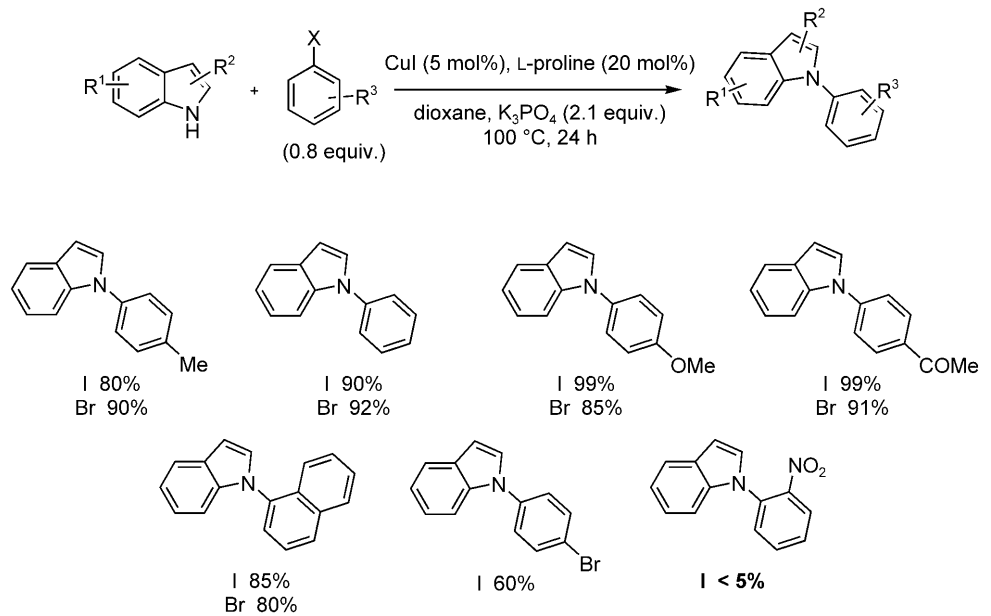


Figure 12. N1-Arylation of indoles catalysed by CuI/L-proline.

2.1.5 Miscellaneous

Liu and co-workers reported the synthesis of air-stable diazaphospholane ligands for the N-arylation of heterocycles, including the indole nucleus. Optimisation of the reaction conditions using iodobenzene as aryl halide and benzylamine revealed that copper bromide was the best catalyst precursor when such ligands are used [reaction conditions: amine (1.2 equiv.), aryl iodide (1.0 equiv.), Cs_2CO_3 (2 equiv.), CuBr (10 mol%), ligand (12 mol%), DMSO, 55 °C, 24 h]. Under these conditions, the N1-arylation of indole by iodobenzene gave a 71% isolated yield.[68]

You and co-workers reported a procedure using copper iodide as catalyst for the N-arylation of various heterocycles. Using 20 mol% CuI in DMF in presence of Cs_2CO_3 as base the authors described the N1-arylation of indole with iodobenzene in 95% yield at 120 °C.[69] Adding *N*-methyl-(*S*)-pyrrolidinylmethylimidazole as ligand allowed them to decrease the catalyst loading down to 5 mol% and to perform the same transformation without loss of activity (98% yield).[70]

The use of the commercially available copper bis(2,2,6,6,-tetramethyl-3,5-heptanedionate) as catalyst [$Cu(TMHD)_2$] in the N1-arylation of indole was reported by Bhanage and co-workers. Good to high yields with either aryl iodides or bromides were achieved under common reaction conditions [indole (2 mmol), aryl halide (1.5 equiv.), *t*-BuOK (2.0 equiv.), $Cu(TMHD)_2$ (20 mol%), DMF, 120 °C, 24 h] (Figure 13).[71]

Recently, several research groups reported ligand variations (Figure 14) for the CuI-catalysed N1-arylation of indoles [general reaction conditions: indole (1.2–1.5 equiv.), iodobenzene (1.0 equiv.), base (2 equiv.), [Cu] (10 mol%), ligand (10–20 mol%), solvent]. Sun, Chen and co-workers reported the use of β-ketoimine **L1** associated with CuO, working in DMF and using *t*-BuOK as base. Under these conditions the N1-arylation of indole with iodobenzene gave 95% yield.[72] Chen and co-workers described the use of pyridine functionalised 1,3-diketones **L2** in DMF with CuI as the pre-catalyst. In these conditions the N1-arylation of indole with bromobenzene gave 85% yield in presence of K_2CO_3 as base.[73] The use of ninhydrin **L3** associated to CuO in DMSO in presence of KOH as base was reported by Xu and co-workers for the N1-arylation of indole by iodobenzene; the reaction afforded 91% yield in 24 h at 110 °C.[74] Ji, Mao and co-workers described the use of hippuric acid **L4** as a ligand in the copper-catalysed N1-arylation of indoles. Associated to $Cu(OAc)_2$ and Cs_2CO_3 in DMF, the N1-arylation of indole with various aryl halides gave moderate to good yields (Figure 15).[75] Surprisingly, an enhanced yield was achieved when replacing 4-iodonitrobenzene by 4-chloronitrobenzene. While this point was not commented by the authors we can postulate that it might be related to a change of mechanism (from N1-arylation to S_NAr). Unfortunately, the authors did not evaluate under these conditions the corresponding fluoro derivative that would have afforded clearer insights into the mechanisms.

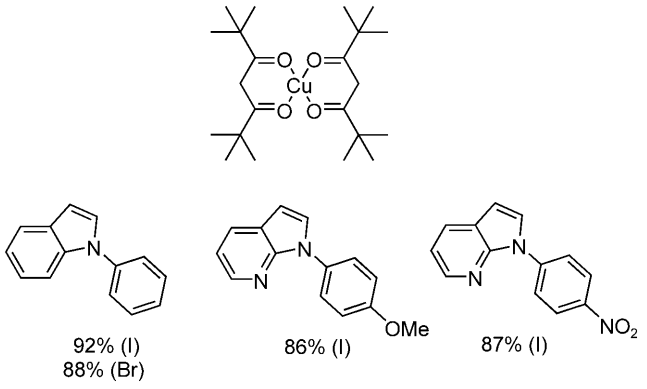


Figure 13. N1-Arylation of indoles catalysed by $Cu(TMHD)_2$ complex.

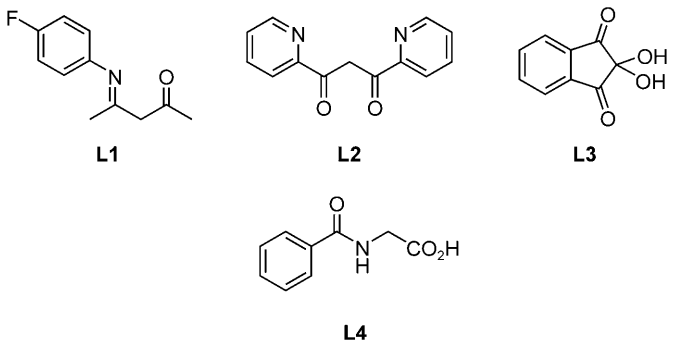


Figure 14. Various ligands described recently in the copper-catalysed N1-arylation of indoles.

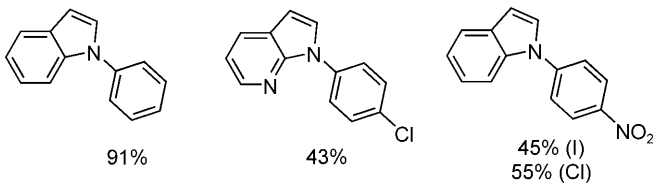


Figure 15. N1-Arylation of indoles with the $Cu(OAc)_2$/hippuric acid (**L4**) catalytic system.

2.2 Palladium-Catalysed Methodologies

2.2.1 Phosphine Ligands

Palladium-catalysed procedures were initially reported by Hartwig and co-workers. Based on studies related to the palladium-catalysed amination of aryl hal-

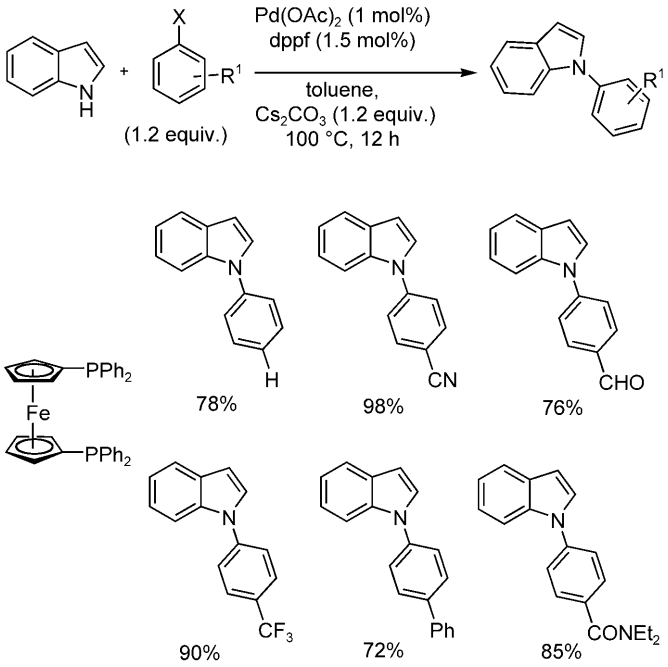


Figure 16. N1-Arylation of indole catalysed by the Pd-$(OAc)_2$/dppf catalytic system.

ides, the authors reported the N-arylation of azoles, including that of indoles (Figure 16). Generally, the reactions were run in toluene as solvent using palladium acetate in presence of dppf [1,1′-bis(diphenylphosphino)ferrocene] as ligand. Cs_2CO_3 was used as base, except for the coupling reaction of indole with bromobenzene for which *t*-BuOK had to be used.[76] In an alternative procedure, these authors reported the N1-arylation of variously substituted indoles using 3–5 mol% $Pd_2(dba)_3$ as the palladium source in the presence of P(*t*-Bu)$_3$, all other reaction conditions remaining identical (Figure 17).[77] This procedure was used by Marugan and co-workers for the preparation of precursors in the synthesis of non-peptidic $\alpha_v\beta_3$ antagonist (i.e., N1-arylation of 5-benzyloxyindole with *meta*- or *para*-bromobenzoic acid ethyl ester).[78]

Similarly, Watanabe and co-workers reported the N1-arylation of indoles using $Pd(OAc)_2$ (1 mol%) with P(*t*-Bu)$_3$ (3 mol%) in the presence of Rb_2CO_3 as base in xylene at 120 °C.[79] Under these conditions, the authors reported 96% isolated yield in 4 h for the coupling of indole with bromobenzene. In the same way, a 78% yield was achieved for the arylation of indole with 4-fluorobromobenzene using the more common K_2CO_3 base; however, when reacting deactivated aryl bromides like 4-bromoanisole, the use of Rb_2CO_3 was helpful (75% yield in 24 h).

Intensive development of the N1-arylation of variously substituted indoles was made by Buchwald and co-workers. The procedure was mainly based on their studies on the amination of aryl halides; as a consequence they applied the best bulky, electron-rich phosphine ligands to this important reaction. Using $Pd_2(dba)_3$ as palladium source, good to high yields in the target compounds irrespective of the use of aryl chloride, bromide, triflate or iodide as aryl coupling partners were achieved (Figure 18).[80] As no reaction time was reported, the completion of the reaction being judged by GC analysis as corresponding to the full consumption of the aryl halide, the reactivities of the different coupling partners cannot be evaluated. However, as it could be expected, the reaction carried out with aryl iodides or triflates gave the highest yields. Further optimisation of the reaction conditions allowed yield improvements in some cases,[81] giving complementary protocols to the copper-catalysed procedure reported by the same group for the N1-arylation of indoles.[47] Interestingly, the authors have shown that the copper-catalysed coupling of 5-aminoindole with simple aryl iodides (or bromides) gave exclusively arylation on the indole nitrogen whereas moderate to high selectivity was achieved for the arylation of the 5-amino group when a palladium catalyst was used (Scheme 6).

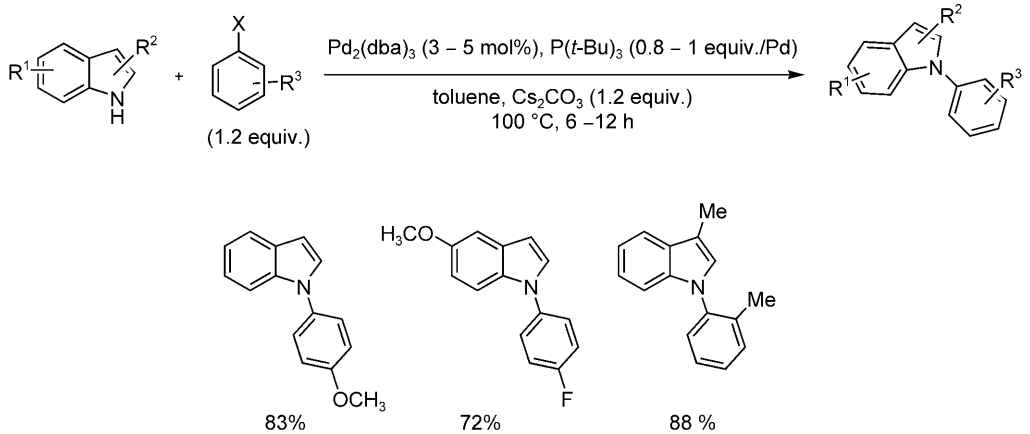


Figure 17. N1-Arylation of indoles catalysed by the $Pd_2(dba)_3$/P(*t*Bu)$_3$ catalytic system.

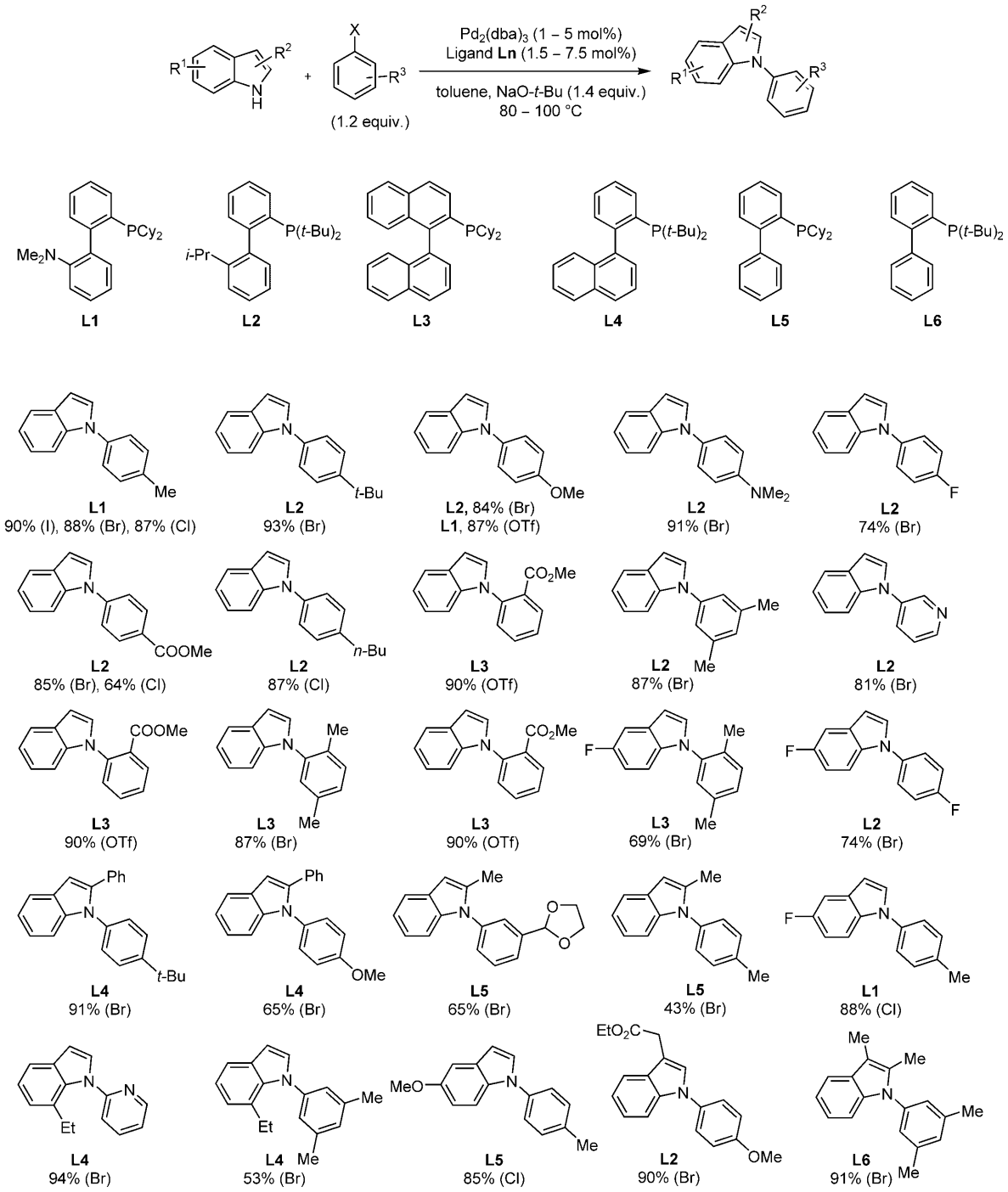
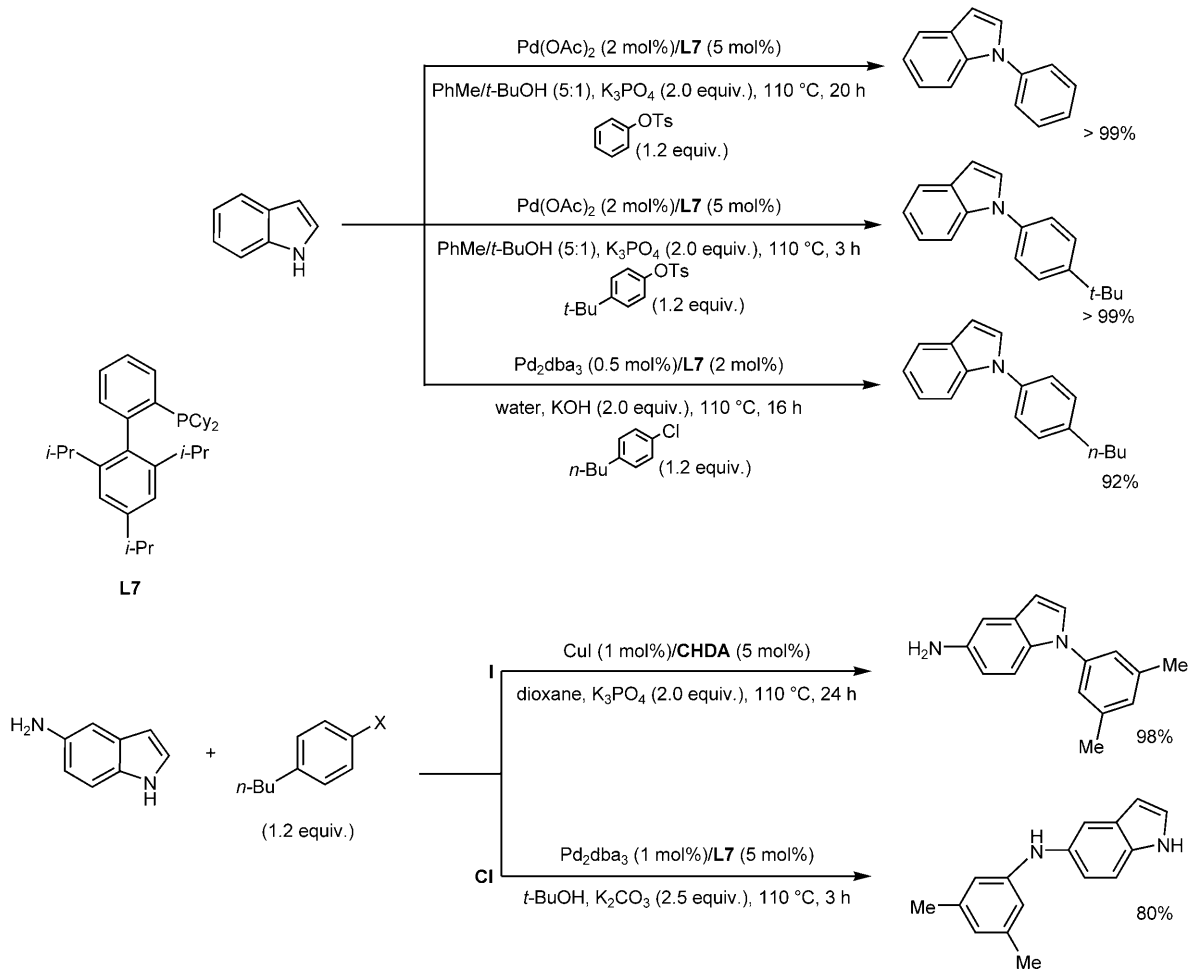


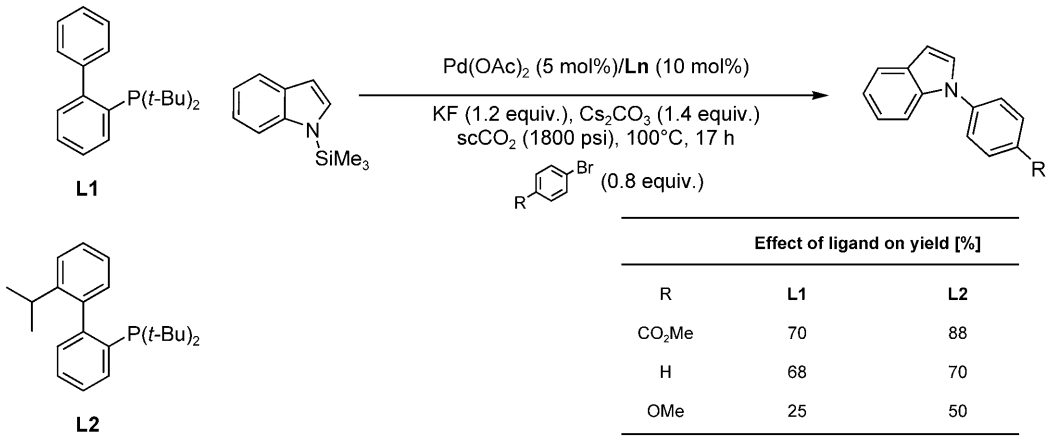
Figure 18. Palladium-catalysed N1-arylation of indoles with bulky and electron-rich phosphine ligands.

As an alternative procedure, Smith and co-workers reported a palladium-catalysed N1-arylation of indoles in supercritical carbon dioxide using aryl bromides; however this procedure was limited to the use of N-trimethylsilylindoles in order to avoid the formation of carbamic acids (Scheme 7).[82] Using a mixture of palladium acetate with a bulky phosphine ligand, moderate to good yields towards the expected compounds were achieved.

Wüst and Kniess reported the N1-arylation of indole derivatives with the 4-[^{18}F]fluoroiodobenzene towards the synthesis of ^{18}F-labelled (Scheme 8) σ_2 receptor ligands for positron emission tomography. They studied several palladium (and copper) catalytic systems and optimised the reaction conditions (base, solvent) in order to achieve the highest radiochemical yields (Table 1).[83]



Scheme 6. Complementary palladium- or copper-catalysed N1-arylation of indoles.

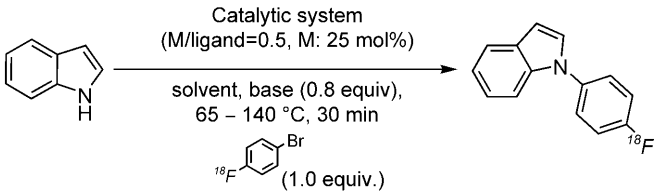


	Effect of ligand on yield [%]	
R	L1	L2
CO_2Me	70	88
H	68	70
OMe	25	50

Scheme 7. Palladium-catalysed N1-arylation of N-trimethylsilylindole in supercritical carbon dioxide.

The N1-arylation of indoles catalysed by commercially available palladium catalysts and phosphine ligands was reported by Pujol and co-workers. The authors reported moderate to high yields (Figure 19) depending on the nature of the aryl bromides and the ligand used at low catalyst loading (0.12 mol%) "*without*" solvent (i.e., an aliquot of solvent is added in order to dissolve the solid reagents).[84]

Willis and co-workers reported the selective N1-arylation of tryptophan derivatives catalysed by Pd-



Scheme 8. N1-Arylation of indole derivatives with the 4-[^{18}F]fluoroiodobenzene.

$(OAc)_2$/Xantphos catalytic system using various aryl bromides (Figure 20).

2.2.2 N-Heterocyclic Carbene Ligands and Related Imidazolium Salts

Few examples dealing with the use of N-heterocyclic carbene ligands or imidazolium salts were reported in this area. To the best of our knowledge, the only successful example was described by Nolan and co-workers. While developing the amination of aryl halides mediated by a palladium/imidazolium salts catalytic system, they reported the N1-arylation of indoles using aryl bromides. Whereas a Pd(0)-based catalytic system [from $Pd_2(dba)_3$] was found to be suitable for almost all evaluated amines, the latter was not efficient when considering the N1-arylation of indoles. Screening various palladium sources and associated ligands afforded suitable reaction conditions [that is, $Pd(OAc)_2$ and SiPr in the presence of NaOH] applied to a range of indoles and aryl halides (Figure 21).[85] A palladium-carbene complex was suggested as the active species, or at least its precursor.

2.3 Heterogeneously Catalysed Methodologies

Few reports deal with the use of heterogeneous catalysts for the N1-arylation of indoles. The first example was reported by Reddy and co-workers using cellulose supported Cu(0) catalyst. However, the only illustration concerning the N1-arylation of indoles deals with the phenylation of indole using iodobenzene that gave 60% yield in 24 h under relatively common reaction conditions [indole (2 mmol), iodobenzene (1.0 equiv.), K_2CO_3 (2 equiv.), Cu catalyst (*ca.* 2 mol%), DMSO, 130 °C].[86]

Choudary and co-workers reported the use of copper exchanged NaY zeolite for the N1-arylation of indoles under similar conditions [indole (1.2 mmol), aryl halide (0.8 equiv.), K_2CO_3 (2 equiv.), Cu/NaY-cat-

Table 1. N1-Arylation of indole derivatives with the 4-[^{18}F]fluoroiodobenzene.

Entry	Catalytic system	Base	Solvent	Radiochemical yield [%]
1	CuI/*trans*-1,2-diaminocyclohexane	K_3PO_4	THF/toluene	0
2	CuI/*trans*-1,2-diaminocyclohexane	K_3PO_4	Toluene	0
3	CuI/ethylenediamine	K_3PO_4	THF/toluene	7
4	CuI/ethylenediamine	K_3PO_4	Toluene	36
5	$Pd_2(dba)_3$/Xantphos	NaO-*t*-Bu	THF	5
6	$Pd_2(dba)_3$/Xantphos	KO-*t*-Bu	THF	6
7	$Pd_2(dba)_3$/Xantphos	NaO-*t*-Bu	THF/toluene	13
8	$Pd_2(dba)_3$/Xantphos	Cs_2CO_3	THF/toluene	0
9	$Pd_2(dba)_3$/Xantphos	K_3PO_4	THF/toluene	16
10	$Pd_2(dba)_3$/Xantphos	NaO-*t*-Bu	Toluene	28
11	$Pd_2(dba)_3$/2-(dicylohexyl-phosphino)-2′-(N,N-diamino)-biphenyl	NaO-*t*-Bu	THF/toluene	22
12	$Pd_2(dba)_3$/2-(dicylohexylphosphino)-2′-(N,N-diamino)-biphenyl	NaO-*t*-Bu	Toluene	71

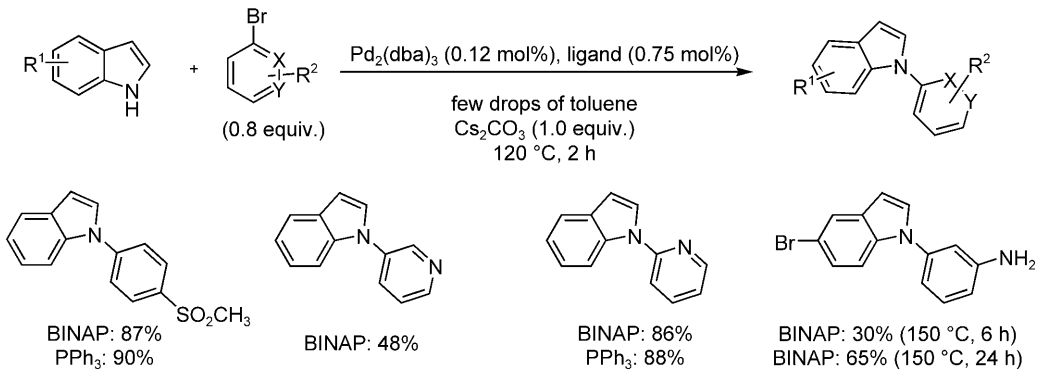


Figure 19. "Solvent-free" N1-arylation of indoles.

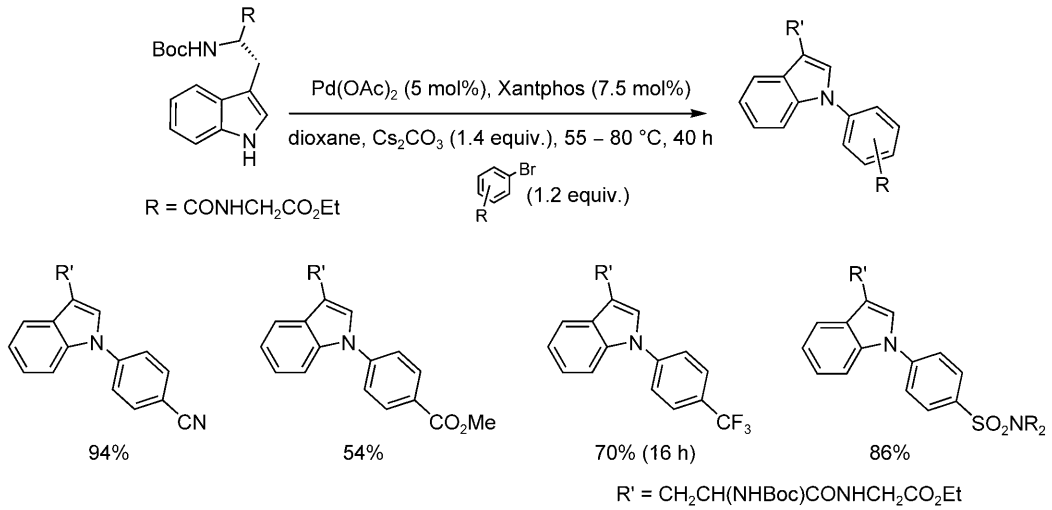


Figure 20. N1-Arylation of tryptophan derivatives [Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene].

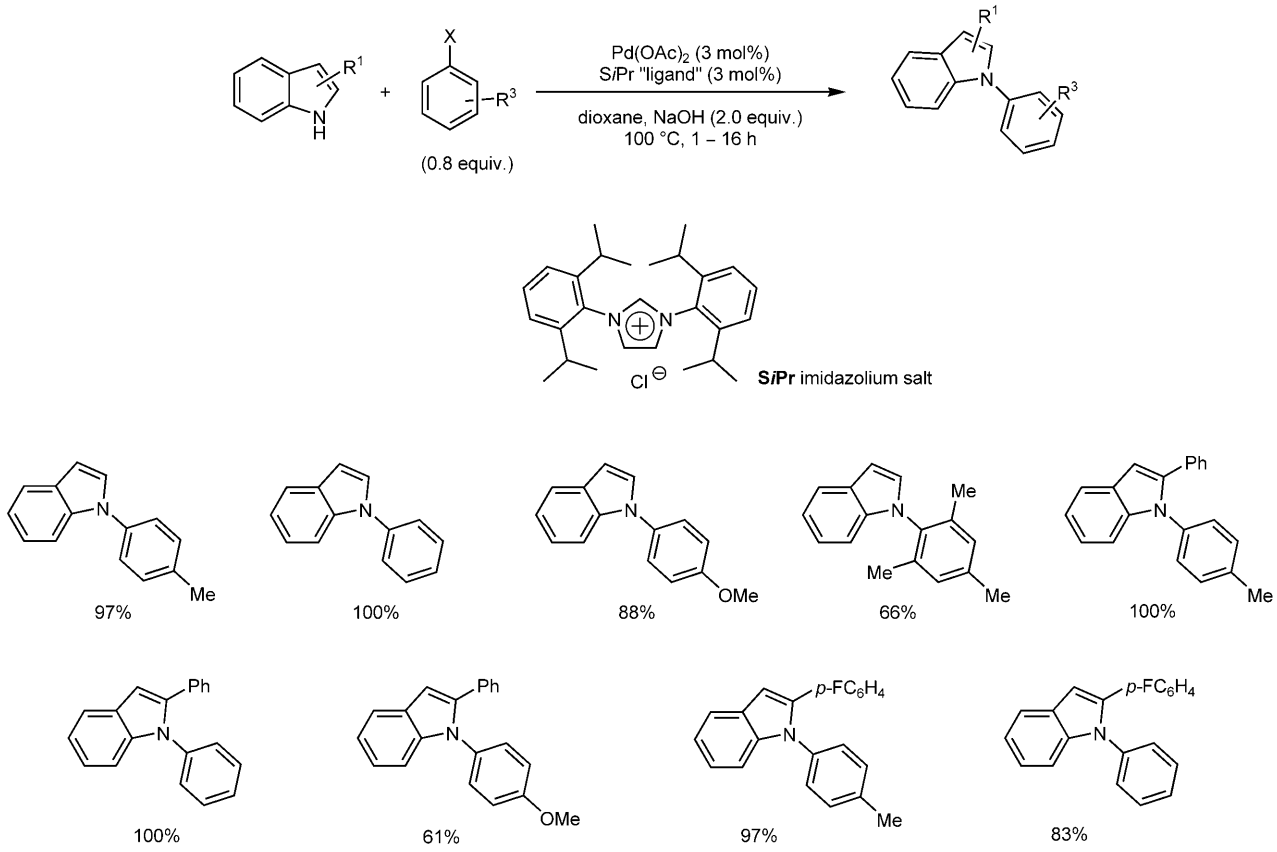


Figure 21. Palladium/imidazolium salts-catalysed N1-arylation of indoles.

alyst (*ca.* 10 mol%), DMF, 120 °C, 24 h]. With such a catalytic system, quantitative yields were achieved for the cross-coupling of indole with either 4-iodotoluene or 4-bromotoluene.[87]

The use of nanocrystalline copper(II) oxide as a recoverable heterogeneous catalyst was reported by Kantam and co-workers.[88] Remarkably, the catalyst is highly effective for the coupling of activated aryl chlorides and was applied to the N-arylation of various heterocycles including the indole nucleus (Figure 22). While this part of the report did not concern the indoles, we can mention that the catalyst

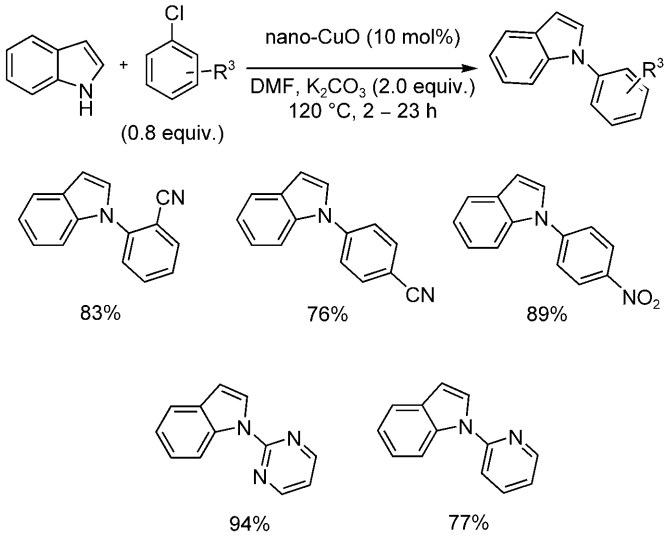


Figure 22. Heterogeneous copper oxide-catalysed N1-arylation of indole.

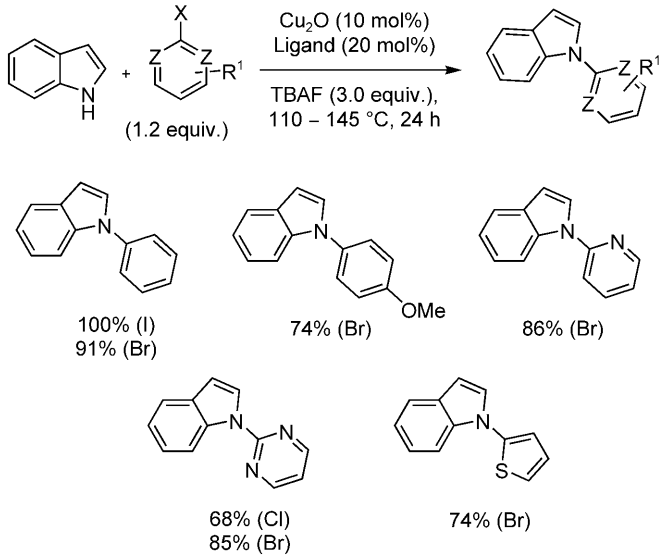


Figure 23. "Heterogeneous-like" N1-arylation of indole by Cu_2O nanoparticles associated to 1,10-phenanthroline.

could be recovered by simple centrifugation and reused; however with slight deactivation. TEM experiments performed both on the fresh and the reused catalyst indicated that the size and the shape of the nanoparticles did not change upon reuse.

Similarly, Punniyamurthy and co-workers reported the use of commercially available CuO nanoparticles as catalyst for the N-arylation of various amines, including indole.[89] The authors compared the activity of homogenous and heterogeneous conditions in the cross-coupling of aryl halides with aniline. Interrestingly, they found that CuO nanoparticles were the best catalyst compared to $CuSO_4$, $Cu(OAc)_2$ or CuO powder. Applied to the N1-arylation of indole with iodobenzene, the optimised reaction conditions [indole (1.2 mmol), iodobenzene (0.8 equiv.), KOH (0.8 equiv.), nano-CuO (1.3 mol%), DMSO, 110 °C, 3.5 h] gave the expected compound in 94% yield. Alternatively, Chen and co-workers reported a procedure using copper(I) oxide as catalyst under very similar reaction conditions [indole (1.5 equiv.), iodobenzene (1.0 mmol), KOH (1 equiv.), Cu_2O (10 mol%), DMSO, 120 °C, 24 h], providing *N*-phenylindole in 90% yield.[90] In this report, recycling of the catalyst was evaluated for the N-arylation of imidazole and pyrrole: the catalyst was found to be stable for at least 4 cycles.

The use of Cu_2O nanoparticles was reported by Li and co-workers. The authors evaluated the activity of various morphologies of Cu_2O nanoparticles (cubic, octahedral, bulky, etc.) associated to diamino ligands (mainly based on the phenanthroline structure). The best association was obtained with cubic nanoparticles/1,10-phenanthroline and applied to the N1-arylation of indole with various aryl halides (Figure 23).[91] While the catalytic system seems to answer to heterogeneous catalysts, no data concerning this point are available. The authors claim that the mechanism is discussed; however they postulated it starting from CuI and not from the Cu_2O nanoparticles used in this report.

Similar to the procedure reported by Taillefer, Wakharkar and co-workers described the use of a copper/iron exchange hydrotalcite. The material was prepared from a layered double hydrotalcite (LDH) by exchange with an aqueous solution of copper nitrate and ferric nitrate in order to obtain a material containing Cu(II) and Fe(II) species in a 3:1 ratio. This material was used for the coupling reaction of indole with either bromobenzene or 4-bromoanisole giving, respectively, 85% and 87% yields. The reactions were carried out in toluene using 10% wt Cu/Fe-LDH (no data are given regarding the metal loadings in the material; therefore, no data are available concerning the molar ratio), at 130 °C for 12 h.[92]

Two recently reported heterogeneous procedures differ from the above described methodologies. Alper and co-workers reported the preparation of magnetic nanoparticles-supported L-proline as a recyclable and recoverable ligand in the CuI-catalysed N-arylation of heterocycles. The ligand was immobilised by the so-called "click chemistry". The magnetite nanoparticles (Fe_3O_4) were modified by grafting azido groups at the surface that were further reacted with modified L-proline bearing a terminal alkyne function (Figure 24). This hybrid material was used in the N1-arylation of indole with 4-bromoacetophenone in DMF at 110 °C using 10 mol% CuI as catalyst and a "ligand" loading of 20 mol%. The reaction gave 85% yield towards the expected compound using Cs_2CO_3 as base.[93] The sep-

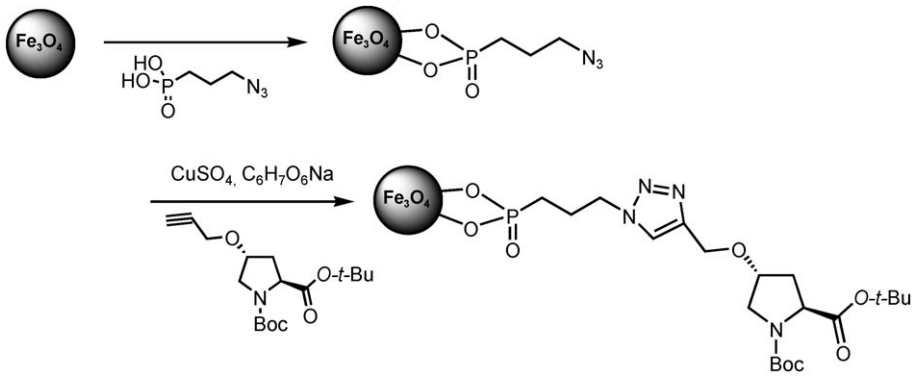


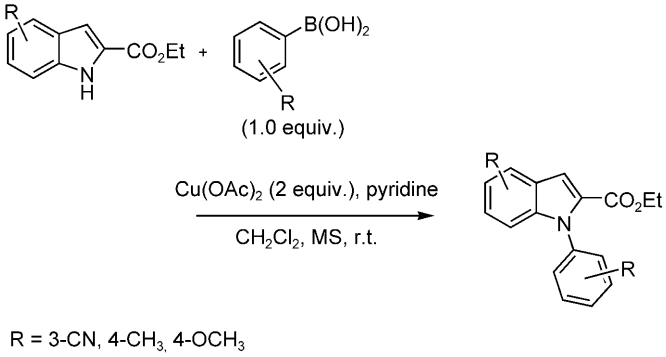
Figure 24. Preparation of the magnetic nanoparticle-supported L-proline.

arated material could be recycled without adding copper iodide.

Likewise, You and co-workers reported a procedure using immobilised ionic liquid on a polystyrene matrix as a metal scavenger for catalytic applications.[94] The material was prepared by radical copolymerisation of styrene, 1,4-divinylbenzene and 1,2-dimethyl-3-(4-vinylbenzene)imidazolium chloride. For catalytic applications, the remaining chloride ions were exchanged through the L-proline moiety. The resulting material showed excellent capacity in trapping transition metals, and particularly copper. It was used in the CuI-catalysed N-arylation of heterocycles and was applied in the N1-arylation of indole with iodo- and bromobenzene under classical reaction conditions [indole (0.5 mmol), bromobenzene (1.2 equiv.), K_2CO_3 (2.4 equiv.), CuI (10 mol%), "ligand" (20 mol%), DMSO, 120 °C, 60 h] giving, respectively, 99% and 68% yields. The authors claimed that this procedure led to higher activities than the corresponding reactions carried out either in ionic liquids (IL) or under homogeneous conditions. However, in this contribution, the high yields were achieved after 60 h whereas reactions conducted in IL or under fully homogeneous conditions required only 12–24 h. Furthermore, the authors reported that the material resulting from a first run loaded with the trapped copper species could be reused without loss of activity for up to nine runs for the N-arylation of imidazole with 4-bromoacetonitrile; however the only data reported concern the first run (95% yield) and the ninth run (73% yield) evidencing a loss of activity.

2.4 Stoichiometric Methodologies

The initial reports on the transition metal-mediated N1-arylation of indoles like the Ullmann coupling[15] or the early works described by Goldberg[16] were generally performed using an excess of transition metal, mainly Cu(I) or Cu(II) salts. Since catalytic



Scheme 9. N1-Arylation of ethyl 1*H*-indole-2-carboxylate with phenylboronic acids "catalysed" by copper acetate.

procedures were reported, few reports deal with the use of such stoichiometric methodologies. Recent descriptions concerned generally the use of arylboronic acids as coupling partners.

Mederski and co-workers reported the use of phenylboronic acids as arylating agents (Scheme 9).[95] Unfortunately, the procedure led to low yields (21–50%) despite an excess of copper acetate to perform the transformation. Similarly, Miyachi and co-workers[96] (Figure 25), and Espinosa and co-workers[97] described the cross-coupling of phenylboronic acid activated by copper acetate to prepare various precursors to cyclooxygenase inhibitors derived from thalidomide. Bekolo reported recently a study on this reaction using electron-defficient indoles and arylboronic acids (Figure 26).[98]

These procedures, while being stoichiometric allow to perform the N1-arylation at room temperature that could be required when preparing sensitive compounds.

Recently, Bellina and co-workers reported the N1-arylation of indoles mediated by copper acetate under base-free conditions using aryl iodides as coupling partners. These *revisited* Mederski conditions allowed, after optimisation, high tolerance of functional groups

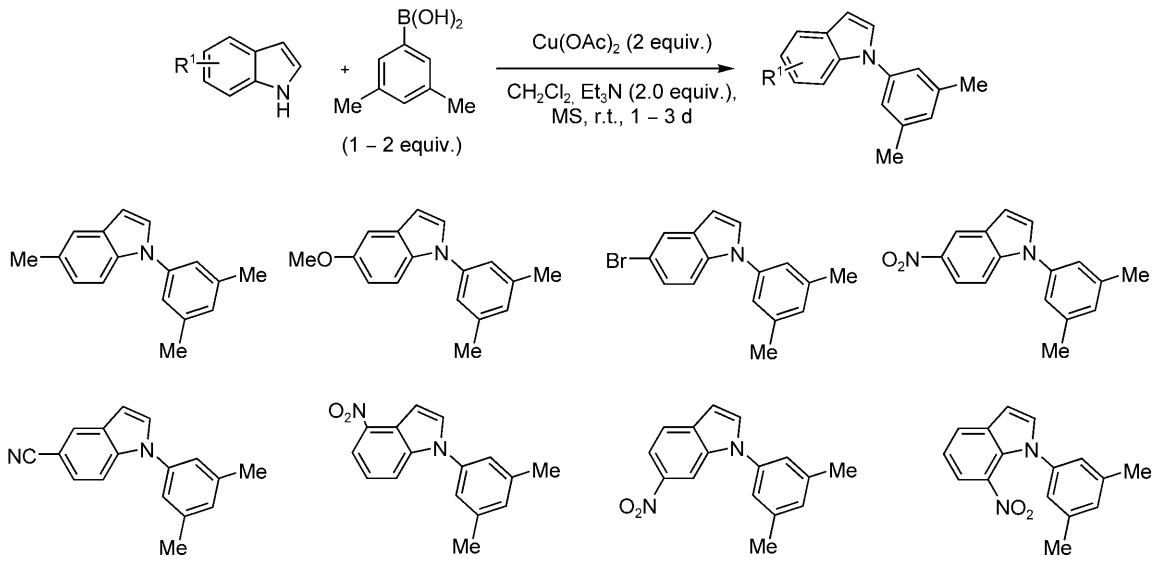


Figure 25. N1-Arylation of indoles with 3,5-dimethylphenylboronic acid.

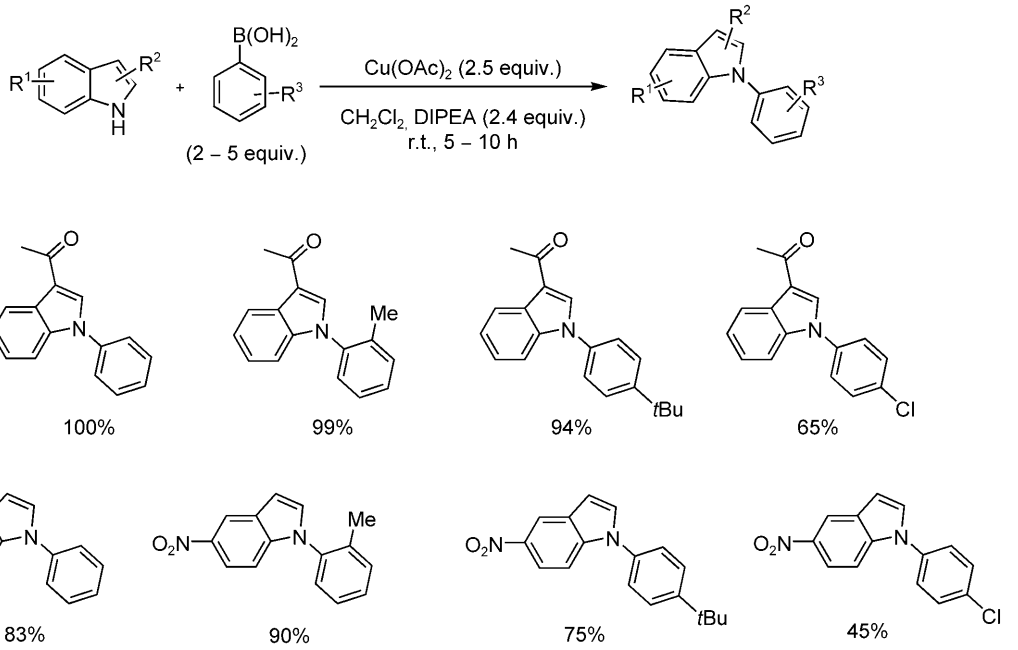


Figure 26. N1-Arylation of indoles with arylboronic acids (DIPEA = *N*-ethyldiisopropylamine).

(Figure 27). The authors compared this procedure to the palladium-catalysed route [5 mol% $Pd(OAc)_2$ in the presence or not of copper acetate] that led generally to lower chemical yields.[99] However, the procedure reported here did not seem to be competitive with the best copper- and palladium-catalysed methodologies, except when considering OH-free iodophenols. This approach is rather limited due to the required high temperatures and long reaction times.

3 Selective C2-Arylation

3.1 Oxidative Couplings

To the best of our knowledge, the first example of a direct C2-arylation of the indole nucleus, involving an oxidative cross-coupling, was reported by Itahara in the early 1980s.[100] The authors have previously reported the intramolecular C2- or C4-arylation of N-methylindoles by employing 0.5 equiv. of $Pd(OAc)_2$ in a refluxing acetic acid solution.[101,102] However, devel-

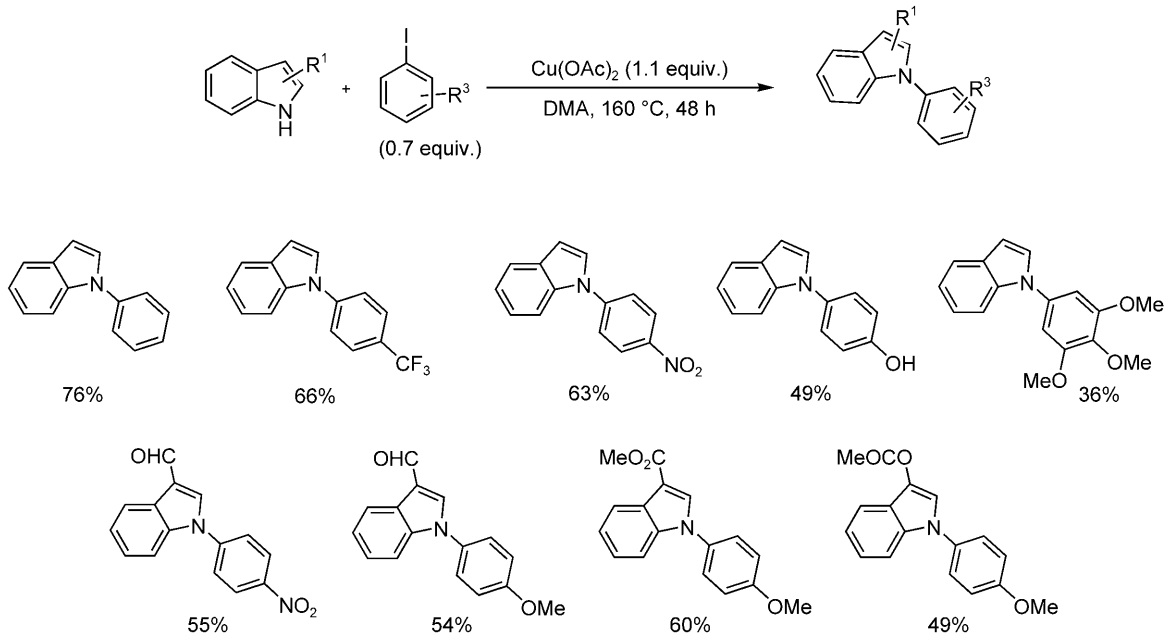


Figure 27. Stoichiometric copper acetate-mediated N1-arylation of indoles with aryl iodides.

oped in an intermolecular manner, this procedure required the use of N-acetylindoles and a stoichiometric amount of palladium catalyst in a refluxing AcOH/ArH solution, leading to the corresponding 2-phenylindoles in low to moderate isolated yields (Figure 28). These conditions were also successfully applied to the oxidative coupling of pyrrole, thiophene and furan derivatives.

The development of catalytic versions of this palladium-catalysed oxidative arene cross-coupling is an emerging alternative to the direct Heck-type coupling, avoiding the use of stoichiometric activating groups. Recently, Fagnou and co-workers have first re-visited this oxidative cross-coupling.[103] They found that the catalytic C2-arylation could be achieved with high selectivities by fine tuning of the nitrogen protecting group, oxidant and additive nature. Thus, employing N-pivaloylindole instead of N-acetylindole, as well as a stoichiometric silver oxidant (AgOAc, 3 equiv.) in the presence of a large excess of pivalic acid allowed the use of 5 mol% $Pd(TFA)_2$ and resulted in a 25/1 C2/C3 ratio and an almost full conversion within 3 h. These conditions are tolerant towards a large range of indole substrates and symmetrical benzenes, albeit with 10 mol% $Pd(TFA)_2$ being required for the latter, affording the corresponding 2-arylindoles in moderate to high yields (Figure 29).

At the same time, DeBoef and co-workers have initially reported an oxidative coupling with N-methyl- or N-acetylindole using high $Pd(OAc)_2$ catalyst loadings (i.e., 15 to 20 mol%) and a *stoichiometric* amount of $Cu(OAc)_2$ (1 to 4 equiv.) in an $AcOH/C_6H_6$ mixture.[104] However, low to poor C2/C3 selectivities (up to 5/1) were achieved under these conditions and the best result was obtained in an intramolecular manner with an activated N-benzoylindole. On the other

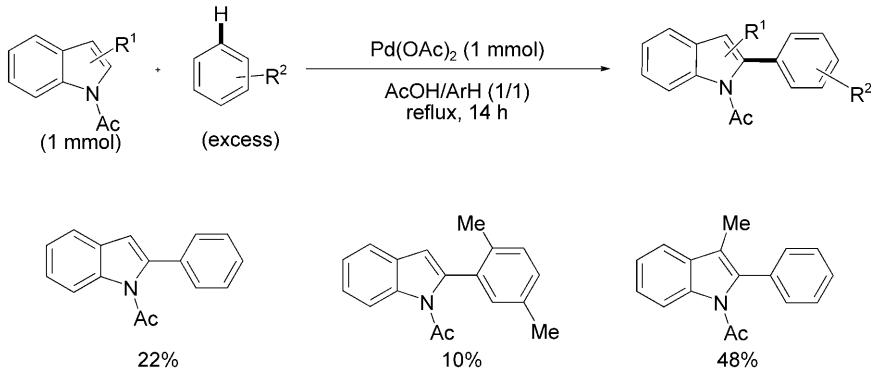


Figure 28. Oxidative coupling of N-acetylindoles in AcOH/ArH media with $Pd(OAc)_2$.

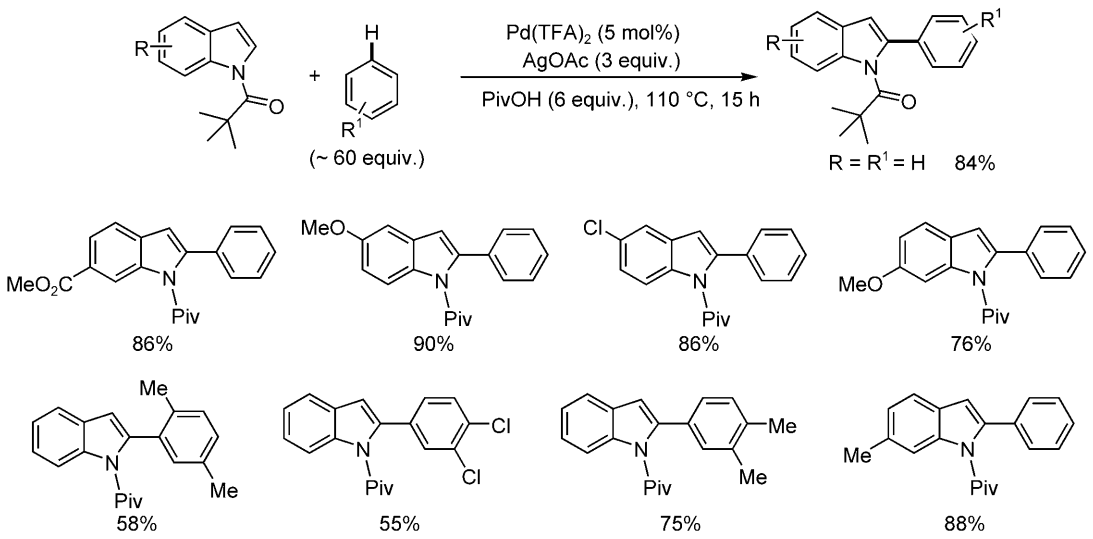


Figure 29. Selective C2 palladium-catalysed oxidative cross-coupling of arenes with N-pivaloylindoles.

hand, they have demonstrated that, in the case of benzo[*b*]furan, replacing $Cu(OAc)_2$ by phosphomolybdovanadic acids (HPMVs) allowed full C2 selectivity and moderate to high yields. In 2008, the same authors found that switching solvents from acetic acid to dioxane produced an inversion in regioselectivity.[105] The use of $Cu(OAc)_2$ as stoichiometric oxidant resulted in a clean C3-arylation (4/1 C3/C2 ratio) while AgOAc favoured the C2-arylation (3.5/1 C2/C3 ratio) as previously observed by Fagnou and co-workers. Under these conditions [$Pd(OAc)_2$, AgOAc, dioxane], low to moderate isolated yields were obtained with a broad range of substituted indoles (Figure 30). Unfortunately, electron-rich arenes such as *p*-xylene or anisole failed to react, as well as N-acetylazaindole. Finally, given that selectivities are only available for N-acetylindole and regarding the high catalyst loading [that is, 25 mol% $Pd(OAc)_2$], this rather low-yielding procedure is not competitive to the one reported by Fagnou.

3.2 Palladium-Catalysed Procedures

3.2.1 Phosphine Ligands

In 1985, Ohta and co-workers reported the first direct C2 intermolecular Heck-type coupling of free (NH)-indole with chloropyrazines (Scheme 10).[106] They used $Pd(PPh_3)_4$ as a palladium source, or a combination of $[Pd(PPh_3)_2Cl_2]$ and CuI as co-catalyst, with, respectively AcOK or K_2CO_3 as base in refluxing DMA. Under such conditions, moderate to good isolated yields in the target 2-pyrazinylindoles were ob-

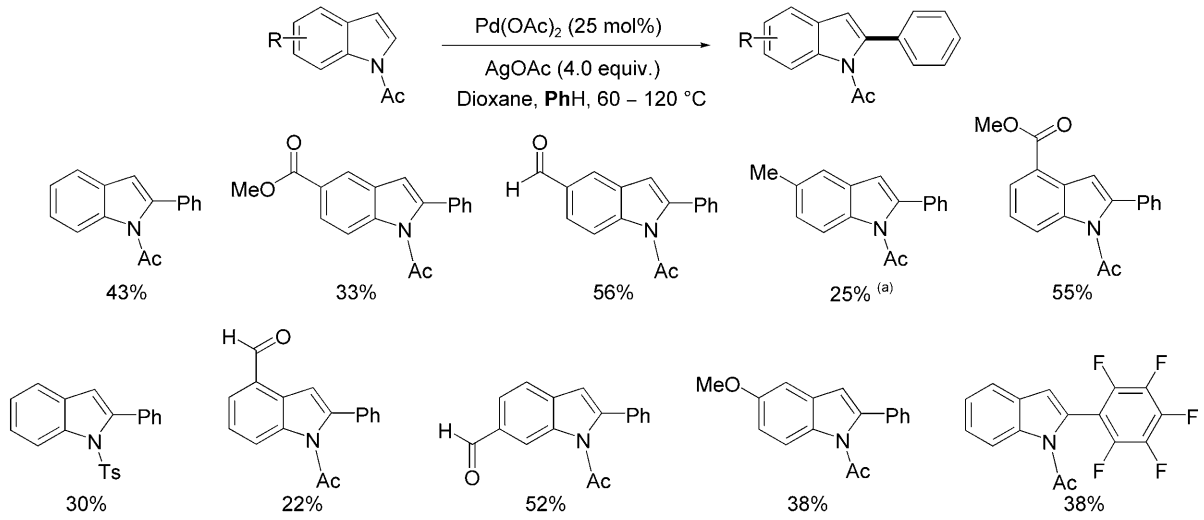
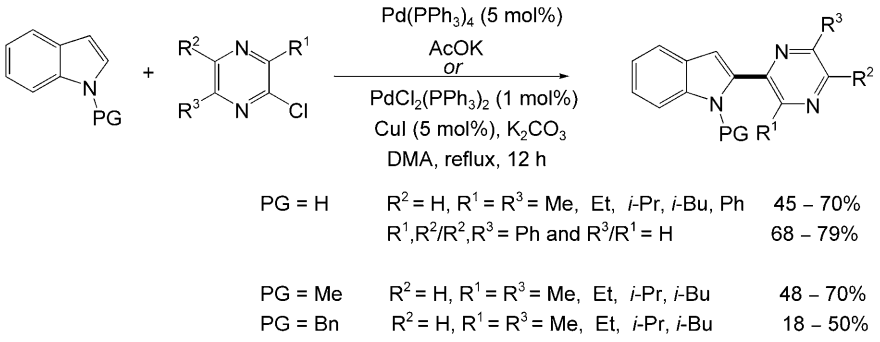


Figure 30. Selective C2 palladium-catalysed oxidative cross-coupling of N-acetylindoles. [a] 1/1 C3/C2 ratio.



Scheme 10. C2-Arylation of free (NH)-indole and N-alkylindoles with chloropyrazines.

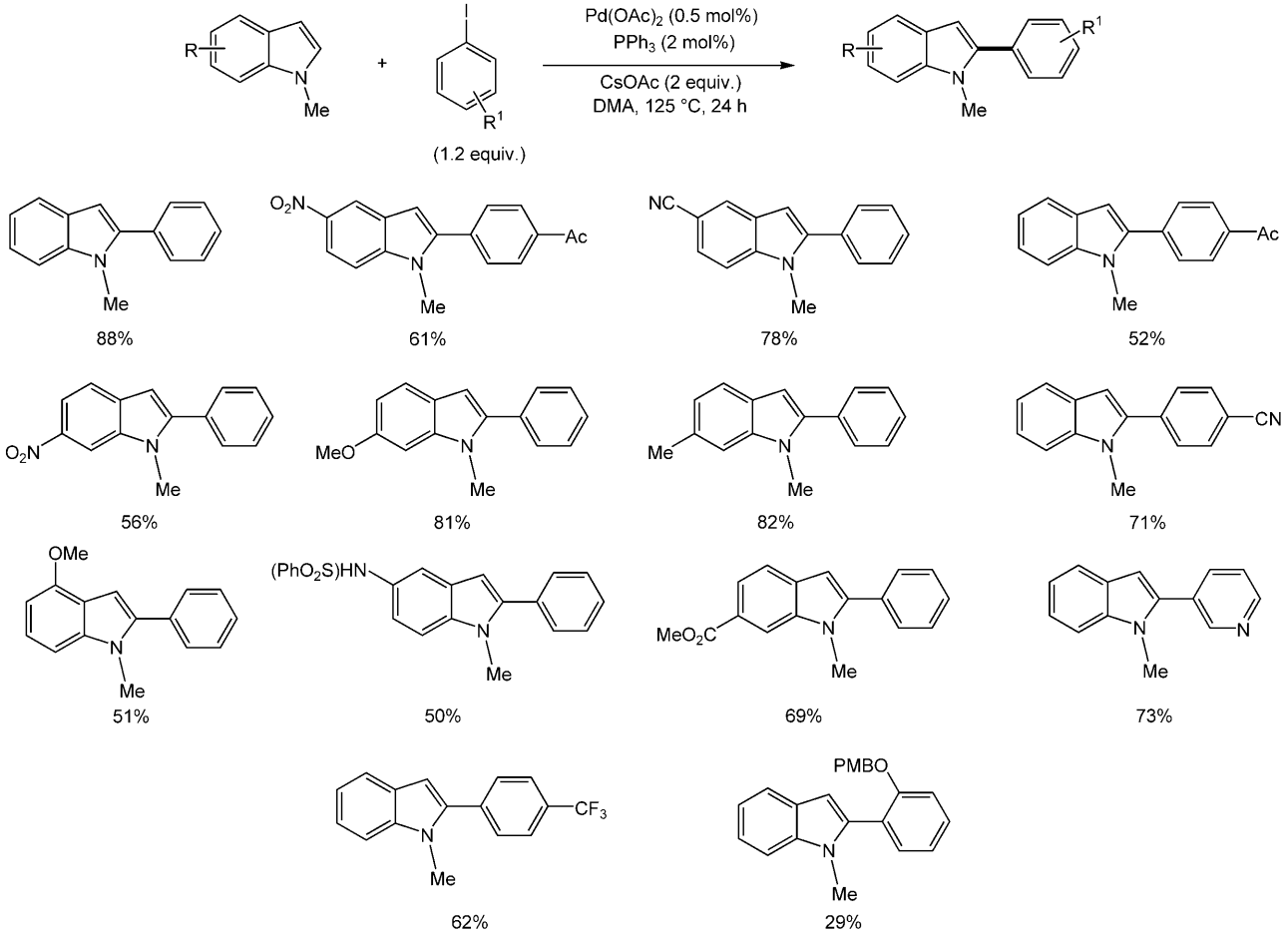


Figure 31. Selective palladium-catalysed C2-arylation of N-methylindoles.

tained. Moreover, they have demonstrated that only C2-arylation occurred as the coupling of 2-methylindole failed when using [$Pd(PPh_3)_4$/AcOK] whereas 3-methylindole reacted successfully under similar conditions. The authors have observed the same selectivity when reacting N-alkylindoles,[39] the N-methyl derivative leading to higher yields than the N-benzyl one. However, more sterically bulky pyrazines like 2-chloro-3,5-diphenylpyrazine failed to react with N-methylindole whereas high yields were obtained with free (NH)-indoles.

Surprisingly, the development of new palladium-catalysed methodologies for the direct C2-arylation of indoles received little attention during the following two decades, whereas one-pot methodologies requiring *in situ* functionalisation of the indole nucleus into indolylzinc,[107–114] indolylindium[115] or indolylboronate[116–119] species prior to a palladium-catalysed C–C

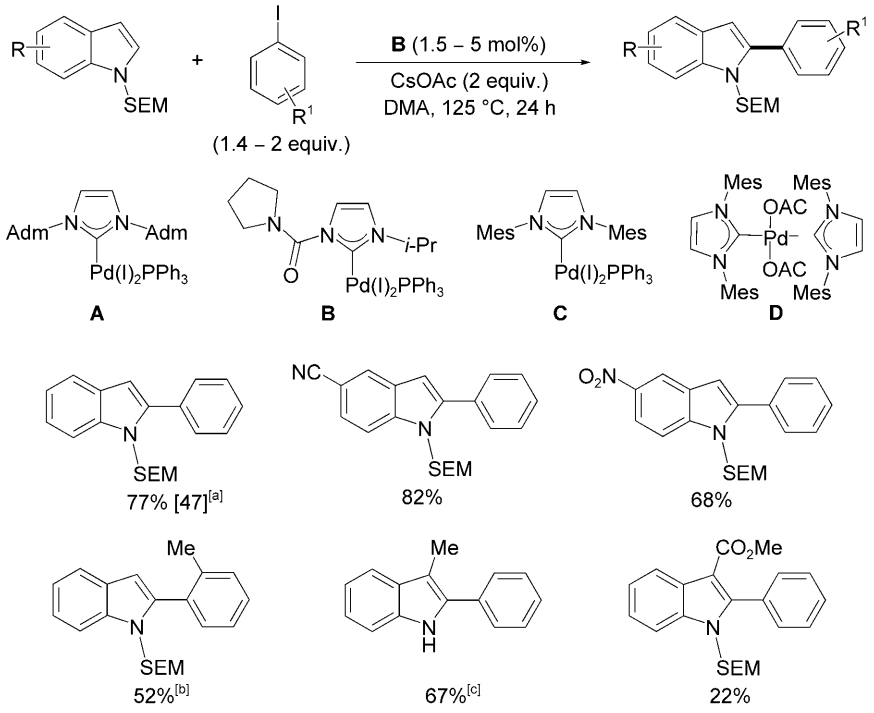


Figure 32. Catalytic C–H arylation of SEM-protected indoles with palladium complexes of NHCs and phosphines. [a] 5 mol% of **B** and bromobenzene were used. [b] 3.5/1 ratio in favour of the C2 regioisomer. [c] Product characterised after deprotection

coupling were extensively used. At the beginning of the 2000s, Sames and co-workers became interested in such challenging chemistry. They first reported a procedure based on the use of MgO as base; however, the non-reproducibility of this work was assessed two years ago. Further studies devoted to this field led these authors to the discovery of a new C2-arylation protocol of N-substituted indoles.[120] The use of a low catalyst loading (i.e., 0.5 mol%), the easiness of the procedure as well as a high degree of functional group tolerance and good isolated yields made this new method useful for organic chemists (Figure 31).

Recently, as an alternative to the use of phosphine ligands, Bhanage and co-workers have described the preparation of the air-stable complex $Pd(TMHD)_2$ (TMHD = 2,2,6,6-tetramethyl-3,5-heptanedionate) and its use as an efficient catalyst for the direct C2-arylation of N-methylindole, as well as various O-, N- and S-containing heterocycles, with K_3PO_4 as base in NMP or DMSO.[121] However, further developments are required in order to decrease the high catalyst loading (i.e., 10 mol%) and to extend this procedure to free (NH)-indoles.

3.2.2 N-Heterocyclic Carbenes

Since the N-methyl protecting group is almost impossible to remove, limiting their Pd/phosphine procedure[120] to access free (NH)-arylindoles, Sames and co-workers pursued their efforts and reported in 2006 a catalytic C–H arylation of SEM-protected indoles with palladium complexes of N-heterocyclic carbenes (NHCs) and phosphines.[122] Although SEMCl is expensive, this class of substrates is of great interest to provide free (NH)-indoles due to their easiness of deprotection in the presence of a fluoride source. Interestingly, among all the NHCs complexes investigated, they found that the activity of the bulky and more electron-rich complex **A** mirrored that of the electron-deficient analogue **B** (easily available on a large scale) implying the predominant role for steric effects. Thus, treatment of SEM-protected indoles under conditions very similar to that reported for N-methylindoles afforded the 2-arylindoles in moderate to good yields (Figure 32), except for the case with an electron-withdrawing group at the C3 position of indole. In addition, this procedure could also be successfully applied to a wide range of other heterocyclic cores like pyrrole, azaindole, imidazole and imidazo[1,2-*a*]pyridine.

In 2006, Sanford and co-workers have first reported the use of aryliodonium salts in a room-temperature palladium-catalysed C2-arylation of indoles.[123] They found that $Pd(OAc)_2$ was a suitable catalyst for this transformation within only 5 min at 25 °C in AcOH, affording N-methyl-2-phenylindole in a moderate 49% yield. Additionally, screening a range of Pd(II) complexes (PdX_2, X = Cl, Br, I, TFA; Na_2PdCl_4; $PdCl_2(BnCN)_2$] revealed that $IMesPd(OAc)_2$, contain-

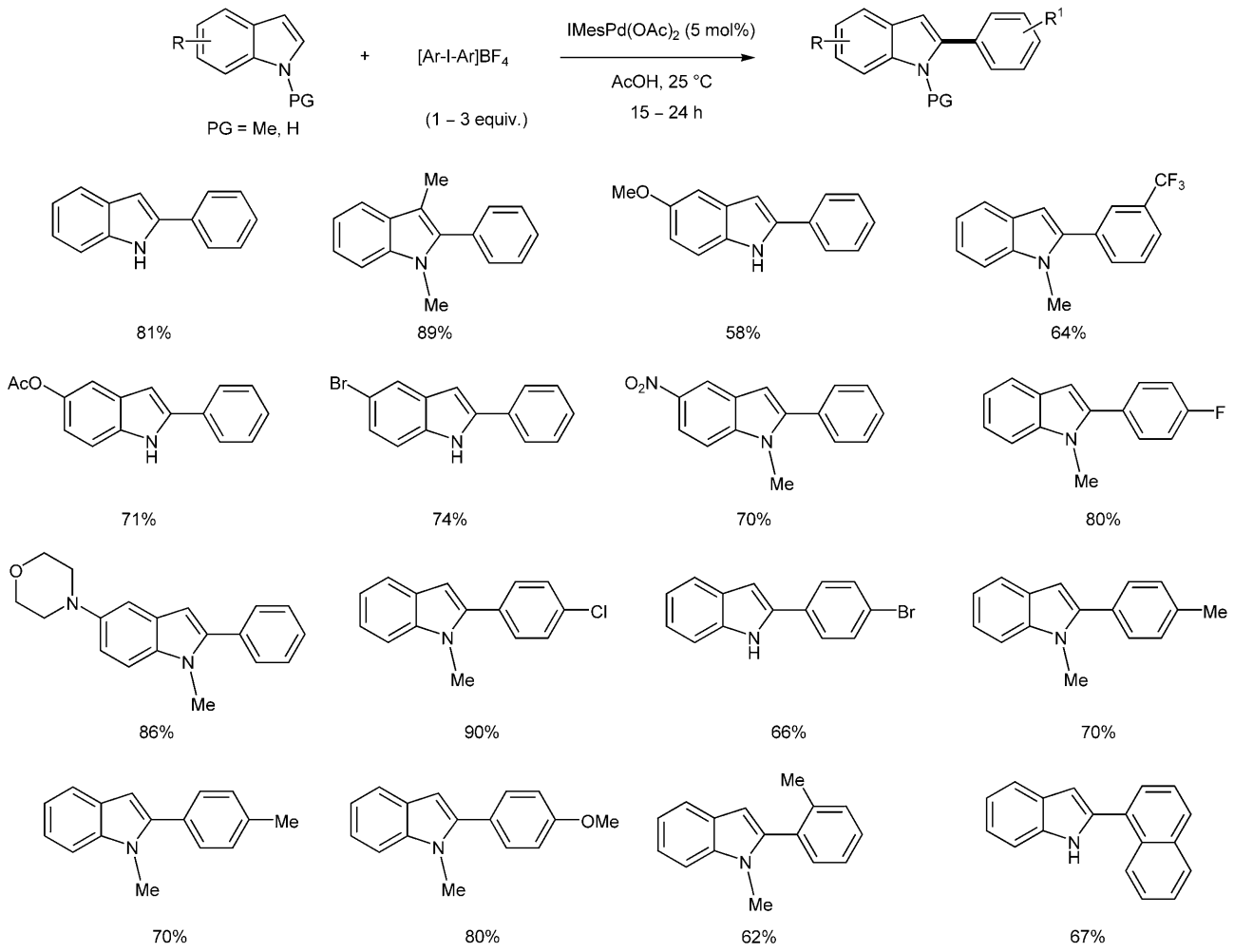


Figure 33. Room temperature palladium-catalysed C2-arylation of indoles with aryliodonium salts.

ing more stabilising ancillary ligands, afforded a significantly enhanced 86% isolated yield, in spite of a longer reaction time (i.e., 18 h). Under such conditions, a wide range of substituted indoles and symmetrical aryliodonium salts afforded the corresponding 2-arylindoles in good to high isolated yields. One can note that free (NH)-indoles have a similar reactivity as their N-methyl analogues; moreover, this cross-coupling is compatible with arenes bearing C–Br bonds (Figure 33). The authors have also develop a one-pot approach to this transformation by *in situ* generation of I(III) arylating reagents from ArI-$(OAc)_2$ and Ar′$B(OH)_2$ to afford the corresponding N-methyl-2-arylindoles in 67–81% isolated yields.

3.3 Ligand-Free Procedures

3.3.1 Aryl Halides as Coupling Partners

Sames and co-workers reported in 2007 a phosphine-free palladium-catalysed C–H arylation of free (NH)-indoles.[124] Using common reaction conditions [that is, $Pd(OAc)_2$, CsOAc, DMA], this ligandless and operationally simple procedure allowed an efficient entry to a wide range of C2-arylated (NH)-indoles in moderate to good isolated yields when aryl iodides were employed [Figure 34, Eq. (1)]. As expected, aryl bromides were less efficient than their iodo analogues; however, this lack of reactivity could be overcome by adding a stoichiometric amount of $(i\text{-Pr})_2NH$ [Figure 34, Eq. (2)]. Under such conditions, the authors have only reported the direct C2-arylation of C3-substituted indoles like 3-methylindole and tryptamine derivatives, affording respectively good and modest isolated yields.

In the meantime, Bellina and co-workers have described a palladium and copper-mediated C2-arylation of free (NH)-indoles under base-free and ligandless conditions.[125,126] Anyway, this rather low yielding procedure requires an excess of a copper co-catalyst and drastic conditions (i.e., 160 °C), which limits applications (Figure 35). However, free (NH)-imidazoles

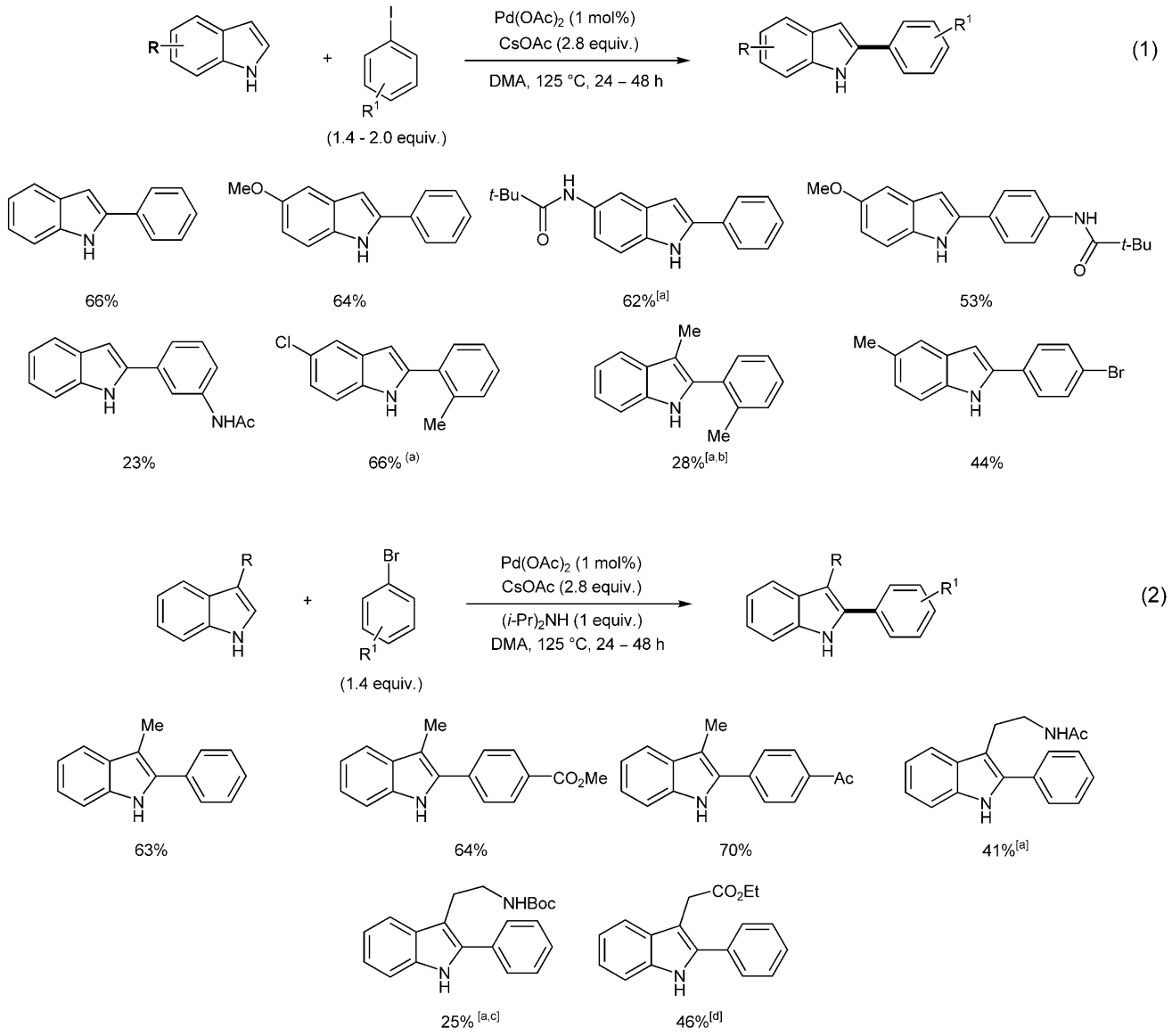


Figure 34. Phosphine-free palladium-catalysed C2-arylation of free (NH)-indoles. [a] $Pd(OAc)_2$ (5 mol%) and PhI or bromoarene (2 equiv.) were employed. [b] *t*-$BuNH_2$ (1 equiv.) was added. [c] $(i\text{-}Pr)_2NH$ (3 equiv.) was used. [d] $Pd(OAc)_2$ (2 mol%) was used.

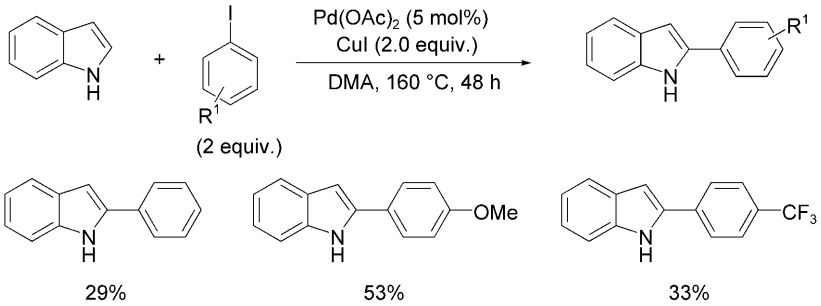


Figure 35. Palladium and copper-mediated direct C2-arylation of free (NH)-indoles under base-free and ligandless conditions.

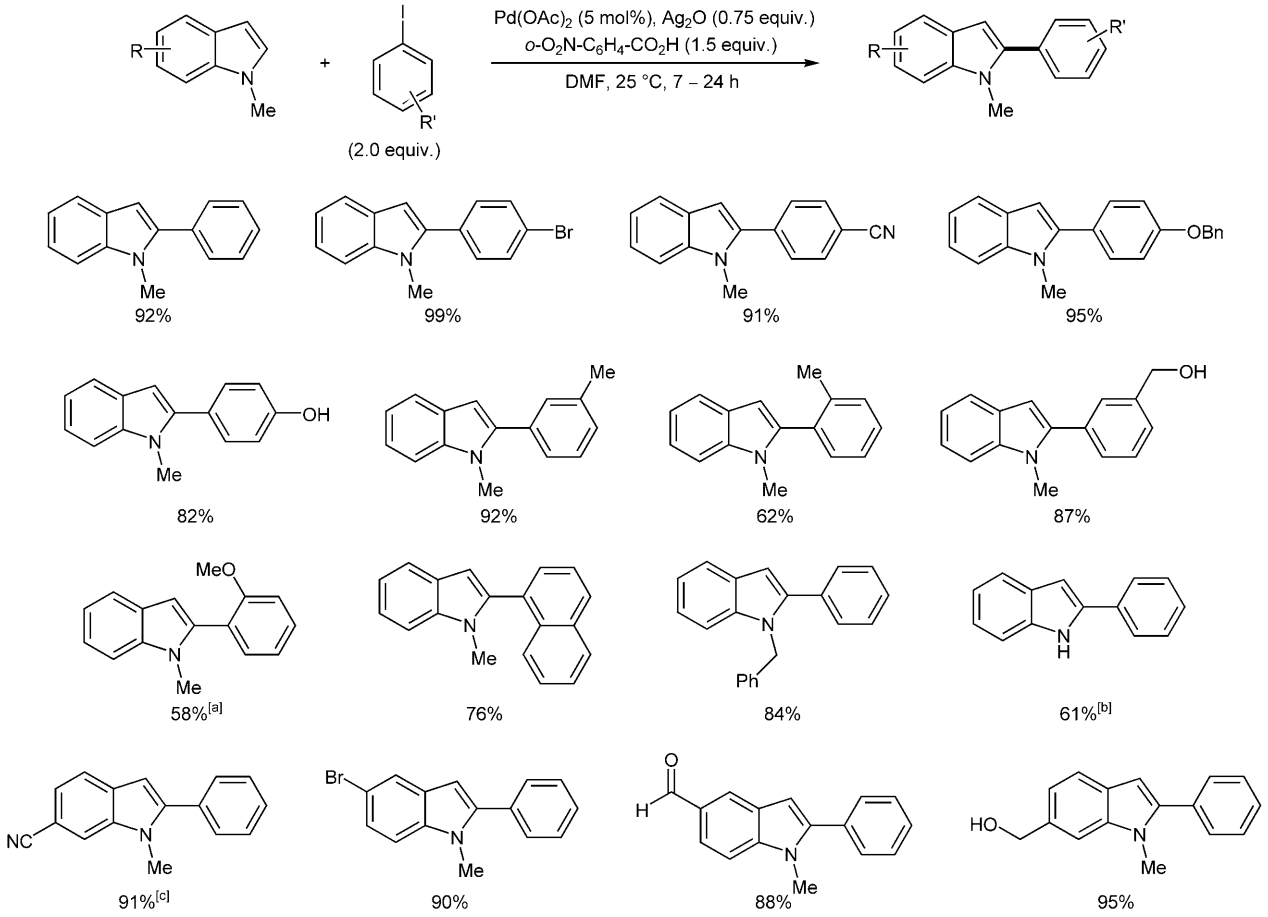


Figure 36. Room temperature and phosphine-free palladium-catalysed direct C2-arylation of N-methylindoles. [a] The reaction was carried out with 5 equiv. of iodoarene for 38 h. [b] 38 h at 50 °C. [c] 10 mol% $Pd(OAc)_2$ was used.

or benzimidazoles as well as thiazoles and oxazoles were particularly reactive under these conditions.

Recently, Larrosa and co-workers described an efficient room-temperature and phosphine-free palladium-catalysed direct C2-arylation of N-methylindoles.[127] They used a combination of Ag_2O as base and *o*-nitrobenzoic acid, which afforded the best reactivity among all the carboxylic acids tested, in order to generate *in situ* the corresponding silver(I) carboxylate. The authors suggested that the formation of more electrophilic cationic palladium species by abstraction of the halides promoted by silver(I) salts would increase the rate of the palladation step. Thus, by employing 5 mol% $Pd(OAc)_2$ in DMF, a broad scope of N-methylindoles and iodoarenes were converted to the desired C2-arylindoles in good to excellent yields even at room temperature (Figure 36). This high yielding cross-coupling procedure, regarding its tolerance toward electron-rich or electron-deficient substrates as well as its efficiency with free (NH)-indole and the full I/Br selectivity under very mild reaction conditions, represents the easiest and most convenient one among all the methods described in this review for the selective C2-arylation of indoles.

3.3.2 Arylboron Reagents as Coupling Partners

Zhang and co-workers reported in 2008 the use of potassium aryltrifluoroborate salts for the Pd(II)/Cu(II)-catalysed direct C2-arylation of N-methyl- and (NH)-indoles.[128] While O_2 was found to be the best oxidant with $Pd(OAc)_2$, adding a catalytic amount of $Cu(OAc)_2$ allowed one to work under an air atmosphere to furnish 2-phenylindole in 81% while a 62% yield was obtained without this co-catalyst. Thus, under very mild conditions [5 mol% $Pd(OAc)_2$, 10 mol% $Cu(OAc)_2$, AcOH, room temperature, air], a wide range of Ar-BF_3K salts and substituted indoles gave the corresponding C2-arylindoles in moderate to high yields, although strong electron-withdrawing groups (CF_3, F, CN, CO_2Et) depressed the cross-coupling efficiency (Figure 37). Noticeably, the authors have compared their results to the use of the corresponding ar-

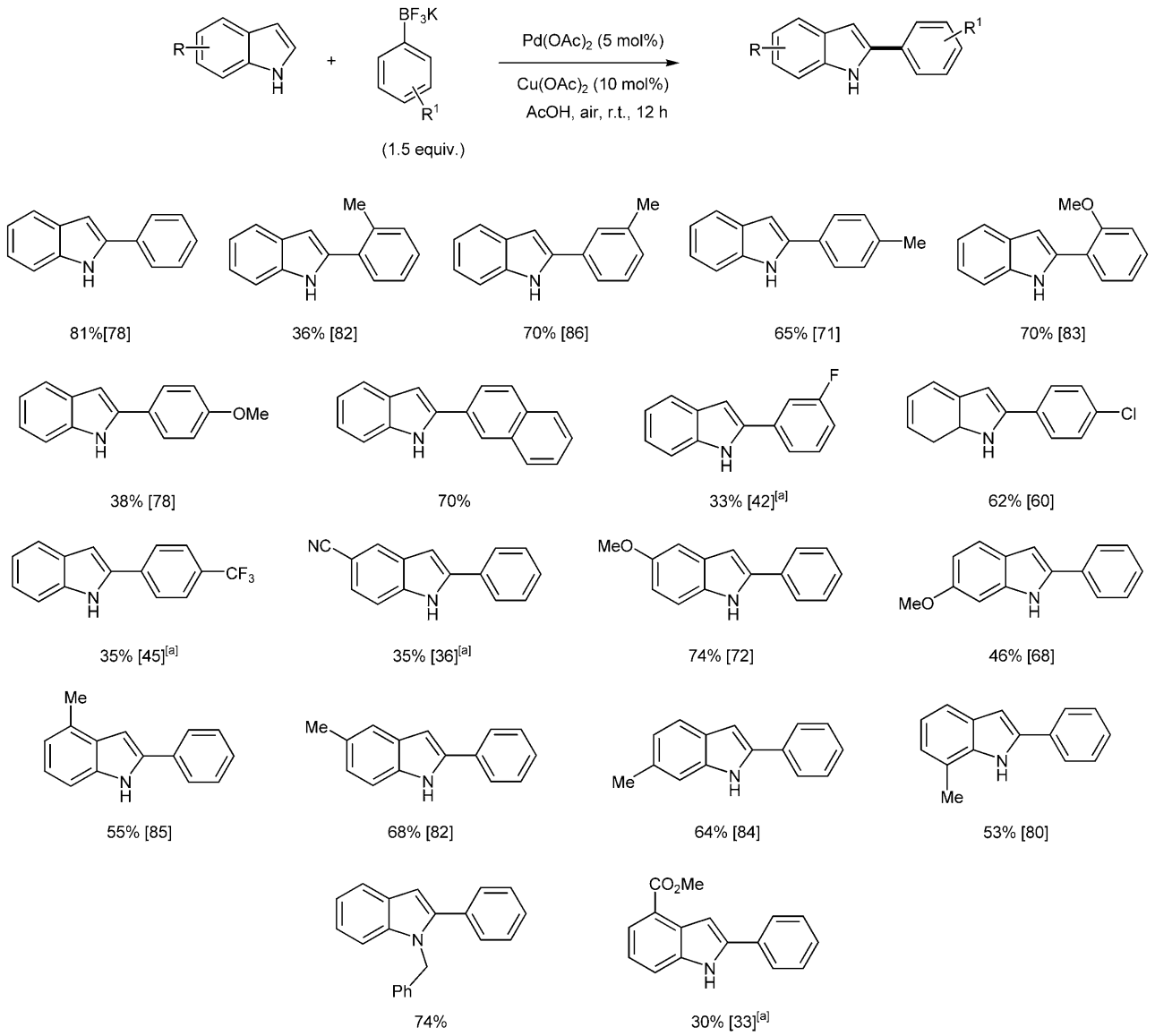


Figure 37. Palladium-catalysed direct C2-arylation of free (NH)-indoles with potassium aryltrifluoroborate salts. [a] 1 equiv. $Cu(OAc)_2$ was used. Values in square brackets refer to the yields obtained with the corresponding N-methylindole.

ylboronic acids and found that higher yields (+10–15%) were generally obtained with Ar-BF_3K salts as well as with N-methylindoles.

At the same time, Shi and co-workers have independently reported the use of arylboronic acids for the palladium-catalysed C2-arylation of (NH)-indoles.[129] Under very similar reaction conditions [5 mol% $Pd(OAc)_2$, AcOH, room temperature, 1 atm O_2] to the ones reported by Zhang and co-workers, although in absence of a copper co-catalyst, moderate to good isolated yields were achieved with a large range of substituted indoles and arylboronic acids (Figure 38). It's noteworthy that under such conditions, boronic acids bearing electron-withdrawing groups gave better yields than those reported by Zhang. Moreover, benzo[*b*]thiophene, benzofuran and even pyrrole reacted smoothly to give the desired C2-heteroaryls.

3.4 Rhodium-Catalysed Procedures

During the course of their studies, Sames and co-workers have also reported a direct C2-arylation of free (NH)-indoles catalysed by Ar–Rh(III) complexes assembled *in situ*.[130] Indeed, mechanistic investigations revealed that the combination of a rhodium catalyst (i.e., $[Rh(coe)_2Cl]_2$), an electron-deficient phosphine such as $[p\text{-}(CF_3)C_6H_4]_3P$ and the weak base CsOPiv with an aryl iodide (ArI) generates *in situ* a

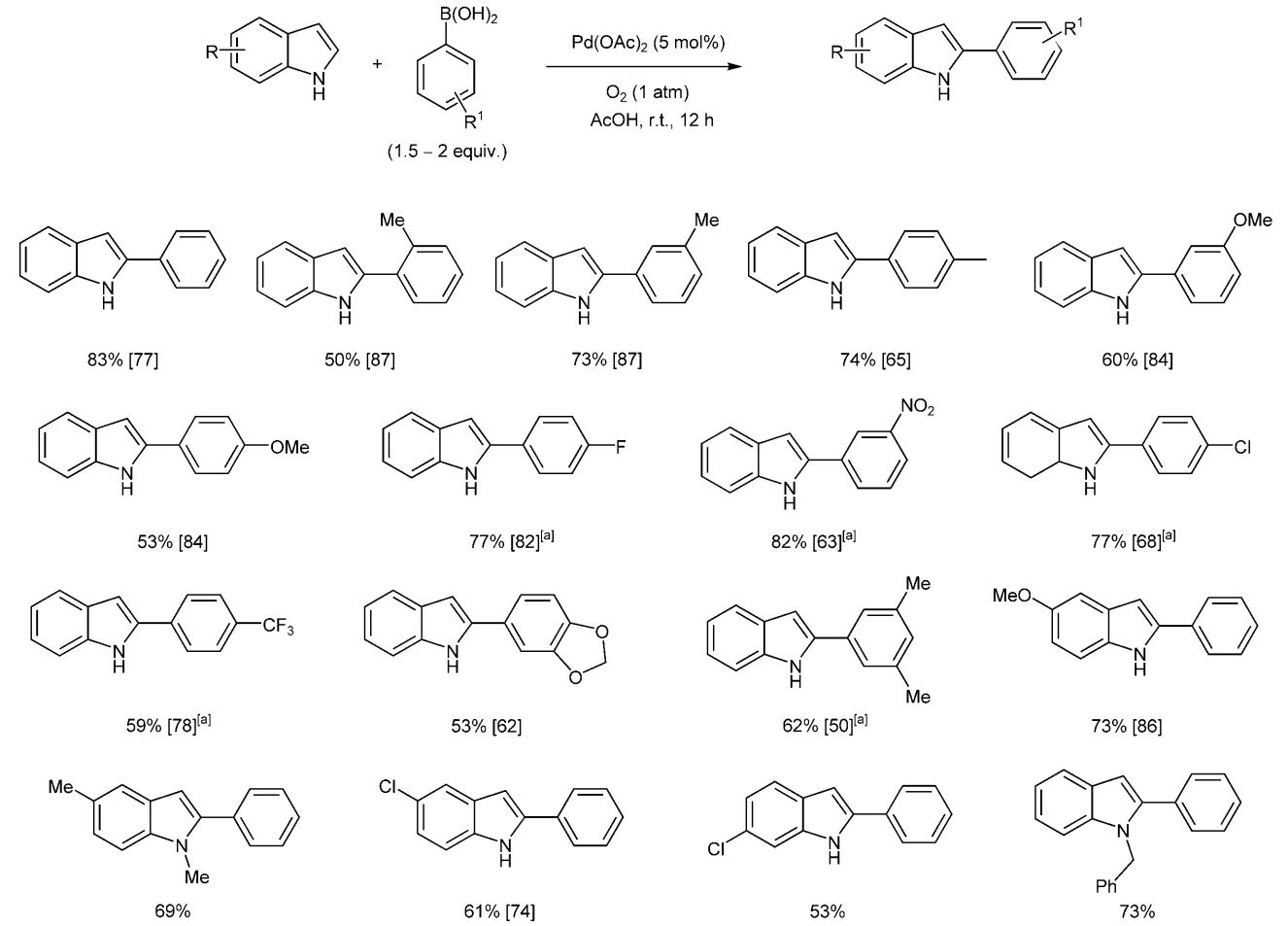


Figure 38. Palladium-catalysed direct C2-arylation of indoles with arylboronic acids. [a] 10 mol% $Pd(OAc)_2$ was used with free (NH)-indoles. Values in square brackets refer to the yields obtained with the corresponding N-methylindole.

highly electrophilic and reactive Ar–Rh(III) species of the general formula $Rh(OPiv)_2(Ar)L_2$ {L = [*p*-$(CF_3)C_6H_4]_3P$}. This protocol was especially applied to indole substrates bearing acidic N–H and even C–Br bonds, and proved tolerance to a wide range of functional groups, affording the corresponding C2-arylindoles in good to high yields (Figure 39). In addition, this methodology was successfully extended to the selective C2-arylation of free (NH)-pyrroles, the 7-azaindole being unreactive under these reaction conditions.

Mechanistic studies and X-ray analyses of the Rh(III) active species, synthesised independently on a preparative scale, were used to get better insights into the mechanism of the reaction. The authors suggested that displacement of a phosphine ligand by indole takes place in a pre-equilibrium, followed by the slow C–H bond metallation step assisted by the coordinated pivalate anion, as supported by the large kinetic isotope effect ($k_H/k_D = 3.0$). The resulting intermediate then undergoes reductive elimination to furnish the desired 2-arylindole. The Rh(I) complex formed in this step is rapidly converted to the active Rh(III) species *via* oxidative addition of iodobenzene and halide-pivalate exchange (Figure 40).

3.5 Copper-Catalysed Procedures

Gaunt and co-workers reported in 2008 the direct and site-selective C2-arylation of N-acetylindoles with aryliodonium salts catalysed by $Cu(OTf)_2$ under mild reaction conditions.[131] This procedure was tolerant toward various substituted indoles, bearing either electron-donating or electron-withdrawing groups, when the symmetrical [Ph-I-Ph]OTf salt was used [Figure 41, Eq. (3)]. The authors have also developed the use of unsymmetrical iodonium salts, of the general formula [TRIP-I-Ar]OTf [Figure 41, Eq. (4)], the more sterically bulky 2,4,6-triisopropylphenyl (TRIP) group allowing the exclusive transfer of the desired aryl group (Ar). Under such conditions, low to good

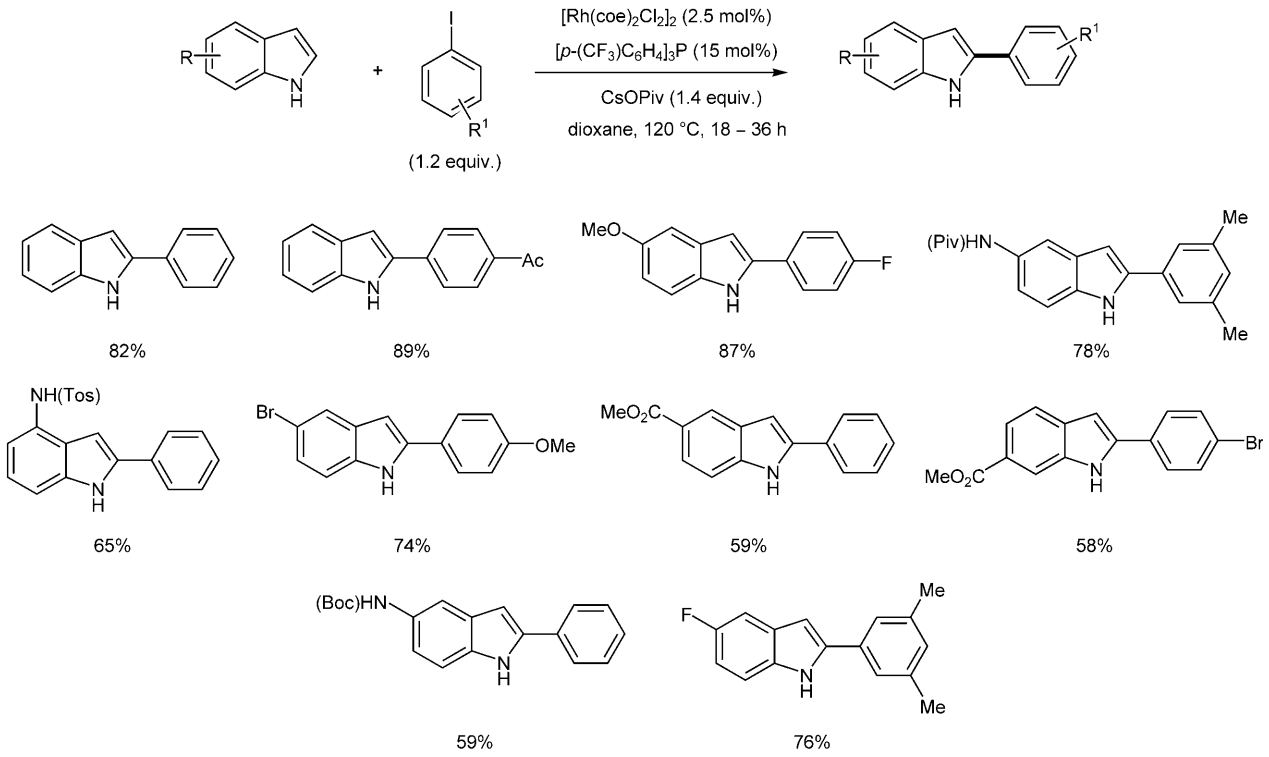


Figure 39. Direct C2-arylation of free (NH)-indoles catalysed by Ar–Rh(III) complexes assembled *in situ*.

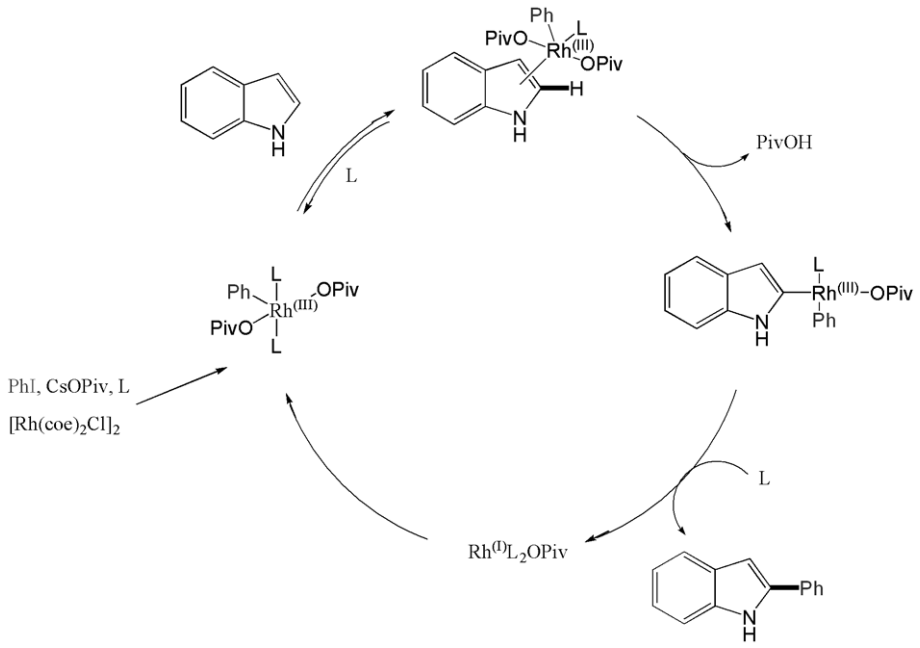


Figure 40. Proposed catalytic cycle for the rhodium-catalysed selective C2-arylation of indoles.

selectivities (up to 9/1 C2/C3) and good yields of the target C2-arylindoles were achieved with either electron-deficient or electron-rich aryl moieties. It is noteworthy that aryl substrates bearing C–Br or even C–I bonds were not affected by this copper-catalysed arylation.

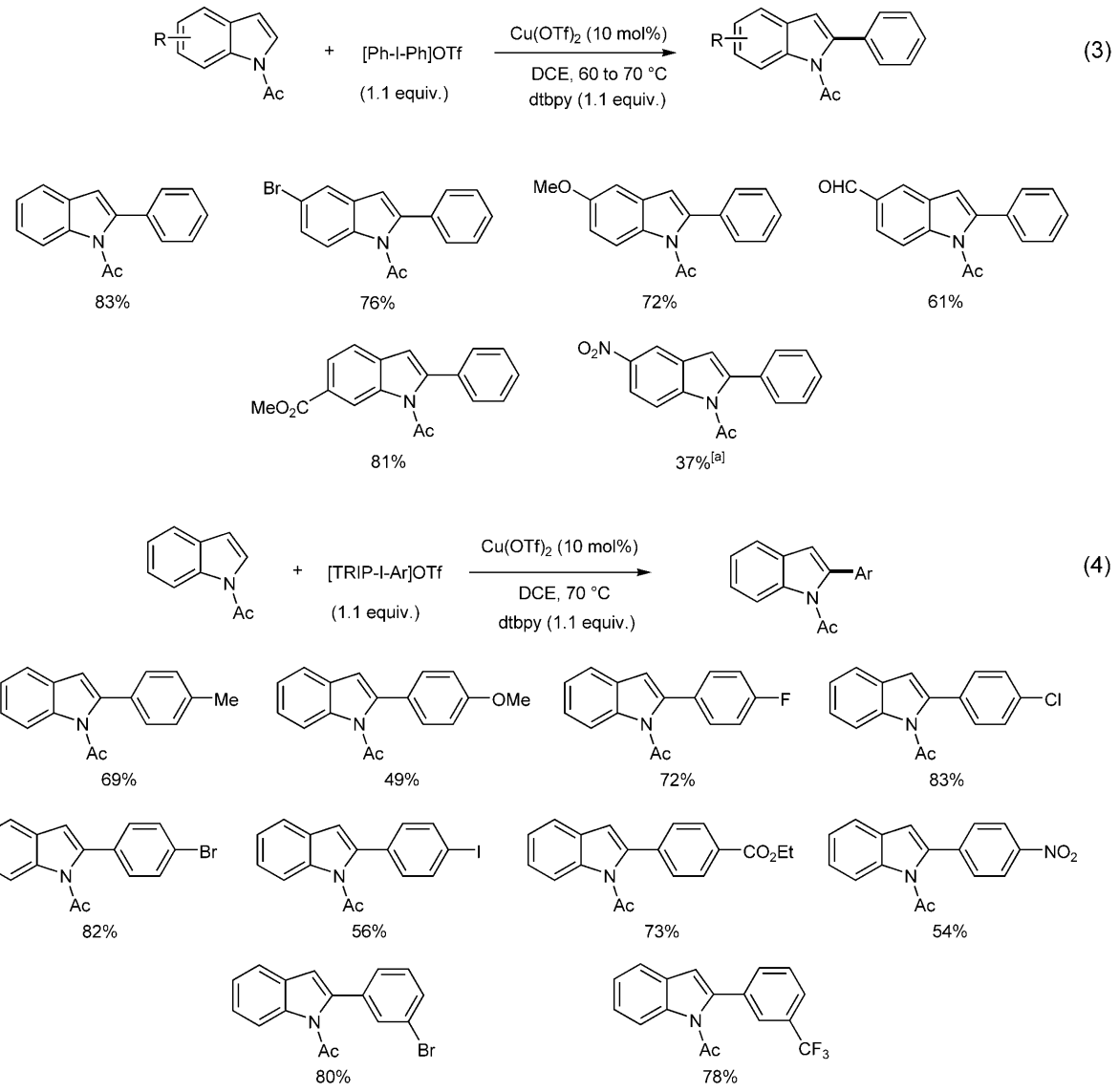


Figure 41. Cu(II)-catalysed C2-arylation of indoles with aryliodonium salts. [a] Isolated yield at 63% conversion of indole using 20 mol% of $Cu(OTf)_2$.

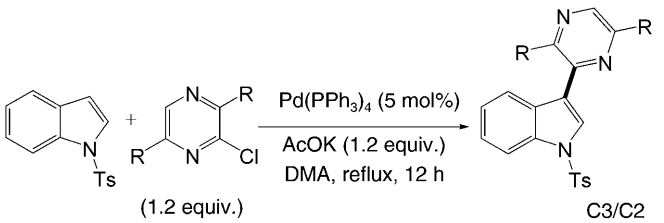
4. Selective C3-Arylation

4.1 Palladium-Catalysed Procedures

4.1.1 Phosphine Ligands

During their investigation on the synthesis of pyrazynilindoles, Otha and co-workers found that the nature of the nitrogen protecting group on indole had a significant effect on the regioselectivity of the palladium-catalysed coupling.[39] They have thus reported for the first time a direct and highly selective C3-arylation of indole with 2-chloropyrazine when the indolic nitrogen was protected with an electron-withdrawing protecting group (Scheme 11). Under similar conditions to those reported for the selective C2-arylation [i.e., $Pd(PPh_3)_4$/AcOK], moderate to good isolated yields were obtained. Additionally, it was found that the more sterically bulky pyrazine moieties (R = *i*-Pr, *i*-Bu) afforded the highest C3/C2 ratios.

During the course of their studies on the selective C2-arylation of indoles, Sames and co-workers found that bulky *o*-iodoarenes led to C3-regioisomers as the major products. Thus, on the basis of mechanistic investigations, they suggested that the use of sterically bulky arylpalladium(II) intermediates and indolylmagnesium salts should favour the C3-arylation.[132] Interestingly, phenylation of the N–MgCl indole Grignard salt gave a 7/1 C3/C2 ratio under classical conditions, despite a low 24% yield [Scheme 12, [Eq. (5)]. It's noteworthy that the addition of TMEDA led to the formation of 3-phenylindole with improved se-



R = Me	40%	8/1
Et	58%	15/1
i-Pr	46%	50/1
i-Bu	68%	50/1

Scheme 11. Selective C3-arylation of N-tosylindole with 2-chloropyrazines.

lectivity (14/1 C3/C2), presumably *via* formation of a sterically demanding magnesium complex [Scheme 12, Eq. (6)]. Moreover, when the bulky IMes ligand was used, an almost full C3/C2 selectivity was achieved even with bromobenzene in a high 96% yield [Scheme 12, Eq. (7)]. Finally, the use of the N-Mg-(HMDS) salt was sufficient to achieve a 26/1 C3/C2 selectivity without the use of the IMes ligand; furthermore, under such conditions, a 77% yield based on indole as limiting reagent was obtained [Scheme 12, Eq. (8)].

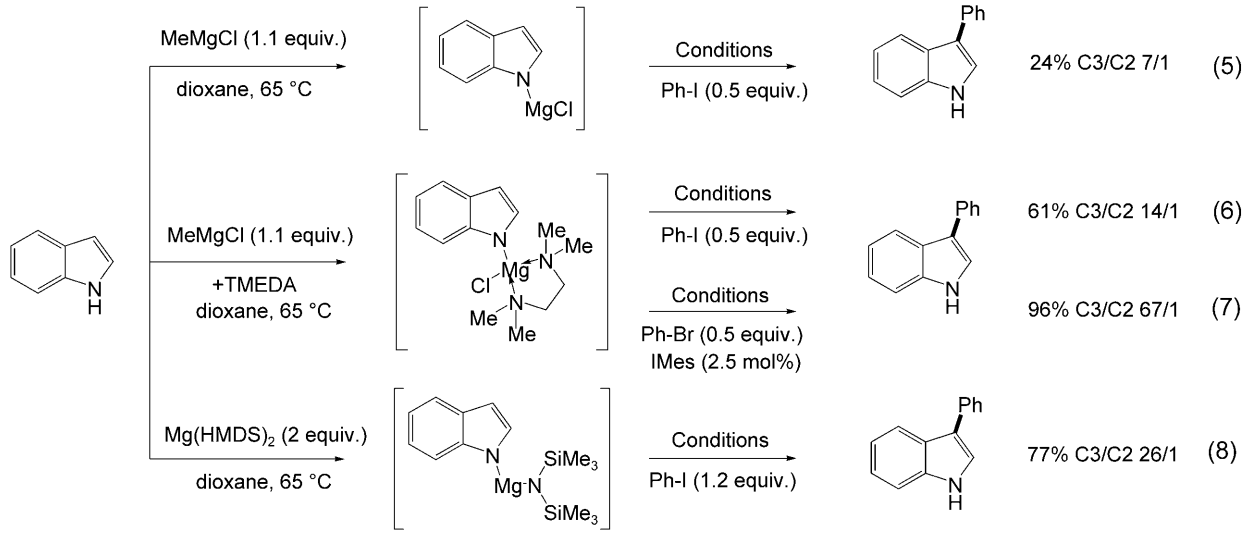
In 2007, Zhang and co-workers reported for the first time the direct palladium-catalysed C3-arylation of free (NH)-indoles with aryl bromides.[133] They found that almost full C3/C2 selectivities (~100/1) were achieved by using the air-stable palladium/phosphinous acid complex $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ in combination with K_2CO_3 in refluxing dioxane. This simple procedure afforded the corresponding C3-arylindoles in moderate to good isolated yields; however, indoles bearing electron-withdrawing groups (such as 2-Ac, 5-CN or 5-NO_2) were quite unreactive under these conditions (Figure 42).

According to their own procedure applied to the benzo[*b*]thiophene scaffold[134] and related to the one reported by Sames, Lemaire and co-workers described the Heck-type cross-coupling of N-methylindole with 4-bromo-3-nitroanisole (Scheme 13).[135] Under classical conditions [$Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (3 equiv.), DMF, 130 °C, 4 h], a 4/1 C3/C2 regioselectivity was observed with a 75% overall yield.

4.1.2 Ligand-Free Procedures

In 2006, Djakovitch and co-workers reported a simple palladium-catalysed procedure for the selective C3-arylation of 2-substituted indoles.[136,137] The combination of aryl bromides and a catalytic amount of $AgBF_4$ gave exclusively the C3-arylated compounds under classical reaction conditions [$Pd(OAc)_2$, AcONa, NMP], whereas iodo derivatives led to the corresponding N1-arylindoles in presence of PPh_3. Surprisingly, a full C3 *versus* N1 regioselectivity was observed with a carboxylate moiety onto the C2 position of indole whatever the nature of the aryl halide, presumably due to the slightly more stable transition state σ-Pd complex **TS1** than the N–Pd one **TS2** (Figure 43).

According to the procedure reported by Zhang, Djakovitch and co-workers described in 2008 the first heterogeneously palladium-catalysed selective C3-arylation of free (NH)-indoles.[138] Under similar conditions, the use of only 1 mol% of the well-known [Pd-$(NH_3)_4$]/NaY was sufficient to achieve high conversions and moderate to good isolated yields with either



Scheme 12. Selective C3-arylation of N-magnesium salts. *Reaction conditions:* $Pd(OAc)_2$ (2.5 mol%), PPh_3 (10 mol%), CsOAc (2 equiv.), dioxane, 125 °C, 24 h.

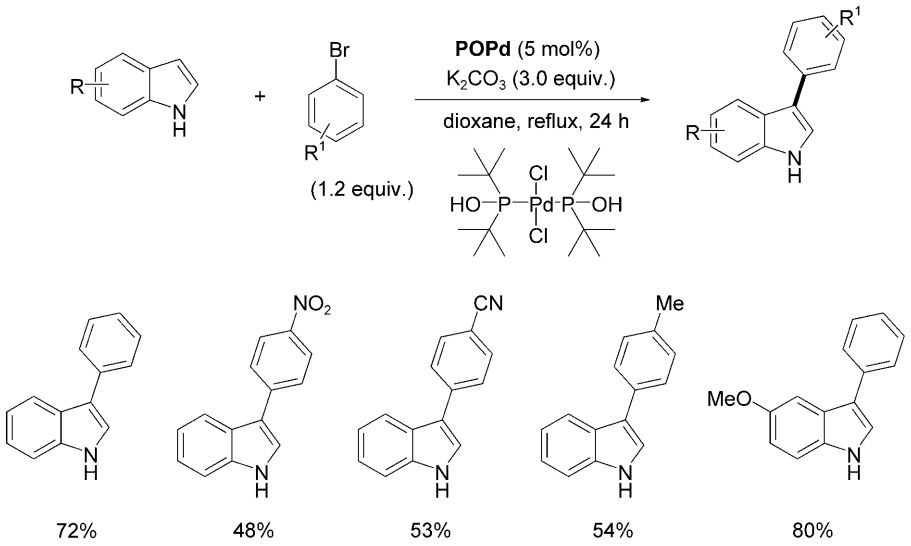
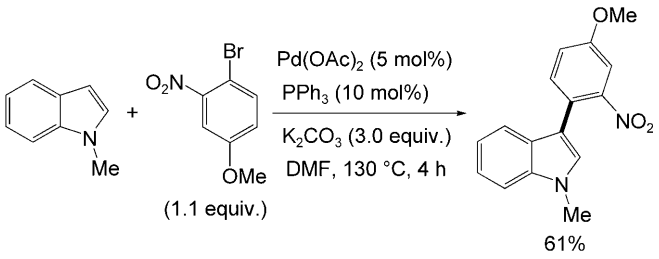


Figure 42. Direct palladium-catalysed C3-arylation of indoles with palladium/phosphinous acid complex.



Scheme 13. Selective C3-arylation of N-methylindole with *p*-bromo-*m*-nitroanisole.

indole, 2-methyl- or 2-phenylindole (Figure 44). Nevertheless, the reactivity was strongly dependent on the electronic nature of the bromoarene, electron-donating substituents giving generally the highest conversions, without a rationale explanation being available at this time.

Recently, Bellina and co-workers proposed a phosphine-free direct palladium-catalysed C3-arylation of free (NH)-indoles with aryl bromides.[139] It was found that replacing dioxane by toluene afforded slightly higher yields (+10%) but traces of C2- and N1-arylindoles, which are not detected in dioxane, were observed. When a catalytic amount of a quaternary ammonium salt [i.e.. $Bn(Bu)_3NCl$], known to stabilise soluble Pd clusters and preventing their aggregation to inactive Pd black, was added instead of a phosphine (PPh_3 or PCy_3) a full C3 *versus* C2/N1 regioselectivity and improved yields of the C3-arylindoles were achieved. These conditions were successfully applied to a range of electron-donating or electron-withdrawing substituted aryl bromides and electron-rich

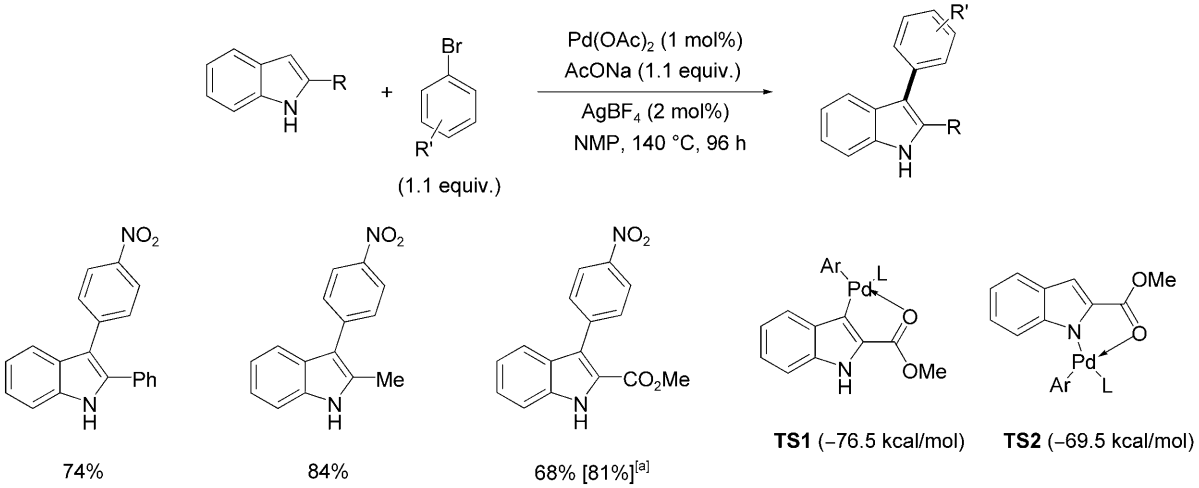


Figure 43. Selective C3-arylation of 2-substituted indoles. [a] 4-Iodonitrobenzene and 2 mol% PPh_3 were used.

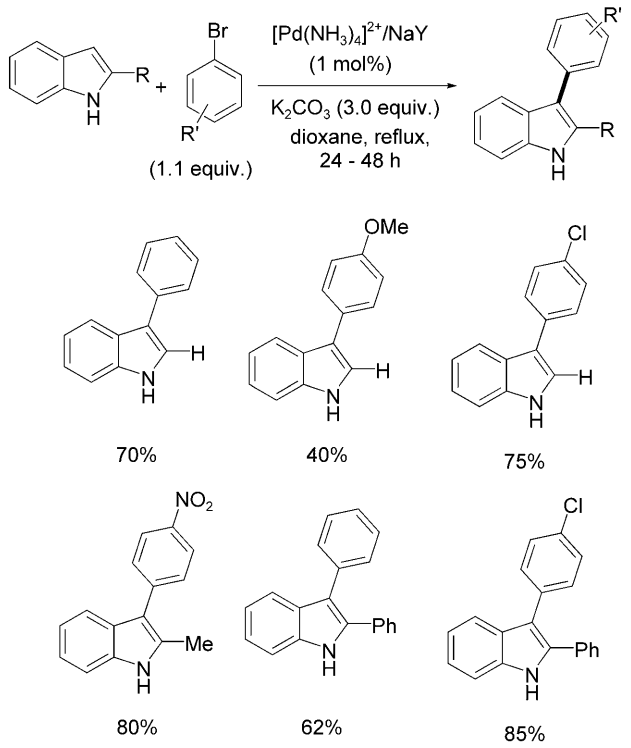


Figure 44. Heterogeneously palladium-catalysed selective C3-arylation of free (NH)-indoles with bromoarenes.

free (NH)-indoles, affording the C3-arylindoles in good to high yields (Figure 45). Some limitations appeared with strongly deactivating groups (i.e., 4-bromonitrobenzene), N-methylindole and indoles bearing electron-withdrawing groups (i.e., 5-CN and 2-CO_2Et).

While such a catalytic system comprising $Pd(OAc)_2$, R_4NX and K_2CO_3 known as Jeffery conditions,[140] was applied here for the first time to the selective C3-arylation of indoles, we wish to point out that it has already been described in the literature for the direct arylation of the thiophene scaffold.[134,141–143]

4.2 Rhodium-Catalysed Procedures

In 2006, Itami and co-workers developed the use of a rhodium complex bearing the strongly π-accepting ligand $P[OCH(CF_3)_2]_3$.[144] While very effective with electron-rich five-membered heterocycles such as thiophene and furan (i.e., the corresponding C2-arylated compounds were obtained in good yields), this protocol led to a poor 2.4/1 C3/C2 regioselectivity when N-methylindole was employed; it is worth noting that N-phenylpyrrole was selectively arylated at the C3 position.

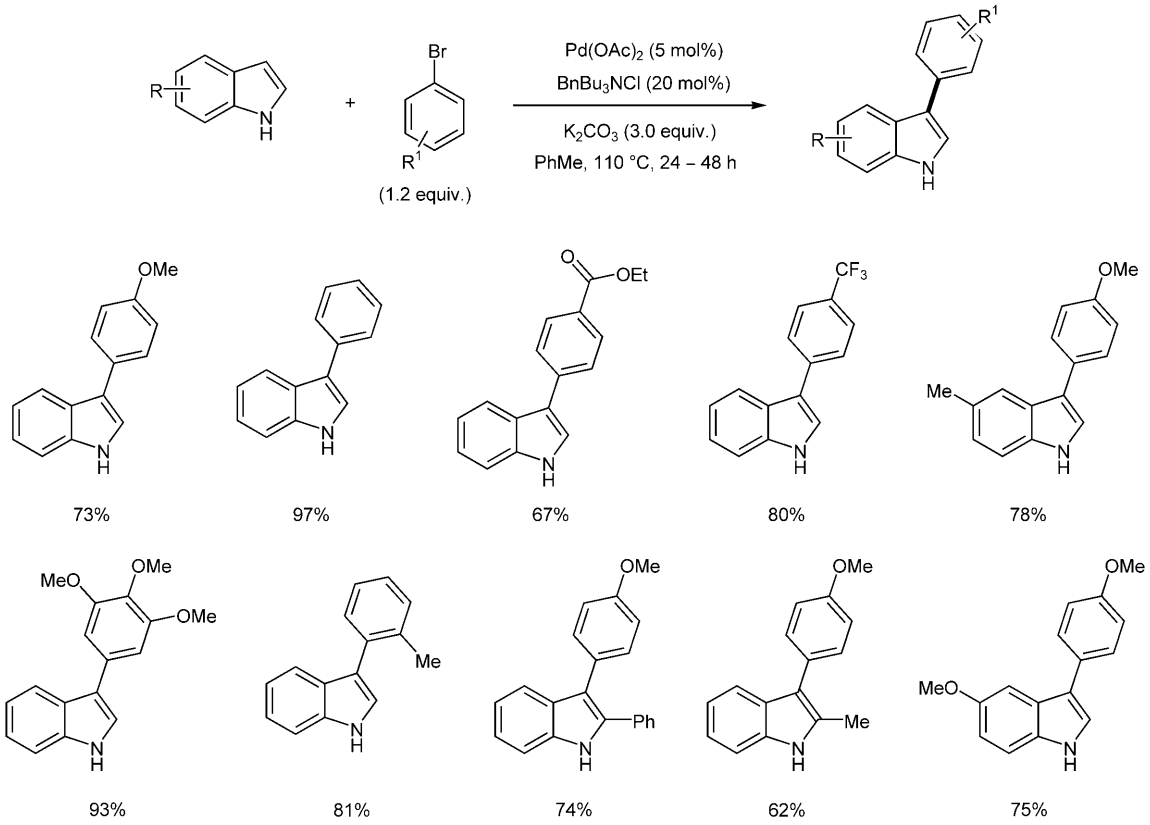


Figure 45. Direct palladium-catalysed C3-arylation of free (NH)-indoles with aryl bromides.

4.3 Copper-Catalysed Procedures

In 1988, Barton and co-workers reported the first copper-catalysed C3-phenylation of indoles with triphenylbismuth(V) bis-trifluoroacetate under very mild conditions [indole (1.0 mmol), $Ph_3Bi(TFA)_2$ (1.0 equiv.), Cu(0) (1 mol%) for indole or $Cu(OAc)_2$ (10 mol%) for 2-methylindole or $Cu(TFA)_2$ (10 mol%) for N-methyl-2-methylindole, CH_2Cl_2, room temperature, 1–24 h.] (Figure 46).[38] The role of the copper catalyst is not clear since arylation of (NH)-indole occurs even in the absence of Cu(0) to afford 3-phenylindole in a moderate 41% isolated yield. A slightly improved yield (i.e., 50%) was achieved by adding 1 mol% of this undefined catalyst. However, when reacting 2-methylindole or N-methyl-2-methylindole, the need for 10 mol% $Cu(OAc)_2$ or $Cu(TFA)_2$ appeared, giving the corresponding C3-phenylindoles in excellent yields.

Recently, Gaunt and co-workers described a copper-catalysed direct and site-selective arylation of indoles[145] with aryliodonium salts depending on the nature of the nitrogen protecting group. It was found that N-methylindole and even (NH)-indole derivatives underwent a clean C3-arylation at room temperature with the catalytic system $Cu(OTf)_2$/dtbpy (while N-acetylindoles afforded the C2 analogues under similar conditions). This cross-coupling process was tolerant with various substituted indoles, bearing either electron-donating or electron-withdrawing groups, when the symmetrical [Ph–I–Ph]X salt was used [Figure 47, Eq. (9)]. The authors also developed the use of unsymmetrical iodonium salts of the general formula [TRIP–I–Ar]OTf, the more sterically bulky 2,4,6-triisopropylphenyl (TRIP) group allowing the exclusive transfer of the desired aryl group (Ar). Under such conditions, high selectivities (up to 20/1 C3/C2) and good yields of the target C3-arylindoles were achieved with either electron-deficient, electron-rich, sterically hindered or heterocyclic aryl moieties [Figure 47, Eq. (10)]. It is noteworthy that aryl substrates bearing C–Br or even C–I bonds were not affected by this copper-catalysed arylation. However, despite the efficiency of this site-selective arylation, the optimisation study is quite surprising regarding 1) the use of 1 mol% $Cu(OAc)_2$ is sufficient to achieve a 57% yield; 2) although the use of dtbpy (2,6-di-*tert*-butylpyridine) prevented indole dimerisation, the conversion (i.e., 14%) and the C3/C2 selectivity were dramatically lower; 3) a comparable 57% yield was obtained by increasing the catalytic amount to 10 mol% while dtbpy was used; 4) replacing $Cu(OAc)_2$ by $Cu(OTf)_2$ slightly improved the yield to 72% and allowed a better selectivity. For all these reasons, the optimisation study is inconsistent given that $Cu(OTf)_2$ has not been evaluated as a single catalyst without the use of dtbpy.

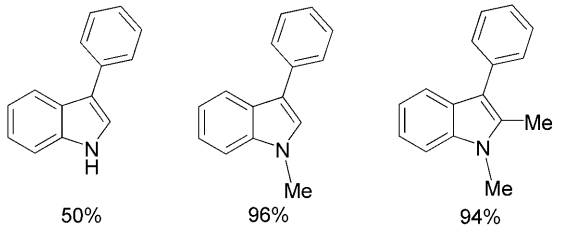


Figure 46. Selective copper-catalysed C3-phenylation of indoles.

4.4 Oxidative Couplings

Recently, Fagnou and co-workers described the use of a Pd(II)/Cu(II) catalytic system for the selective C3 oxidative cross-coupling of N-acetylindoles with arenes.[146] The optimal catalytic reactivity was achieved with $Pd(TFA)_2$ in combination with catalytic quantities of 3-nitropyridine and CsOPiv, superior turnover numbers and reproducibility being associated with the use of these two additives. Under such conditions, a broad range of substituted indoles and arenes gave the desired C3-arylindoles with good C3/C2 regioselectivities (up to 11.2/1) and moderate to high yields (Figure 48). However, despite the scope of this successful and highly challenging chemistry, this procedure still does not represent a competitive alternative to the direct Heck-type coupling of free (NH)-indoles with regard to the complex and drastic reaction conditions (i.e., high catalyst loading, excess of a copper oxidant, additives, microwave heating) as well as the need for an indolic nitrogen protecting group and the use of symmetrical arenes.

5. Mechanisms

5.1 N1-Arylation

Whether or not the N1-arylation is performed with copper- or palladium-based catalysts, mechanisms have been reported in the literature and are today generally accepted.

Initially, the first mechanistic consideration for the copper-catalysed procedure was described by Barton and co-workers who suggested that the copper salts formed *in situ* an indolyl copper(III) species.[38] Cristau and co-workers studied in detail the possible mechanisms of the N1-arylation of indoles catalysed by copper oxide.[59] Based on their experience, the authors support the formation of copper(III) species resulting from an oxidative addition of the aryl halides at the metal centre. The mechanism involves three elementary steps: (i) oxidative addition of the aryl

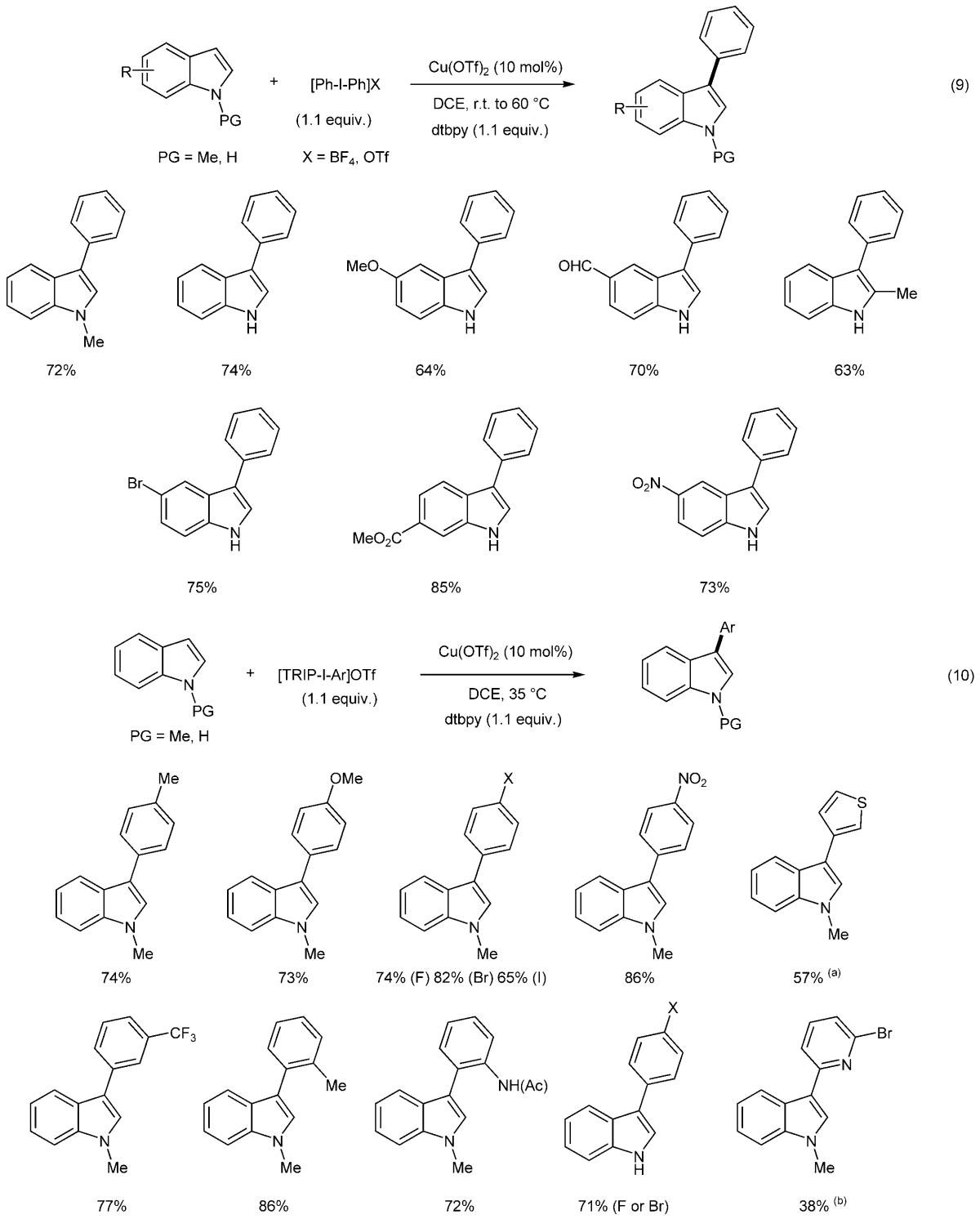


Figure 47. Cu(II)-catalysed C3-arylation of indoles with aryliodonium salts. (a) BF_4 salt at 60 °C; (b) 25 mol% $Cu(OTf)_2$.

halide to copper(I) generating a transient copper(III) species, (ii) nucleophilic substitution of copper-bound halide by the indole anion, and (iii) reductive elimination of the coupling product regenerating the active copper(I) species (Figure 49, a). What is not really clear is to know if the nucleophilic substitution takes place before the oxidative addition step. This mechanism is today generally accepted, and most of the authors consider that the oxidative addition takes place before the nucleophilic substitution as both the reactivity of the aryl halides and the ligand effects in this reaction are better explained thus. This mechanism

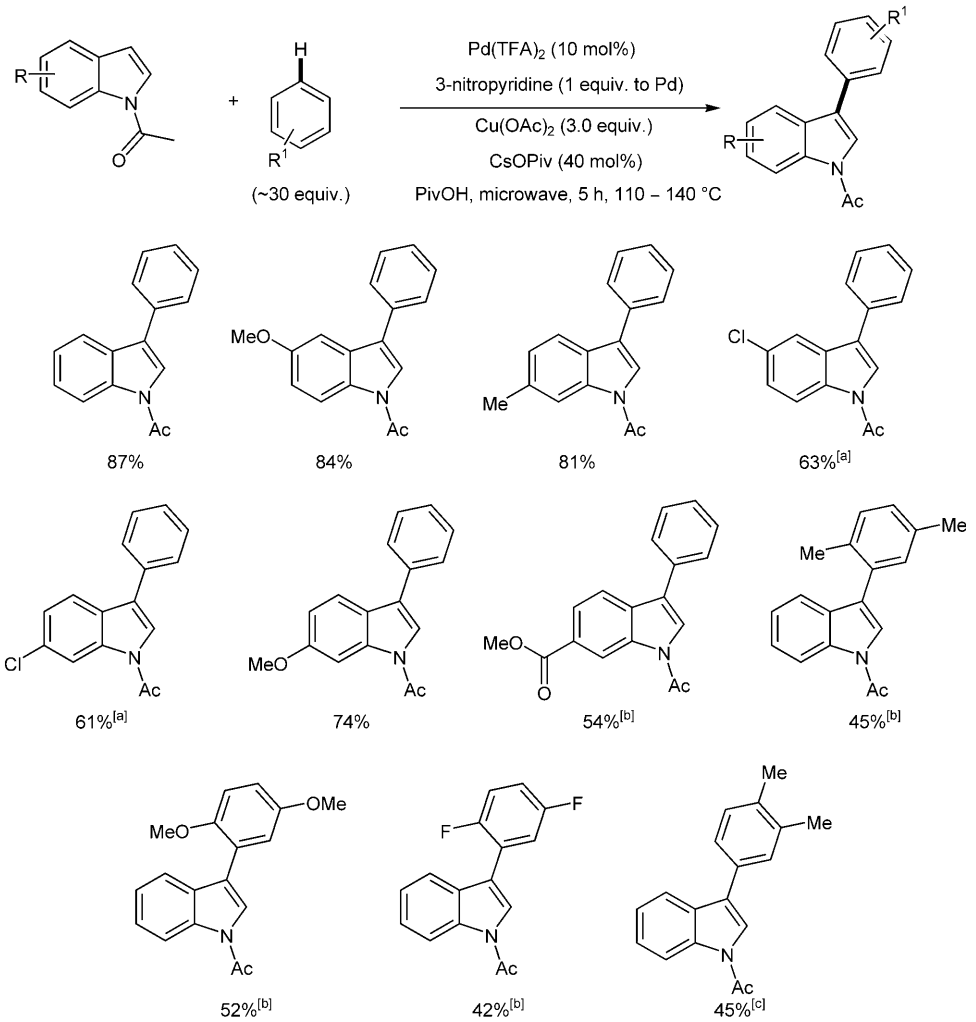


Figure 48. Oxidative site-selective C3-arylation of N-acetylindoles with arenes. [a] Conventional heating in a Schlenk tube due to significant amounts of hydrodechlorination under microwave heating. [b] 20 mol% $Pd(TFA)_2$. [c] 10 mol% $Pd(acac)_2$ under conventional heating.

supports very well the results reported when using heterogeneous catalysts that could run similarly to palladium cross-coupling reactions through dissolved copper species. Additionally, it accounts also for the stoichiometric N1-arylation of indoles involving phenylboronic acids.[147]

Recent investigations from Liu and co-workers indicate that the nucleophilic substitution is the first step in the reaction, based on quantum chemical calculations at the B3LYP/LANL2DZ level as long as imidazoles are considered.[56] However, the results of the calculation did not give the order of the elementary steps but only that the two intermediates considered in this mechanism may exist since the authors have not evaluated the other possibility.

Mechanistically, the palladium-catalysed N1-arylation of indole is similar to the copper-catalysed one. The generally accepted mechanism is related to the Buchwald–Hartwig amination of aryl halides for which intensive studies have been reported and reviewed in recent papers.[28,29,148] It involves (i) the formation of palladium catalytically active species chelated by donor ligands from the precatalyst, (ii) the oxidative addition of the aryl halide on the Pd(0) centre leading to the formation of Pd(II) species, (iii) the indole binding to the metallic centre, (iv) the deprotonation of the chelated amine by the base followed by the halide abstraction generating a palladium-amido complex, and (v) the reductive elimination of coupling products regenerating the active Pd(0) species (Figure 49, b).

5.2 C2- and C3-Arylation through Palladium-Catalysed Cross-Coupling

Both Pd(0)/Pd(II) and Pd(II)/Pd(IV) catalytic cycles have been proposed for the C2/C3-arylation of in-

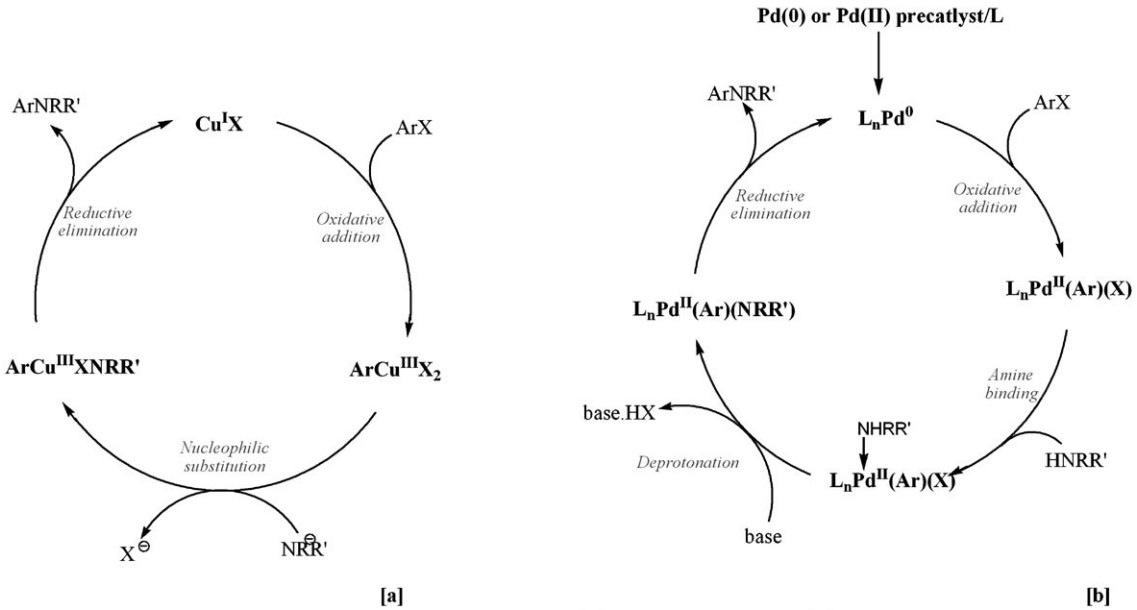


Figure 49. Generally accepted mechanisms for the copper- [**a**] and palladium- [**b**] catalysed N1-arylation of indoles (HNRR′).

doles; however no clear insights have been reported for the latter that is mainly based on related C–H arylations in presence of silver salts in acetic or trifluoroacetic acid at high reaction temperatures. Alternatively, Larrossa and co-workers suggested that under such conditions (silver salts, polar solvent like DMF) the palladium-catalysed C2/C3-arylation of indoles involves cationic Pd(II) species issued from the abstraction of the halide from the metal centre in the presence of silver salts or silver oxide after the oxidative addition step; these species being thus more reactive towards the coordination of the indole ring than the corresponding neutral complexes allowing one to perform the reaction at room temperature.[127]

Nevertheless, the main outcomes concern the Pd(0)/Pd(II) catalytic cycle that was mainly investigated by Sames and co-workers.[132] Except for a few reports that explain the selective C3-arylation through a "pure" S_NAr mechanism, three mechanisms allow rationalisation of the results reported in the literature (Figure 50): (i) the electrophilic metallation/migration, (ii) the non-electrophilic metallation, and (iii) the carbometallation that is very similar to the Heck reaction

Although direct palladation of the indole ring *via* σ-bond metathesis has been reported,[149] it generally requires strong directing groups in order to explain the C2/C3 selectivity and did not account for all results reported. Likewise, the Heck-type mechanism, while feasible and often suggested, can be discarded as it implies an *anti*-deshydrogenation (i.e., *anti*-β-hydride elimination) step that is not conventional (i.e., the Heck mechanism involves a *syn*-β-hydride elimination step) and as it was never supported by experimental observations. Alternatively, a Heck-type mechanism in which an isomerisation to afford an intermediate allowing the *syn*-β-hydride elimination step could also be considered; however while known with other transition metals (i.e., Pt, Ru) such reaction pathways have never been observed with palladium.

As a consequence, the electrophilic metallation/migration appears to be the most reasonable mechanism that explains both the reactivities and the selectivities observed. This mechanism is based on the well established direct electrophilic substitution at the C3-position of the indole ring and implies a 1,2-migration (i.e., C3→C2 migration) of the palladium centre. Based on previous results related to the rhodium-catalysed C2-arylation of indoles,[150] Sames and co-workers investigated this hypothesis in depth for the reaction of indole with iodobenzene catalysed by $Pd(OAc)_2$. After determining the reaction rate for each partner as zero order for iodobenzene and first order for both indole and the catalyst, the authors performed kinetic isotope experiments. Both 3- and 2-*deutero*-N-methylindoles were used in these kinetic experiments giving KIE values of, respectively, 1.6 and 1.2. These rather surprising values encouraged the authors to perform competitive studies using N-methyl- and N-ethylindole derivatives under the reaction conditions used for the arylation of indoles. While different from the kinetic experiments, this method confirms the presence and the magnitude of the KIE. Additionally, the authors investigated the substitution effect on the reaction rate (Hammet plot) for 6-substituted N-methylindoles. A good relationship between the σ°_R values and the rate constants

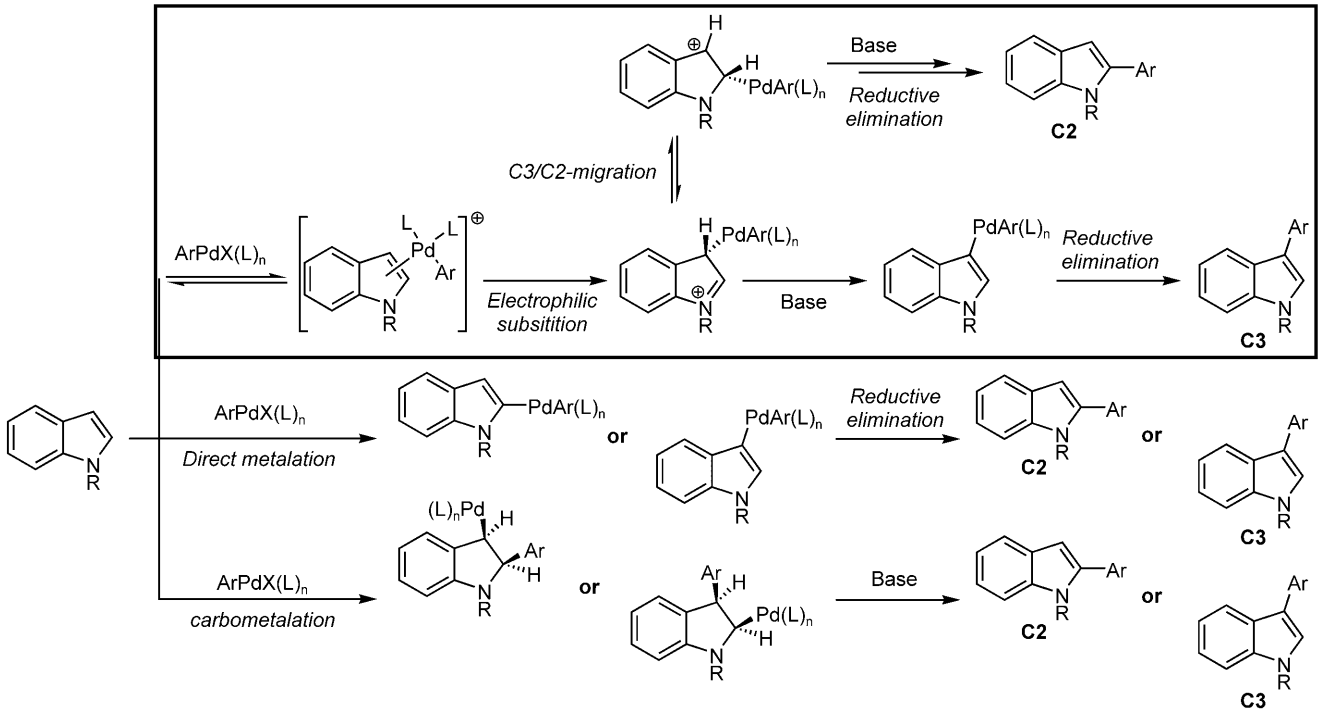


Figure 50. Different plausible reaction pathways (mechanisms) leading either to C2- or C3-arylated indoles. The most reasonable mechanism is outlined.

was observed for almost all evaluated substrates giving a negative ρ value (−0.71) in agreement with a positive charge at the C3 position of the indole ring. All these experiments (i.e., KIE, competitive studies and Hammet plot) support the electrophilic substitution mechanism followed (eventually) by a C3→C2 palladium migration, the driving force for the latter being related to the stabilisation of the carbon-palladium bond by the adjacent nitrogen atom. Both the electrophilic substitution at C3 and/or the C3→C2 palladium migration are considered as the limiting steps of the catalytic cycle; the relative rates accounting for the C2/C3 selectivity. Additional experiments support such an interpretation as the use of both a bulky protecting group at the N1-position and bulky phosphine ligands tends to favour the C3-arylation.

5.3 C2- and C3-Arylation through Oxidative Cross-Coupling

Arylation of indoles by unactivated aromatic compounds (i.e., benzene, xylenes, anisoles, etc. and penta-substituted aromatics) was reported by few groups. This rather recent research area emerged in 2007 and there are significantly less reported results in the literature to help give clear insights. Therefore, all attempted mechanistic explanations, based on few observations, still remain in the range of hypotheses.

Initially, one of the first mechanistic accounts was reported by Fagnou and co-workers.[103,151] Using a catalytic system made from (palladium trifluoroacetate/3-nitropyridine/cesium pivalate) in presence of copper acetate as oxidant, the authors obtained high conversions with high selectivities towards the C3-arylated indoles. Using low palladium loading (i.e., 2 mol%) increased further the selectivity (i.e., 96% for the arylation of N-acetylindole with benzene). Developing further the catalytic system, the authors discovered that they could manage the C2/C3-selectivity. Replacing the $Cu(OAc)_2$ by AgOAc produced an inversion of the selectivity towards the C2-arylated compound (i.e., 90%). Caesium acetate used as additive gave very similar results. The authors ruled out the metallation of the indole nucleus by either the Cu(II) species or the Ag(I) species as no reaction was observed with the corresponding salt used alone. However, the authors suggested that the key of the selectivity is either due to the formation of [Pd/Cu] clusters towards the C3-arylated compounds, or due to the formation of monomeric palladium species as the acetate anion introduced as a silver or caesium salt could induce the cleavage of higher order palladium clusters favouring thus the C2-arylation.

Recently, DeBoef and co-workers reported similar observations.[105] While the use of $Cu(OAc)_2$ favours the C3-arylation of indoles, the use of AgOAc favoured strongly the C2-arylation. Similarly to Fagnou, these authors proposed that the oxidant-controlled se-

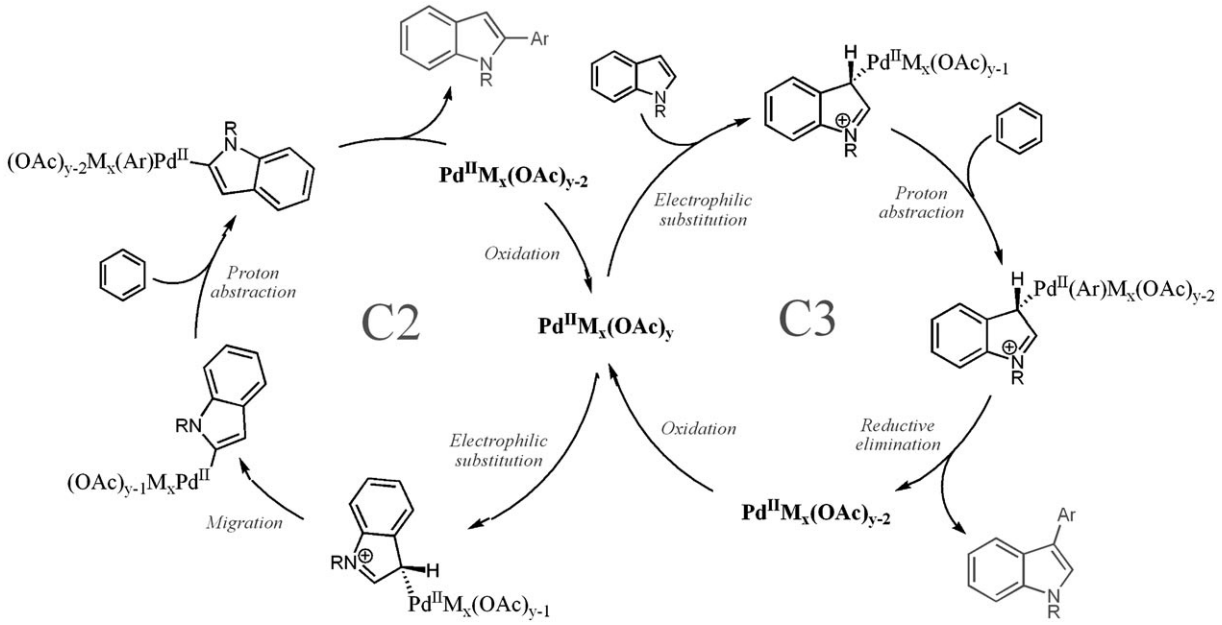


Figure 51. C2- *versus* C3-arylation of indoles by oxidative coupling reaction catalysed by palladium complexes.

lectivity resulted from the formation of poly-(hetero)metallic catalytically active species like [Pd/Cu] or [Pd/Ag] clusters (Figure 51). Attempting to support such explanation by KIE, the authors noted that it was significantly different for both oxidising agents, therefore they concluded that the oxidant is not only present in the metallation of indole step but also in the proton abstraction step as well.

As a comment, it is noteworthy that the catalytic cycle presented by DeBoef is very similar to the electrophilic mechanism reported by Sames and co-workers (see above). The conclusion applied by Sames to rationalise the C2/C3-selectivity through a palladium migration could be applied here as well. Indeed, the initial step of the reaction could be the activation of the aromatic compound followed by intramolecular deprotonation to give *in fine* a $[Pd(II)Ar(OAc)(L)_n]$ complex able to coordinate the indole nucleus leading to electrophilic substitution mechanism with possible C3→C2 palladium migration. At this stage of the investigations reported in the literature we cannot decide upon the "most reasonable" mechanism that can account for the results observed.

6 Concluding Remarks

The development of new catalytic systems for the direct N–H or C–H arylation of the indole core has grown considerably over the last 10 years.

Following their studies on the amination of aryl halides, Buchwald and Hartwig revisited the *old* Ullmann and Goldberg copper-based procedures affording efficient and complementary Cu- and Pd-catalysed solutions for the N1-arylation of indoles. Except for a few developments mainly related to modification of the ligands, we can consider that this area is today mature. Therefore, these valuable tools are of great interest for both academic and industrial chemists.

On the other hand, the C–H arylation of indole remained undeveloped for a long time despite the pioneering works of Ohta in the middle of the 1980s. At the beginning of the 2000s, following the considerable developments on C–H activation, the catalytic and site-selective C2 and C3 arylations experienced new developments mainly under the impule of Sames. Recently, studies have focussed on the development of milder, phosphine-free and room temperature direct C–H activations, conditions achieved by varying the nature of the coupling partners (from iodonium salts to boronic acids) and additives. Lately, Fagnou reintroduced the Pd-catalysed oxidative arene cross-coupling as an alternative to the *classical Heck-type couplings*, avoiding thus the use of stoichiometric activating groups. In this context, the next "generation" of catalytic systems will probably be related to the discovery of fully catalytic procedures avoiding the use of stoichiometric transition metal salts as oxidants similarly to procedures reported for the alkenylation of indoles.[152,153]

Under the light of these 20 years of improvements, we believe that the future of catalytic procedures for the selective arylation of indoles, and more generally heterocycles, will be greatly related to the discovery of industrially attractive heterogeneous catalysts allowing the use of *economic* aryl chlorides and even

unactivated arenes. In our opinion, this area is still in its infancy and we hope that this review will stimulate further work.

Acknowledgements

The authors thank M.-G. and J. Sherman for proof-reading of the manuscript. LJ thanks the CNRS for a grant.

References

[1] P. N. Craig, in: *Comprehensive Medicinal Chemistry*, Vol. 8, (Ed.: C. J. Drayton), Pergamon, New York, **1991**.
[2] M. Negwer, *Organic Drugs and Their Synonyms: An International Survey*, 7th edn., Akademie Verlag, Berlin, **1994**.
[3] S. R. Stabler, Jahangir, *Synth. Commun.* **1994**, *24*, 123.
[4] G. Spadoni, C. Balsamini, A. Bedini, G. Diamantini, B. Di Giacomo, A. Tontini, G. Tarzia, M. Mor, P. V. Plazzi, S. Rivara, R. Nonno, M. Pannacci, V. Lucini, F. Fraschini, B. M. Stankov, *J. Med. Chem.* **1998**, *41*, 3624.
[5] K. Andersen, T. Liljefors, J. Hyttel, J. Perregaard, *J. Med. Chem.* **1996**, *39*, 3723.
[6] R. Sarges, H. R. Howard, B. K. Koe, A. Weissman, *J. Med. Chem.* **1989**, *32*, 437.
[7] S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873.
[8] S. L. Colletti, C. Li, M. H. Fisher, M. J. Wyvratt, P. T. Meinke, *Tetrahedron Lett.* **2000**, *41*, 7825.
[9] L. Chu, J. E. Hutchins, A. E. Weber, J.-L. Lo, Y.-T. Yang, K. Cheng, R. G. Smith, M. H. Fisher, M. J. Wyvratt, M. T. Goulet, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 509.
[10] G. I. Stevenson, A. L. Smith, S. Lewis, S. G. Michie, J. G. Neduvelil, S. Patel, R. Marwood, S. Patel, J. L. Castro, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2697.
[11] Other arylated indoles, that is, on the "benzene ring", represent also a class of interesting compound regarding their biological activities; however their syntheses are still today related to the specific preparation of the starting material by functionalisation at the desired position followed by, generally, a Suzuki–Miyura cross-coupling. To the best of our knowledge, no direct arylation method has been reported to date for their synthesis and therefore, these compounds are not considered here.
[12] S. R. Stabler, Jahangir, *Synth. Commun.* **1994**, *24*, 123.
[13] K. Seki, K. Ohkura, M. Terashima, Y. Kanaoka, *Heterocycles* **1994**, *37*, 993.
[14] W. J. Smith, III, J. S. Sawyer, *Tetrahedron Lett.* **1996**, *37*, 299.
[15] F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382.
[16] I. Goldberg, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.
[17] S. Maiorana, C. Baldoli, P. Del Buttero, M. Di Ciolo, A. Papagni, *Synthesis* **1998**, 735.
[18] C. Baldoli, S. Maiorana, E. Licandro, L. Casiraghi, G. Zinzalla, P. Seneci, E. De Magistris, A. Paio, C. Marchioro, *J. Comb. Chem.* **2003**, *5*, 809.
[19] K. Kamikawa, S. Kinoshita, H. Matsuzaka, M. Uemura, *Org. Lett.* **2006**, *8*, 1097.
[20] K. Kamikawa, S. Kinoshita, M. Furusyo, S. Takemoto, H. Matsuzaka, M. Uemura, *J. Org. Chem.* **2007**, *72*, 3394.
[21] H. Xu, L. Lv, L.-l. Fan, X.-q. He, *Heterocycles* **2008**, *76*, 249.
[22] L. Shi, M. Wang, C.-A. Fan, F.-M. Zhang, Y.-Q. Tu, *Org. Lett.* **2003**, *5*, 3515.
[23] B. Robinson, *The Fischer Indole Synthesis* John Wiley & Sons, Chichester, **1982**.
[24] G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644.
[25] Y.-Q. Fang, M. Lautens, *J. Org. Chem.* **2008**, *73*, 538.
[26] Y.-Q. Fang, M. Lautens, *Org. Lett.* **2005**, *7*, 3549.
[27] C. S. Bryan, M. Lautens, *Org. Lett.* **2008**, *10*, 4633.
[28] David S. Surry, Stephen L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.
[29] J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534.
[30] P. C. Unangst, D. T. Connor, S. R. Stabler, R. J. Weikert, *J. Heterocycl. Chem.* **1987**, *24*, 811.
[31] S. Olgen, E. Akaho, D. Nebioglu, *Eur. J. Med. Chem.* **2001**, *36*, 747.
[32] J. Perregaard, K. Andersen, J. Hyttel, C. Sanchez, *J. Med. Chem.* **1992**, *35*, 4813.
[33] K. Andersen, J. Perregaard, J. Arn, J. B. Nielsen, M. Begtrup, *J. Med. Chem.* **1992**, *35*, 4823.
[34] G. Spadoni, C. Balsamini, A. Bedini, G. Diamantini, B. Di Giacomo, A. Tontini, G. Tarzia, M. Mor, P. V. Plazzi, S. Rivara, R. Nonno, M. Pannacci, V. Lucini, F. Fraschini, B. M. Stankov, *J. Med. Chem.* **1998**, *41*, 3624.
[35] A. Lira-Rocha, O. Espejo-Gonzalez, E. B. Naranjo-Rodriguez, *Eur. J. Med. Chem.* **2002**, *37*, 945.
[36] T. Balle, J. Perregaard, A. K. Larsen, M. T. Ramirez, K. Krojer Soby, T. Liljefors, K. Andersen, *Bioorg. Med. Chem.* **2003**, *11*, 1065.
[37] R. A. Pearlstein, R. J. Vaz, J. Kang, X.-L. Chen, M. Preobrazhenskaya, A. E. Shchekotikhin, A. M. Korolev, L. N. Lysenkova, O. V. Miroshnikova, J. Hendrix, D. Rampe, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1829.
[38] D. H. R. Barton, J. P. Finet, J. Khamsi, *Tetrahedron Lett.* **1988**, *29*, 1115.
[39] Y. Akita, Y. Itagaki, S. Takizawa, A. Ohta, *Chem. Pharm. Bull.* **1989**, *37*, 1477.
[40] T. Zhou, Z.-C. Chen, *Synth. Commun.* **2002**, *32*, 903.
[41] K. Okano, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2003**, *5*, 4987.
[42] T. M. McCormick, Q. Liu, S. Wang, *Org. Lett.* **2007**, *9*, 4087.
[43] A. Correa, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 2673.
[44] A. Correa, C. Bolm, *Angew. Chem.* **2007**, *119*, 9018; *Angew. Chem. Int. Ed.* **2007**, *46*, 8862.
[45] J. W. W. Chang, X. Xu, P. W. H. Chan, *Tehnol. Mesa Tet* **2007**, *48*, 245.
[46] M. Taillefer, N. Xia, A. Ouali, *Angew. Chem.* **2007**, *119*, 952; *Angew. Chem. Int. Ed.* **2007**, *46*, 934.
[47] A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727.
[48] T. Y. H. Wu, P. G. Schultz, *Org. Lett.* **2002**, *4*, 4033.
[49] C. Xie, Y. Zhang, Z. Huang, P. Xu, *J. Org. Chem.* **2007**, *72*, 5431.

[50] J. C. Antilla, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 11684.
[51] F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 793.
[52] S.-K. Kang, D.-H. Kim, J.-N. Park, *Synlett* **2002**, 427.
[53] M. Kuil, E. K. Bekedam, G. M. Visser, A. van den Hoogenband, J. W. Terpstra, P. C. J. Kamer, P. W. N. M. van Leeuwen, G. P. F. van Strijdonck, *Tetrahedron Lett.* **2005**, *46*, 2405.
[54] S. Chandrasekhar, S. S. Sultana, S. R. Yaragorla, N. R. Reddy, *Synthesis* **2006**, 839.
[55] K.-T. Wong, S.-Y. Ku, F.-W. Yen, *Tetrahedron Lett.* **2007**, *48*, 5051.
[56] S. Chen, H. Huang, X. Liu, J. Shen, H. Jiang, H. Liu, *J. Comb. Chem.* **2008**, *10*, 358.
[57] T. Mino, Y. Harada, H. Shindo, M. Sakamoto, T. Fujita, *Synlett* **2008**, 614.
[58] M. Periasamy, P. Vairaprakash, M. Dalai, *Organometallics* **2008**, *27*, 1963.
[59] H.-J. Cristau, P. P. Cellier, J.-F. Spindler, M. Taillefer, *Chem. Eur. J.* **2004**, *10*, 5607.
[60] L. Xu, D. Zhu, F. Wu, R. Wang, B. Wan, *Tetrahedron* **2005**, *61*, 6553.
[61] M. Alam, R. E. Beevers, T. Ceska, R. J. Davenport, K. M. Dickson, M. Fortunato, L. Gowers, A. F. Haughan, L. A. James, M. W. Jones, N. Kinsella, C. Lowe, J. W. G. Meissner, A.-L. Nicolas, B. G. Perry, D. J. Phillips, W. R. Pitt, A. Platt, A. J. Ratcliffe, A. Sharpe, L. J. Tait, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3463.
[62] D. Ma, Q. Cai, *Synlett* **2004**, 128.
[63] Q. Cai, W. Zhu, H. Zhang, Y. Zhang, D. Ma, *Synthesis* **2005**, 496.
[64] H. Zhang, Q. Cai, D. Ma, *J. Org. Chem.* **2005**, *70*, 5164.
[65] W. Deng, Y. F. Wang, C. Zhang, L. Liu, Q. X. Guo, *Chin. Chem. Lett.* **2006**, *17*, 313.
[66] X. Guo, H. Rao, H. Fu, Y. Jiang, Y. Zhao, *Adv. Synth. Catal.* **2006**, *348*, 2197.
[67] H. Rao, Y. Jin, H. Fu, Y. Jiang, Y. Zhao, *Chem. Eur. J.* **2006**, *12*, 3636.
[68] M. Yang, F. Liu, *J. Org. Chem.* **2007**, *72*, 8969.
[69] L. Zhu, P. Guo, G. Li, J. Lan, R. Xie, J. You, *J. Org. Chem.* **2007**, *72*, 8535.
[70] L. Zhu, L. Cheng, Y. Zhang, R. Xie, J. You, *J. Org. Chem.* **2007**, *72*, 2737.
[71] N. S. Nandurkar, M. J. Bhanushali, M. D. Bhor, B. M. Bhanage, *Tetrahedron Lett.* **2007**, *48*, 6573.
[72] F. Xue, C. Cai, H. Sun, Q. Shen, J. Rui, *Tetrahedron Lett.* **2008**, *49*, 4386.
[73] Z. Xi, F. Liu, Y. Zhou, W. Chen, *Tetrahedron* **2008**, *64*, 4254.
[74] Y.-Z. Huang, J. Gao, H. Ma, H. Miao, J. Xu, *Tetrahedron Lett.* **2008**, *49*, 948.
[75] J. Mao, J. Guo, H. Song, S.-J. Ji, *Tetrahedron* **2008**, *64*, 1383.
[76] G. Mann, J. F. Hartwig, f. M. S. Driver, C. Fernandez-Rivas, *J. Am. Chem. Soc.* **1998**, *120*, 827.
[77] J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575.
[78] K. Leonard, W. Pan, B. Anaclerio, J. M. Gushue, Z. Guo, R. L. DesJarlais, M. A. Chaikin, J. Lattanze, C. Crysler, C. L. Manthey, B. E. Tomczuk, J. J. Marugan, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2679.
[79] M. Watanabe, M. Nishiyama, T. Yamamoto, Y. Koie, *Tetrahedron Lett.* **2000**, *41*, 481.
[80] D. W. Old, M. C. Harris, S. L. Buchwald, *Org. Lett.* **2000**, *2*, 1403.
[81] X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653.
[82] C. J. Smith, M. W. S. Tsang, A. B. Holmes, R. L. Danheiser, J. W. Tester, *Org. Biomol. Chem.* **2005**, *3*, 3767.
[83] F. R. Wuest, T. Kniess, *J. Labelled Compd. Radiopharm.* **2005**, *48*, 31.
[84] M. Romero, Y. Harrak, J. Basset, L. Ginet, P. Constans, M. D. Pujol, *Tetrahedron* **2006**, *62*, 9010.
[85] G. A. Grasa, M. S. Viciu, J. Huang, S. P. Nolan, *J. Org. Chem.* **2001**, *66*, 7729.
[86] K. R. Reddy, N. S. Kumar, B. Sreedhar, M. L. Kantam, *J. Mol. Catal. A: Chem.* **2006**, *252*, 136.
[87] M. L. Kantam, B. P. C. Rao, B. M. Choudary, R. S. Reddy, *Synlett* **2006**, 2195.
[88] M. L. Kantam, J. Yadav, S. Laha, B. Sreedhar, S. Jha, *Adv. Synth. Catal.* **2007**, *349*, 1938.
[89] L. Rout, S. Jammi, T. Punniyamurthy, *Org. Lett.* **2007**, *9*, 3397.
[90] Y.-Z. Huang, H. Miao, Q.-H. Zhang, C. Chen, J. Xu, *Catal. Lett.* **2008**, *122*, 344.
[91] B.-X. Tang, S.-M. Guo, M.-B. Zhang, J.-H. Li, *Synthesis* **2008**, 1707.
[92] V. H. Jadhav, D. K. Dumbre, V. B. Phapale, H. B. Borate, R. D. Wakharkar, *Catal. Commun.* **2007**, *8*, 65.
[93] G. Chouhan, D. Wang, H. Alper, *Chem. Commun.* **2007**, 4809.
[94] W. Chen, Y. Zhang, L. Zhu, J. Lan, R. Xie, J. You, *J. Am. Chem. Soc.* **2007**, *129*, 13879.
[95] W. W. K. R. Mederski, M. Lefort, M. Germann, D. Kux, *Tetrahedron* **1999**, *55*, 12757.
[96] H. Sano, T. Noguchi, A. Tanatani, Y. Hashimoto, H. Miyachi, *Bioorg. Med. Chem.* **2005**, *13*, 3079.
[97] O. Cruz-Lopez, J. J. Diaz-Mochon, J. M. Campos, A. Entrena, M. T. Nunez, L. Labeaga, A. Orjales, M. A. Gallo, A. Espinosa, *ChemMedChem* **2007**, *2*, 88.
[98] H. Bekolo, *Can. J. Chem.* **2007**, *85*, 42.
[99] F. Bellina, C. Calandri, S. Cauteruccio, R. Rossi, *Eur. J. Org. Chem.* **2007**, 2147.
[100] T. Itahara, *J. Chem. Soc. Chem. Commun.* **1981**, 254.
[101] T. Itahara, T. Sakakibara, *Synthesis* **1978**, 607.
[102] T. Itahara, *Synthesis* **1979**, 151.
[103] D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072.
[104] T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn, B. DeBoef, *Org. Lett.* **2007**, *9*, 3137.
[105] S. Potavathri, A. S. Dumas, T. A. Dwight, G. R. Naumiec, J. M. Hammann, B. DeBoef, *Tetrahedron Lett.* **2008**, *49*, 4050.
[106] Y. Akita, A. Inoue, K. Yamamoto, A. Ohta, T. Kurihara, M. Shimizu, *Heterocycles* **1985**, *23*, 2327.
[107] T. Sakamoto, Y. Kondo, N. Takazawa, H. Yamanaka, *Heterocycles* **1993**, *36*, 941.
[108] M. Amat, S. Hadida, J. Bosch, *Tetrahedron Lett.* **1993**, *34*, 5005.

[109] E. J. Griffen, D. G. Roe, V. Snieckus, *J. Org. Chem.* **1995**, *60*, 1484.
[110] T. Sakamoto, Y. Kondo, N. Takazawa, H. Yamanaka, *J. Chem. Soc. Perkin Trans. 1* **1996**, 1927.
[111] M. Amat, S. Hadida, G. Pshenichnyi, J. Bosch, *J. Org. Chem.* **1997**, *62*, 3158.
[112] M. Amat, N. Llor, G. Pshenichnyi, J. Bosch, *ARKIVOC* **2002**, 73.
[113] Q.-D. Liu, M. S. Mudadu, R. Thummel, Y. Tao, S. Wang, *Adv. Func. Mater.* **2005**, *15*, 143.
[114] M. Amat, S. Hadida, S. Sathyanarayana, J. Bosch, *Tetrahedron Lett.* **1996**, *37*, 3071.
[115] M. A. Pena, J. P. Sestelo, L. A. Sarandeses, *J. Org. Chem.* **2007**, *72*, 1271.
[116] M. Ishikura, I. Agata, N. Katagiri, *J. Heterocycl. Chem.* **1999**, *36*, 873.
[117] M. Murase, K. Watanabe, T. Kurihara, S. Tobinaga, *Chem. Pharm. Bull.* **1998**, *46*, 889.
[118] M. Ishikura, Y. Matsuzaki, I. Agata, *Heterocycles* **1997**, *45*, 2309.
[119] M. Ishikura, M. Terashima, *J. Chem. Soc. Chem. Commun.* **1989**, 135.
[120] B. S. Lane, D. Sames, *Org. Lett.* **2004**, *6*, 2897.
[121] N. S. Nandurkar, M. J. Bhanushali, M. D. Bhor, B. M. Bhanage, *Tetrahedron Lett.* **2008**, *49*, 1045.
[122] B. B. Toure, B. S. Lane, D. Sames, *Org. Lett.* **2006**, *8*, 1979.
[123] N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972.
[124] X. Wang, D. V. Gribkov, D. Sames, *J. Org. Chem.* **2007**, *72*, 1476.
[125] F. Bellina, S. Cauteruccio, R. Rossi, *Eur. J. Org. Chem.* **2006**, *2006*, 1379.
[126] F. Bellina, C. Calandri, S. Cauteruccio, R. Rossi, *Tetrahedron* **2007**, *63*, 1970.
[127] N. Lebrasseur, I. Larrosa, *J. Am. Chem. Soc.* **2008**, *130*, 2926.
[128] J. Zhao, Y. Zhang, K. Cheng, *J. Org. Chem.* **2008**, *73*, 7428.
[129] Shang-Dong Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, *Angew. Chem.* **2008**, *120*, 1495; *Angew. Chem. Int. Ed.* **2008**, *47*, 1473.
[130] X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996.
[131] R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172.
[132] B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050.
[133] Z. Zhang, Z. Hu, Z. Yu, P. Lei, H. Chi, Y. Wang, R. He, *Tetrahedron Lett.* **2007**, *48*, 2415.
[134] J. Fournier Dit Chabert, L. Joucla, E. David, M. Lemaire, *Tetrahedron* **2004**, *60*, 3221.
[135] E. David, J. Lejeune, S. Pellet-Rostaing, J. Schulz, M. Lemaire, J. Chauvin, A. Deronzier, *Tetrahedron Lett.* **2008**, *49*, 1860.
[136] L. Djakovitch, V. Dufaud, R. Zaidi, *Adv. Synth. Catal.* **2006**, *348*, 715.
[137] L. Djakovitch, P. Rouge, R. Zaidi, *Catal. Commun.* **2007**, *8*, 1561.
[138] G. Cusati, L. Djakovitch, *Tetrahedron Lett.* **2008**, *49*, 2499.
[139] F. Bellina, F. Benelli, R. Rossi, *J. Org. Chem.* **2008**, *73*, 5529.
[140] T. Jeffery, *Tetrahedron* **1996**, *52*, 10113.
[141] C. Gozzi, L. Lavenot, K. Ilg, V. Penalva, M. Lemaire, *Tetrahedron Lett.* **1997**, *38*, 8867.
[142] J. Fournier Dit Chabert, C. Gozzi, M. Lemaire, *Tetrahedron Lett.* **2002**, *43*, 1829.
[143] J. Fournier dit Chabert, B. Marquez, L. Neville, L. Joucla, S. Broussous, P. Bouhours, E. David, S. Pellet-Rostaing, B. Marquet, N. Moreau, M. Lemaire, *Bioorg. Med. Chem.* **2007**, *15*, 4482.
[144] S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748.
[145] R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172.
[146] D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172.
[147] S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.
[148] A. R. Muci, S. L. Buchwald, *Top. Curr. Chem. Top. Cur. Chem.* **2002**, *219*, 133.
[149] S. Tollari, F. Demartin, S. Cenini, G. Palmisano, P. Raimondi, *J. Organomet. Chem.* **1997**, *527*, 93.
[150] X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996.
[151] D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172.
[152] L. Djakovitch, P. Rouge, *J. Mol. Catal. A: Chem.* **2007**, *273*, 230.
[153] L. Djakovitch, P. Rouge, *Catal. Today* **2009**, *140*, 90.

