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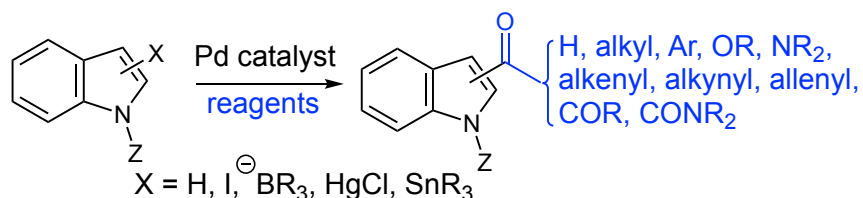
Carbonylated indoles from Pd^{II}-catalyzed intermolecular reactions of indolyl cores

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Abstract This review summarizes the Pd-catalyzed carbonylation, transmetalation and cross-coupling reactions which lead to carbonylated indoles from indoles and indolyl compounds. Special attention is drawn to procedures involving the C(sp²)-H substitution of free (NH)-indoles or (N-substituted)-indoles. Proposed mechanisms are described with, in some cases, personal comments.

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Key words Acylation, Carbonylation, Palladium, Catalysis, Indoles

1. Introduction

Indole chemistry received particularly strong interest due to the various biological and pharmaceutical properties of

functionalized indoles.^{1,2} Palladium catalysis has been strongly involved in the preparation of indole derivatives.³ The Pd-catalyzed C(sp²)-H substitutions of free (NH)-indoles and (N-alkyl)-indoles occur predominantly at C3, while the C2-reactions mainly arise from indoles bearing a regiodirecting group at the nitrogen atom. Such chelation assistance may also lead to activation of the C7-H bond. The regioselectivity may nevertheless depend on the solvent,⁴ additives,⁵⁻⁷ ligands⁸ and acidity of the reaction medium.^{9,10} Reaction at other positions requires indole derivatives as starting substrates. Significant investigations concerned the Pd-catalyzed functionalization of the indole nucleus with a carbonylated tether. They occur via carbonylation or cross-coupling reactions, and are the matter of the present review.

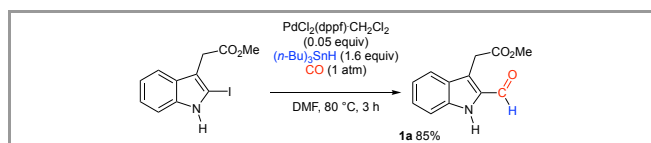
2. Carbonylative reactions

The Pd-catalyzed carbonylative functionalizations of indoles arise from interactions of Pd species with either an indole derivative or a C(sp²)-H bond of the indolyl core.

2.1. Indolyl halides as starting substrates

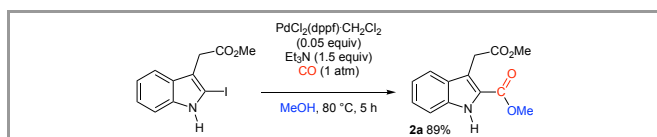
Under an atmosphere of carbon monoxide, Pd catalysis and various experimental conditions, N-unprotected and N-protected iodo- or bromoindoles afford the corresponding carbonylpalladium complex which may evolve towards

- Carbaldehyde **1a** by reduction with tri-*n*-butyltin hydride (Scheme 1),¹¹



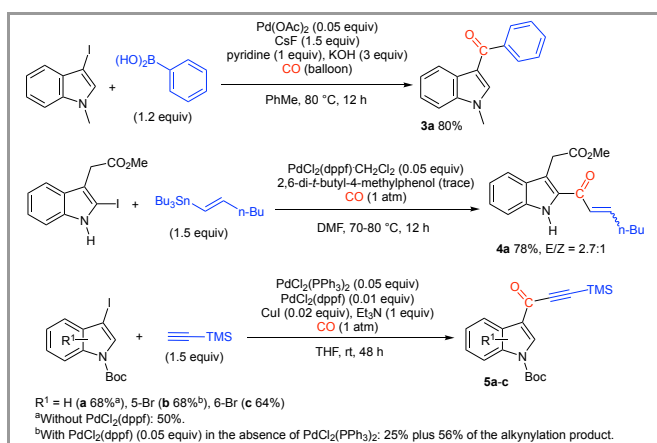
Scheme 1 Formylation of methyl 2-(2-iodo-1H-indol-3-yl)acetate

- Methyl ester **2a** by methanolysis (Scheme 2),¹¹



Scheme 2 Alkoxy-carbonylation of methyl 2-(2-iodo-1H-indol-3-yl)acetate

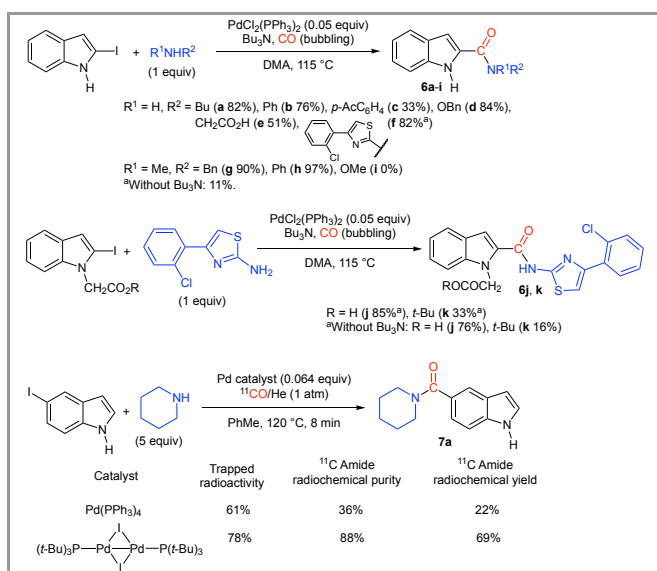
- Ketones **3a**, **4a** and **5a-c** by reaction with phenylboronic acid,¹² (*E*)-tributyl(hex-1-en-1-yl)stannane,¹¹ or ethynyltrimethylsilane, respectively (Scheme 3).¹³



Scheme 3 Ketones from iodoindoles, CO and various reagents

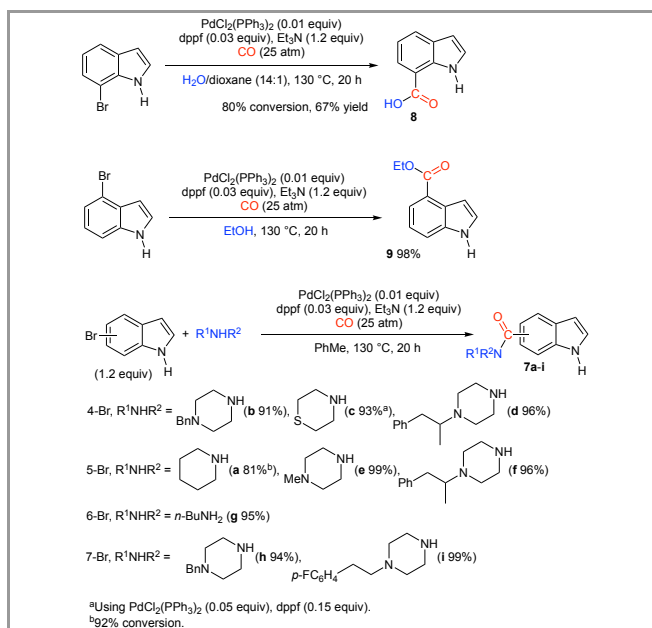
or

- Indolyl carboxamides **6a-k** by reaction with a primary or secondary amine (Scheme 4).¹⁴ The strategy has been applied to the synthesis of ¹¹C-radiolabelled amides **7a** for positron emission tomography imaging (Scheme 4).¹⁵



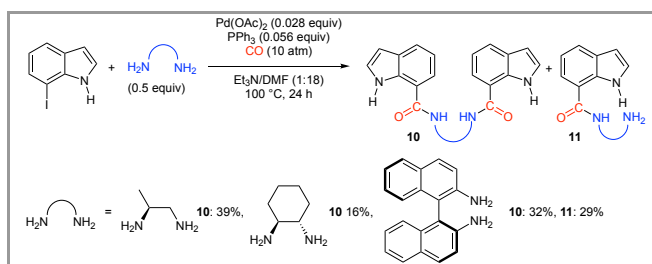
Scheme 4 Indolyl carboxamides from iodoindoles, CO and amines

Pd-catalyzed carboxylation, alkoxy-carbonylation and aminocarbonylation of bromoindoles were performed under 25 bar CO pressure (Scheme 5), large yield decrease occurring under 10 bar pressure.¹⁶



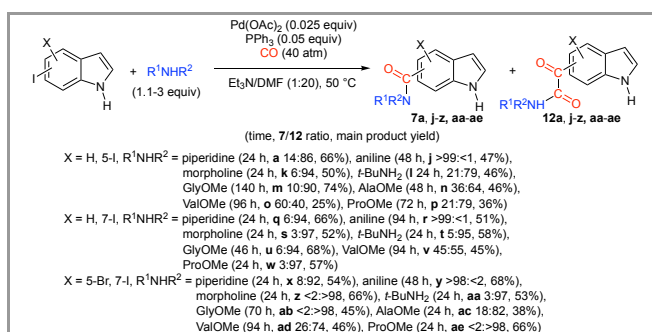
Scheme 5 Carboxylation, alkoxy-carbonylation and aminocarbonylation of bromoindoles

In the presence of diamines, palladium-catalysed carbonylation of 7-iodoindole under 10 bar CO pressure led mainly to carboxamide dimers **10** (Scheme 6).¹⁷



Scheme 6 Carboxamide dimers from 7-iodoindole, CO and diamines

α -Ketoamides **12a, j-z, aa-ae** were the major compounds obtained from the Pd-catalyzed reaction of unprotected iodoindoles using 40 bar CO pressure and a variety of amines except aniline, the low basicity of the latter leading mainly to the monocarbonylation coupling products **7** (Scheme 7).¹⁷ It is interesting to point out that the bromoaryl moiety of 5-bromo-7-iodoindole remained intact under the used conditions (Scheme 7).

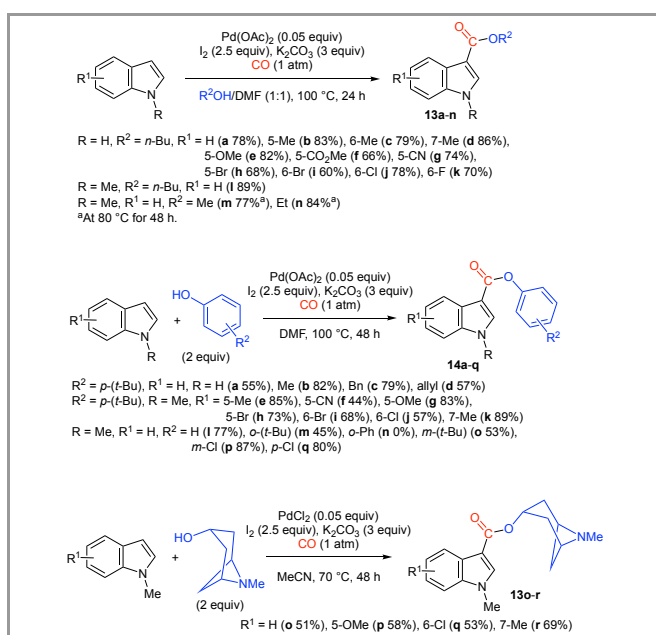


Scheme 7 α -Ketoamides from iodoindoles, CO and amines

2.2. Indolyl iodides as intermediates

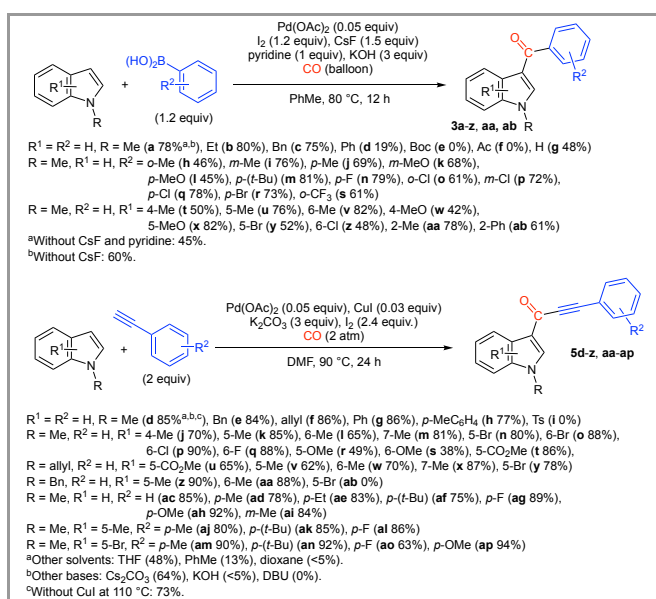
Molecular iodine in a basic media has been used as one of the reagents of copper-catalyzed arylations of C(sp²)-H bonds.¹⁸ Its role is the transformation of the C(sp²)-H bond into the corresponding C(sp²)-I bond which then reacts with the catalyst. This strategy has been applied to the Pd-catalyzed functionalization of the C(3)-H of indoles through a domino iodination/carbonylation/cross-coupling reaction. Thus, *N*-protected or unprotected indoles led to corresponding

- alkyl esters **13a-n** and aryl esters **14a-q** (Scheme 8),¹⁹ that methodology being conveniently applied to the synthesis of biologically active tropisetron **13o** (Scheme 8),¹⁹



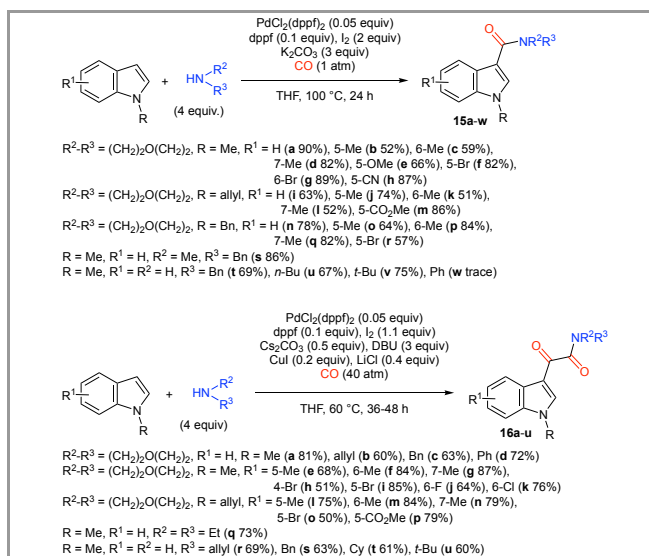
Scheme 8 Indolyl carboxylates from indoles, CO and alcohols

- aryl ketones **3a-z**, **aa**, **ab**¹² and alkyneones **5d-z**, **aa-ap** (Scheme 9),²⁰



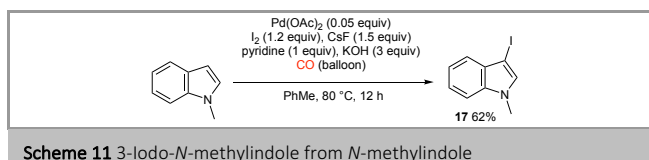
Scheme 9 Aryl and acetylenic ketones from indoles, CO and boronic acids or alkynes

- amides **15a-w**,²¹ or α -ketoamides **16a-u** under increased CO pressure (Scheme 10).²¹



Scheme 10 Amides and α -ketoamides from indoles, CO and amines

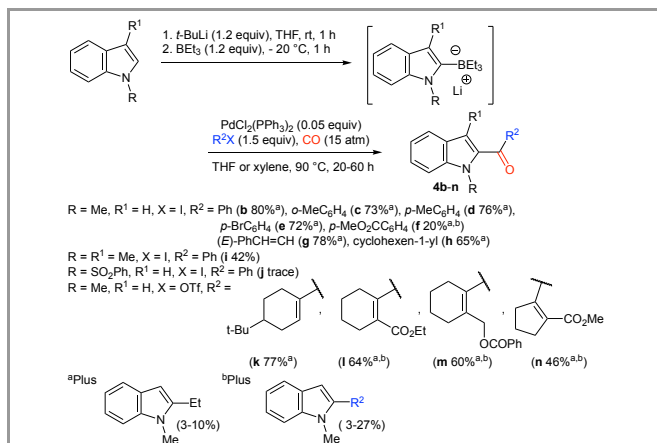
The use of copper iodide as co-catalyst for the synthesis of **5** and **16** could favor the iodination step. Indeed, the C3-iodination of indole with CuI has been recently reported.²² The formation of 3-iodo-*N*-methylindole **17** from *N*-methylindole under experimental conditions leading to **3** (Scheme 9) except the presence of an aromatic boronic acid (Scheme 11),¹² and its reaction with CO and phenylboronic acid (Scheme 3) are consistent with 3-iodoindoles as intermediates of the above domino reactions.



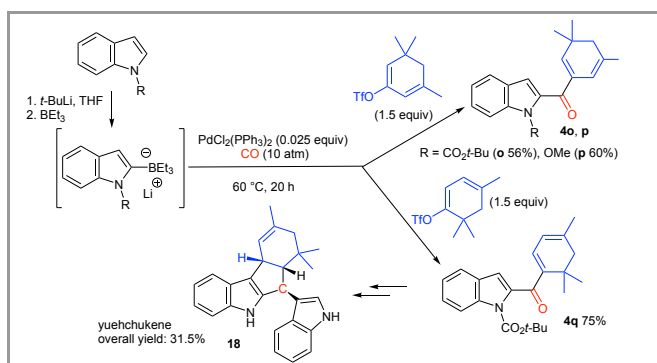
Scheme 11 3-Iodo-*N*-methylindole from *N*-methylindole

2.3. Indolyl borates as intermediates

In 1994, Ishikura and Terashima disclosed the one-pot reaction of *N*-substituted indoles leading to 2-acyl derivatives **4b-n** via the Pd-catalyzed carbonylation of *in situ* produced indolylborates and the subsequent cross-coupling with aryl or alkenyl iodides as well as alkenyl triflates (Scheme 12).²³ The procedure was then used for carbonylative cross-coupling with dienyl triflates providing a way to the total synthesis of yuehchukene **18** (Scheme 13).²⁴ The latter would be a “lead compound for the design of drugs to treat infertility and breast cancer”.²⁴

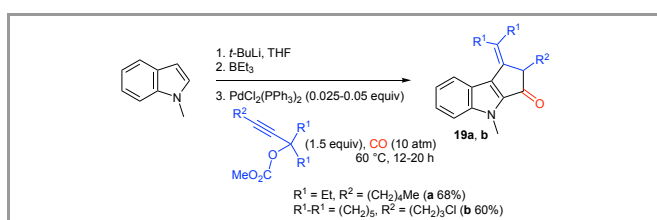


Scheme 12 Ketones from *N*-substituted indoles, CO and aryl or alkenyl derivatives



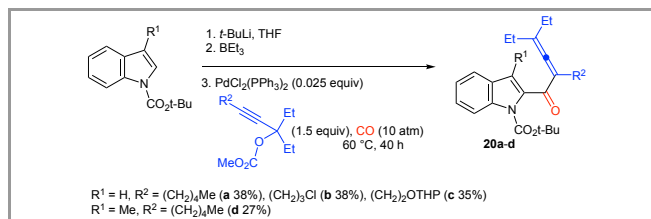
Scheme 13 Ketones from *N*-substituted indoles, CO and dienyl triflates

Interestingly, *N*-methyl indole underwent a cascade reaction with prop-2-ynyl carbonates involving the intramolecular nucleophilic addition of the C3 carbon of indole to the internal allenic carbon, leading to cyclopenta[*b*]indoles **19a, b** (Scheme 14), which are basic frameworks of indole alkaloids.^{25,26}



Scheme 14 Cyclopenta[*b*]indoles from *N*-methylindole, CO and prop-2-ynyl carbonates

Substitution of the *N*-atom with an electron withdrawing group suppressed the nucleophilicity of the C3-carbon, precluding the domino reaction, thus leading to allenyl ketones **20a-d** (Scheme 15).²⁶

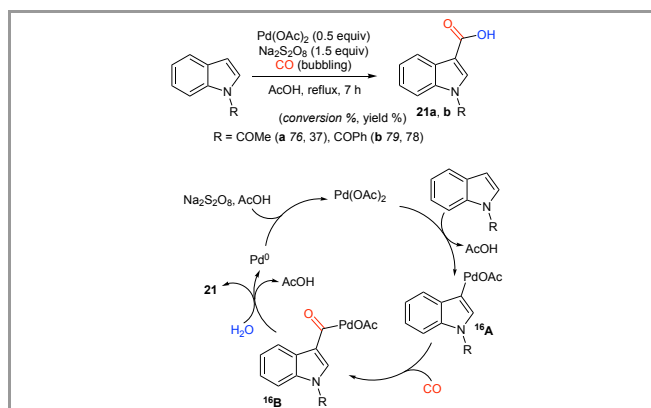


Scheme 15 Allenyl ketones from *tert*-butyl 1*H*-indole-1-carboxylate, CO and prop-2-ynyl carbonates

2.4. C(sp²)-H reactions

2.4.1. Carboxylation

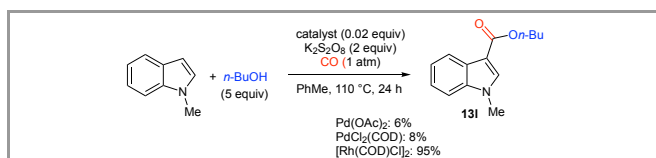
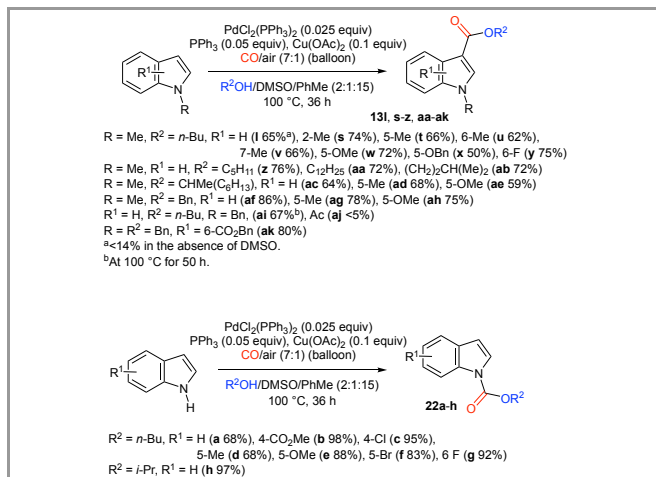
In 1982, Itahara disclosed the Pd-catalyzed C3-carboxylation of *N*-acylindoles using carbon monoxide atmosphere in AcOH, and sodium peroxydisulfate to regenerate active Pd^{II} species (Scheme 16).²⁷ We suspect that the reaction mixture contained trace of water. Thus, the reaction would arise from C3-H activation leading to palladium indolyl complex **16A** (Scheme 16). Carbonylation of the latter affords **16B**, which undergoes hydrolysis to deliver product **21**.



Scheme 16 C3-Carboxylation of *N*-acylindoles and plausible catalytic cycle

2.4.2. Carbonylative alkoxylation

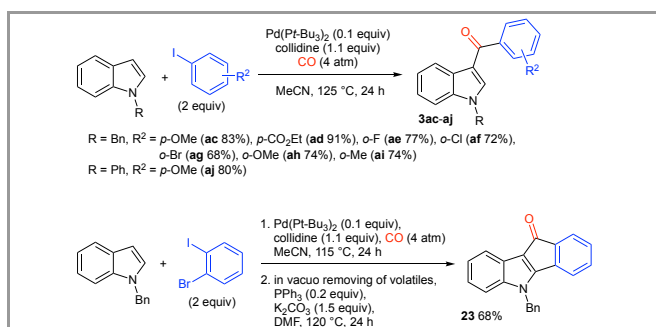
In 2011, the teams of Xia-Li²⁸ and Lei²⁹ independently reported the C3-alkoxycarbonylation of *N*-substituted indoles. Conditions similar to those of the above carboxylation (Scheme 16), except butanol as reagent and toluene as solvent, were inefficient, but shifting to a rhodium catalyst provided good yields of **131** (Scheme 17).²⁸ An effective Pd procedure was nevertheless proposed by Lei and co-workers: various ethyl *N*-methyl(or benzyl)indole-3-carboxylates **131, s-z, aa-ak** were obtained in fair yields with PdCl₂(PPh₃)₂ as the catalyst and Cu(OAc)₂/air in DMSO/toluene (Scheme 18).²⁹ *N*-acetylindole was reluctant to react under the latter conditions (Scheme 18), while unprotected indoles underwent the *N*-H alkoxylation to afford **22a-h** (Scheme 18).²⁹ The C3-alkoxycarbonylation occurs via the alcoholysis of **II**. Apparently, DMSO is involved in the regeneration of active Pd^{II} species, its absence provoking a drastic yield depreciation (Scheme 18). Such a role of DMSO has been initially disclosed by Larock's team.³⁰

Scheme 17 Rhodium-catalyzed alkoxycarbonylation of *N*-methylindole

Scheme 18 Palladium-catalyzed C3- and NH-alkoxycarbonylation of indoles

2.4.3. Carbonylative arylation.

In 2015, Arndtsen and Tjutrins disclosed the synthesis of 3-aryl *N*-phenyl(or benzyl)indoles **3ac-aj** from the Pd(*Pt*-Bu₃)₂-catalyzed reaction of corresponding *N*-substituted indoles with carbon monoxide and aryl iodides (Scheme 19).^{31,32} A one-pot reaction generating polycyclic compound **23** was carried out with *o*-bromiodobenzene as arylating agent, the carbonylative C-H functionalization being followed by an intramolecular Heck reaction (Scheme 19).

Scheme 19 Ketones and cyclic ketones from *N*-substituted indoles, CO and aryl iodides

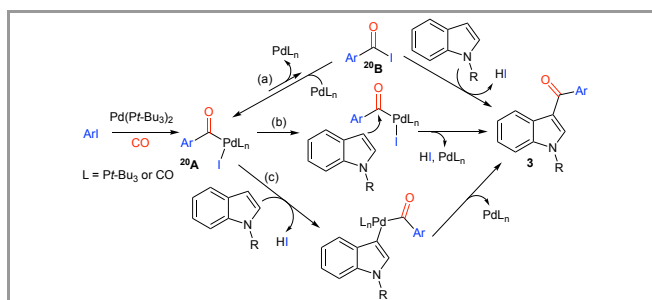
Three plausible reactive pathways were retained for the carbonylative arylation (Scheme 20);³¹ the palladium aroyl complex **20A** formed as intermediate could

- lead to aroyl iodide **20B** which would add to the substrate (path *a*),
- suffer addition of the substrate to its aroyl ligand (path *b*),

or

- undergo a reaction analog to the Pd-catalyzed arylation of indoles (path *c*).

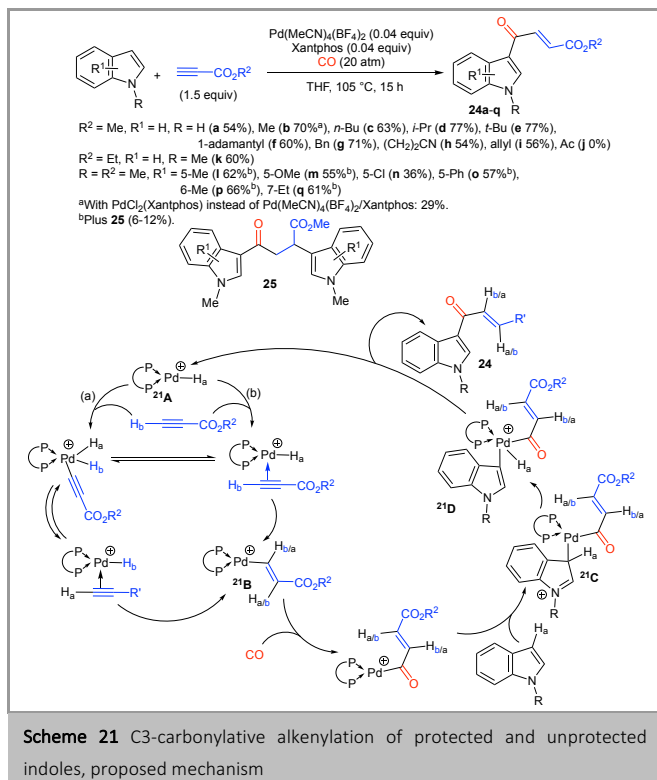
The authors assumed that **IV** reacts with PdL_n rather than with the substrate, hence a disadvantage for path *a*. We suggest that path *c* can be discarded because the Pd-catalyzed arylation of *N*-methylindole with phenyl chloride³³ or *p*-bromotoluene³⁴ occurred selectively or mainly in C2 position. Path *c* also disagrees with the recent report of the absence of coupling between *N*-methylindole and nonanoyl chloride in the presence of catalytic amounts of PdCl₂, Xantphos and *p*-TsOH at 120 °C in PhMe.³⁵ The formation of the C3-substituted product **3** from Friedel-Crafts acylation of *N*-substituted indoles^{34,36} is consistent with path *b*.



Scheme 20 Proposed mechanisms for the carbonylative arylation reaction

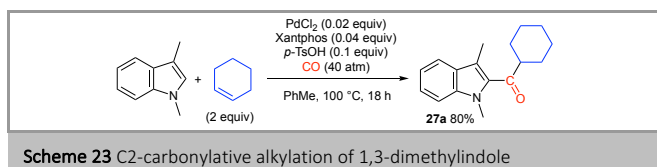
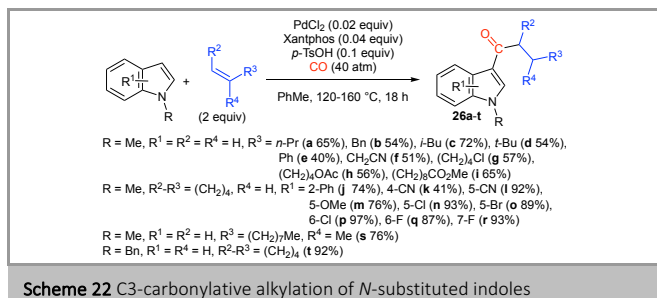
2.4.4. Carbonylative alkenylation

A number of catalytic systems was tested by Alper and Zeng to perform the coupling of indoles with carbon monoxide and methyl or ethyl propiolates.³⁷ Except from *N*-acetylindole, good yields of α,β -unsaturated ketones **24a-i, k-q** were obtained using a cationic complex, Pd(MeCN)₄(BF₄)₂, associated to Xantphos (Scheme 21). The catalyst may also promote the subsequent addition of the substrate to the α,β -unsaturated ketone, giving compound **25**. Mechanism studies using *N*-methyl-3-D-indole and methyl 3-D-propiolate led to propose the formation of the active cationic palladium hydride complex **21A** (Scheme 21).³⁸ According to the deuterium distribution in deuterium-labeling reactions, two parallel pathways - *a* and *b* - are responsible for the formation of the alkenylpalladium intermediate **21B**. Carbonylation of the latter followed by nucleophilic attack of the indole affords **21C**. Subsequent rearomatization of the indole unit provides Pd^{IV} complex **21D**, which is reduced to **21A** by forming product **24**.



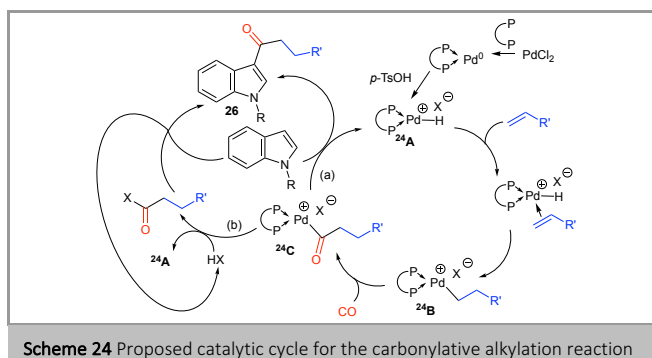
2.4.5. Carbonylative alkylation.

Recently, Beller and co-workers reported the C3-acylation of *N*-methyl(or benzyl)indoles with carbon monoxide and alkenes using catalytic amounts of PdCl_2 , Xantphos and *p*-TsOH in toluene (Scheme 22).³⁵ Low amounts of the C2-acylation product were detected. Such a coupling product was efficiently obtained from 1,3-dimethylindole (Scheme 23).

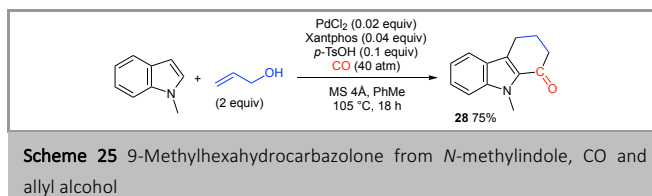


The authors envisaged three catalytic cycles leading to the C3-acylation. Two of them involve the reduction of PdCl_2 by the phosphine and subsequent reaction with *p*-TsOH to provide the hydride complex **24A** (Scheme 24). Coordination of the alkene to **24A** leads to alkylpalladium intermediate **24B** which coordinates CO to afford acylpalladium complex **24C**. The product would be obtained from **24C** via either nucleophilic attack of the indole (Scheme 24, path *a*) as depicted in Schemes 20 (path *b*) and 21, or formation of the acyl halide or acid followed by Friedel-Crafts

reaction (Scheme 24, path *b*). Pathway *b* was discarded because the coupling product was not detected using nonanoyl chloride or acid instead of the corresponding alkene under the same experimental conditions. The third suspected catalytic cycle started with Pd^{II} -mediated C3-H activation of the indole to afford the 3-indolyl palladium complex as depicted in Scheme 16. After reaction of the latter with CO and the alkene, protonolysis will give the product. Kinetic experiments have shown that, in contrast to Pd^0 , Pd^{II} catalyst led to a large induction period. These results are incompatible with the initial C-H activation of the indole. Thus, the most likely pathway is, as for the above carbonylative arylation and alkenylation, the nucleophilic attack of the indole to the cationic acylpalladium complex (Scheme 24, path *a*).

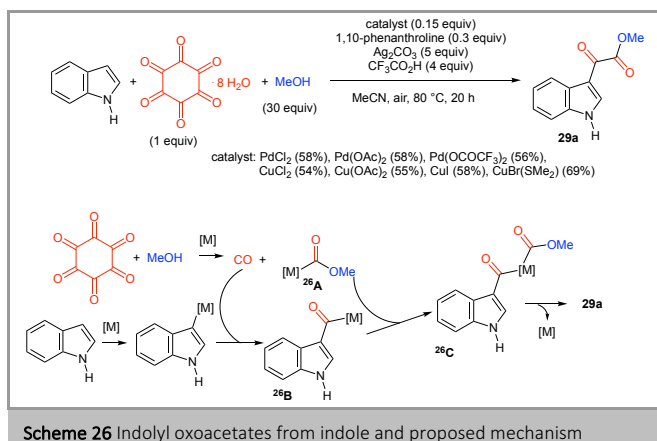


The Pd-catalyzed reaction between *N*-methylindole, CO and allyl alcohol afforded tricyclic ketone **28** (Scheme 25). That occurs through C3-allylation^{39,40} and subsequent intramolecular carbonylation.³⁵



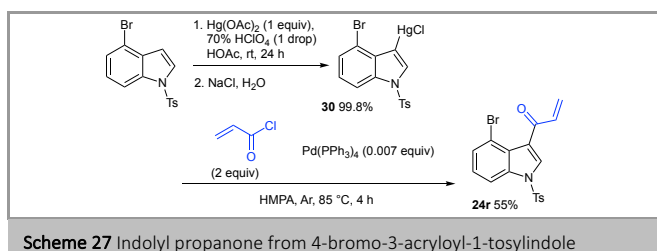
2.4.6. Double carbonylation

Recently, the double carbonylation of indole leading to methyl 2-(1*H*-indol-3-yl)-2-oxoacetate **29a** was reported by Wu and co-workers.⁴¹ Various Pd and Cu catalysts were efficient with hexaketocyclohexane octahydrate as the CO source, $\text{CuBr}(\text{SME})_2$ providing the best yield (Scheme 26). Transition metal-catalyzed decomposition of hexaketocyclohexane in the presence of methanol would afford carbon monoxide and carboalkoxy complex **26A**. Transmetalation of the latter with alkoxy complex **26B** leads to **26C**; subsequent reductive elimination produces the double carbonylation product.

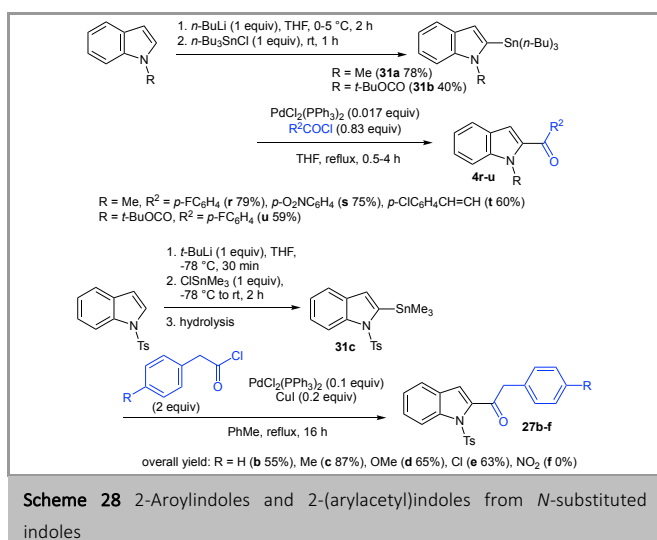


3. Stannyl- and mercurioindoles cross-couplings

In 1989, Hegedus team disclosed the two steps-synthesis of 4-bromo-3-acryloyl-1-tosylindole **24r** (Scheme 27).⁴² 4-Bromo-1-tosylindole was firstly transformed into the mercurioindole **30**.⁴³ Treatment of the latter with acryloyl chloride and catalytic Pd(PPh₃)₄ led to **24r**. That occurs via oxidative addition of the acid chloride to Pd⁰, Hg^{II}/Pd^{II} transmetalation and reductive elimination.^{42,44}



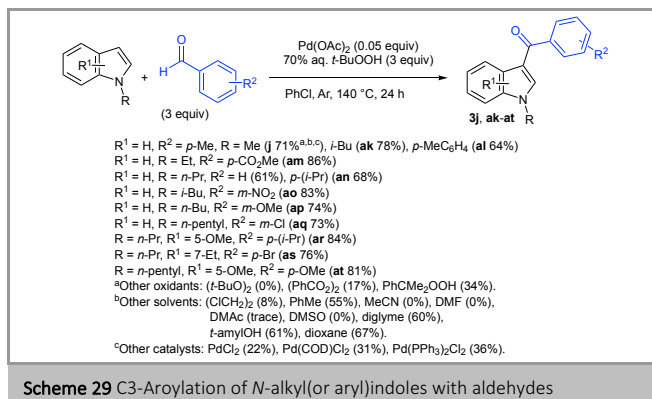
2-Aroylindoles **4r-u** and 2-(arylacetyl)indoles **27b-f** were obtained via Pd-catalyzed cross-couplings of aroyl chlorides or arylacetyl chlorides with *N*-substituted indol-2-ylstannanes **31a-c** obtained from lithiation of the corresponding indoles, and subsequent trapping of the 2-lithio species with a trialkyltin chloride⁴⁵ (Schemes 28).^{46,47} Such procedures involve also transmetalation and subsequent reductive elimination of Pd⁰.⁴⁸



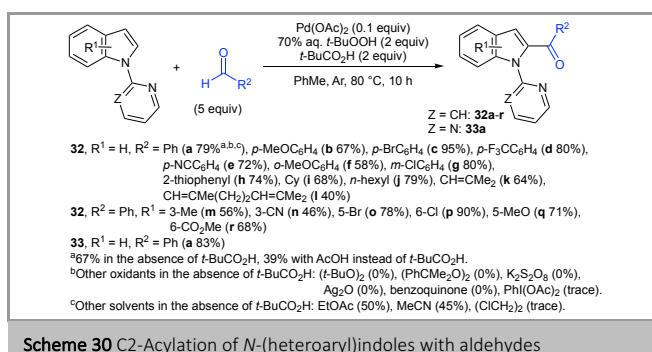
4. Cross-coupling of indoles with:

4.1. Aldehydes

In 2013, Kianmehr and co-workers reported the Pd(OAc)₂-catalyzed the C3-arylation of *N*-alkyl(or aryl)indoles using benzaldehydes and *t*-BuOOH at 140 °C in chlorobenzene (Scheme 29).⁴⁹ Efficiency of the process greatly decreased using other solvents, peroxides or catalysts.

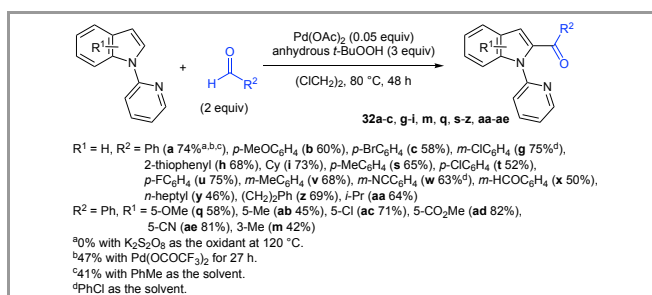


A few months later, the C2-acylation was disclosed by Liu's team using a 2-pyridinyl or 2-pyrimidinyl directing group and again *t*-BuOOH as the most optimal oxidant (Scheme 30).⁵⁰ The reaction was carried at 80 °C in toluene, with pivalic acid as additive to improve the efficiency. The latter may stabilize Pd-indole species¹⁰ and may inhibit side reactions.⁵¹

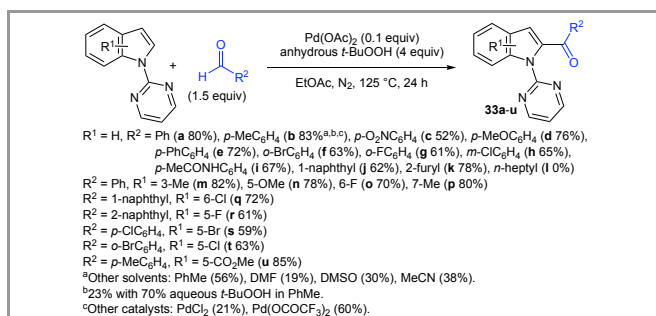


Pd(OAc)₂ catalysis, anhydrous *t*-BuOOH and a variety of aldehydes were then used in the absence of pivalic acid for the C2-acylation of

- *N*-(pyridin-2-yl)indoles in 1,2-dichloroethane or chlorobenzene at 80 °C (Scheme 31),⁵²



- *N*-(pyrimidin-2-yl)indoles in ethyl acetate at 125 °C (Scheme 32),⁵³

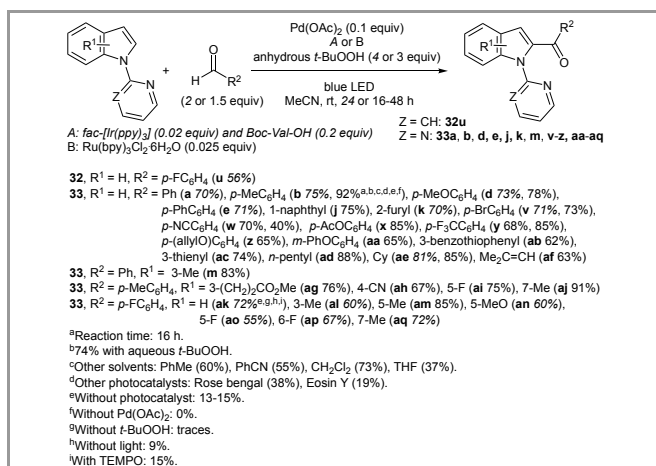


Scheme 32 C2-Acylation of *N*-(pyrimidin-2-yl)indoles with aldehydes

and

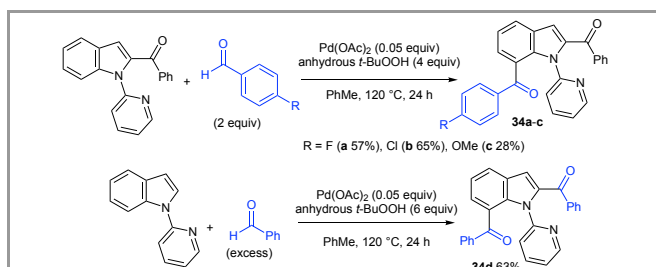
- *N*-(pyridin-2-yl)indoles and *N*-(pyrimidin-2-yl)indoles at room temperature in acetonitrile under visible light photoredox assistance (Scheme 33).^{54,55}

As above exemplified, the yields strongly depend on the experimental conditions.



Scheme 33 C2-Acylation of *N*-(pyrimidin-2-yl)indoles under visible light photoredox assistance

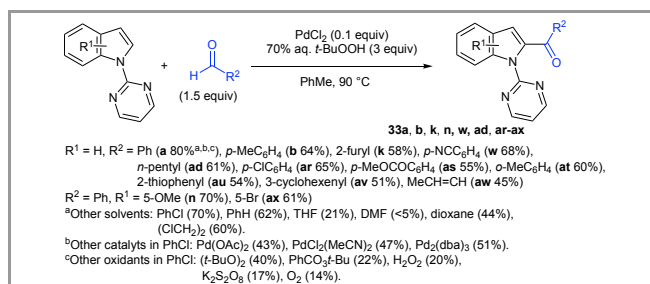
N-(Pyridin-2-yl)indoles **34a-d** acylated in 2 and 7 positions have been synthesized using the Pd(OAc)₂/*t*-BuOOH system as well (Scheme 34).⁵²



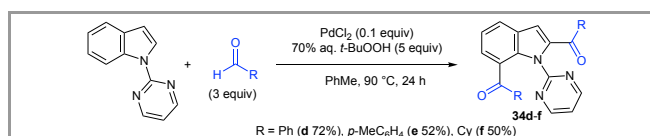
Scheme 34 C2 and C7-Acylation of *N*-(pyridine-2-yl)indoles with aldehydes

In contrast to the above low efficiency of the PdCl₂-catalyzed acylations (Schemes 29 and 32), Sekar and Kumar obtained better results in the C2-acylation of *N*-(pyrimidin-2-yl)indoles with PdCl₂ instead of Pd(OAc)₂ as the catalyst (Scheme 35).⁵⁶

They also carried out the C2,C7-diacylation using a threefold excess of aldehyde (Scheme 36).

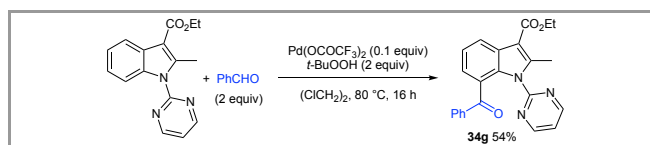


Scheme 35 C2-Acylation of *N*-(pyrimidin-2-yl)indoles with aldehydes



Scheme 36 C2,C7-Diacylation of *N*-(pyrimidin-2-yl)indoles with aldehydes

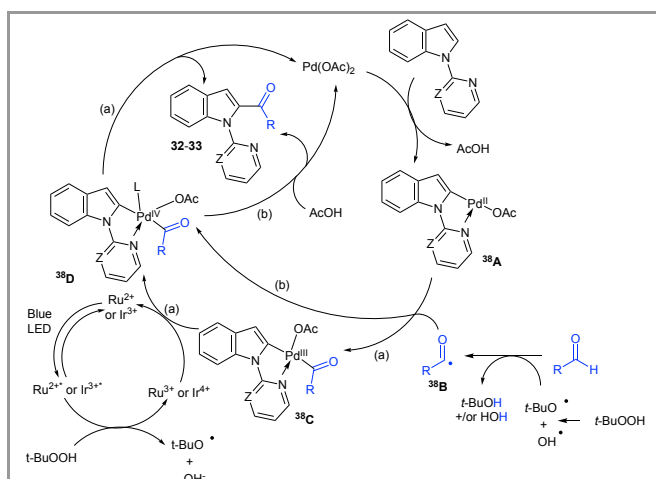
The C7-benzylation of ethyl 2-methyl-1-(pyrimidin-2-yl)-1*H*-indole-3-carboxylate was performed using Pd(OAcF₃)₂ as the catalyst in 1,2-dichloroethane (Scheme 37).⁵⁷



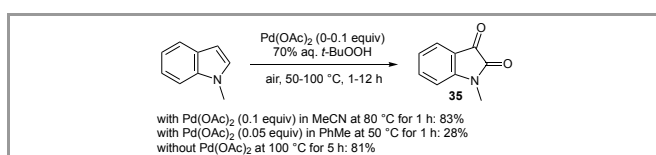
Scheme 37 C7-Benzylation of ethyl 2-methyl-1-(pyrimidin-2-yl)-1*H*-indole-3-carboxylate with benzaldehyde

In the absence of a chelating substituent, the reaction occurs via the complex **I** (Scheme 16)⁴⁹ while ligation of the 2-pyridinyl or 2-pyrimidinyl group to palladium directs towards the formation of chelated complex **38A** (Scheme 38).^{50,52-55} The latter reacts with acyl radical **38B** which is formed from the reaction of the aldehyde with *tert*-butoxy^{49,50,53} or hydroxy^{53,58} radical. Heat-mediated homolytic cleavage of *t*-BuOOH leads to these two radicals.^{50,53,58} *t*-BuO[•] may also be produced at room temperature via the oxidation of the excited state of Ir³⁺ or Ru²⁺ by *t*-BuOOH (Scheme 38).^{54,55} The proposal of acyl radical **38B** is consistent with its trapping with radical scavenger TEMPO,^{54,55} leading to concomitant large decrease of yields.^{50,53,55} According to the Van der Eycken and Jana teams, the reaction of **38A** with **38B** leads to Pd^{III} complex **38C** which is oxidized with the photoredox system into Pd^{IV} complex **38D** (path *a*). Subsequent reductive elimination affords products **32-33** and active Pd^{II} species.^{54,55} The other procedures were also carried out with *t*-BuOOH, but at 80-140 °C instead of both room temperature and photoredox assistance. Kianmehr and co-workers assumed that, under these conditions, **38A** would react with **38B** "to afford the Pd^{IV} intermediate" (path *b*).⁴⁹ They nevertheless involved AcOH in the regeneration of the Pd^{II} catalyst.⁴⁹ According to Zhang's team which studied different acylation reactions, a Pd^{IV} species could be formed from the addition of both acyl and *t*-butoxy radicals to a Pd^{II} complex.⁵⁸ Liu and co-workers also proposed contribution of the acid in the catalyst regeneration⁵⁰ but, like the teams of Zhang and Tan,^{52,53} they noted that III or IV would

be the plausible oxidation state of the acyl palladium complex delivering the product. Thus, the mechanism remains a matter of debate. We suspect that the role of *t*-BuOOH under photoredox-free conditions is not limited to the formation of **38B**: it could participate in the regeneration of the catalyst and, if any, in the formation of the Pd^{IV} intermediate. Apparently, the presence of the acylating agent precludes the oxidation of the indole into the corresponding isatin **35**, a reaction subsequently reported with⁵⁹ and without⁶⁰ Pd catalysis (Scheme 39).



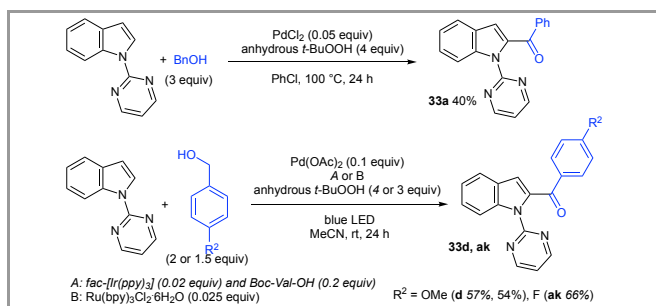
Scheme 38 Proposed mechanism for the C2-acylation of *N*-pyridinyl or *N*-pyrimidinyl indoles with aldehydes



Scheme 39 Formation of isatin from 1-methylindole

4.2. Alcohols

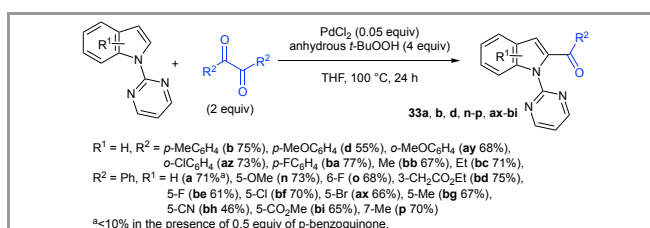
The C2-arylation of *N*-(pyrimidin-2-yl) indole with benzylic alcohols and *t*-BuOOH occurs either at 100 °C under PdCl₂ catalysis⁶¹ or at room temperature using the Pd(OAc)₂/photoredox procedure (Scheme 40).^{55,62} The benzylic alcohols would be oxidized into the corresponding aldehydes under the reaction conditions, hence a mechanism leading to the coupling products as depicted in Scheme 38 would operate. The alcohol oxidation with the Pd(OAc)₂/*t*-BuOOH association was proposed,⁵⁵ but a previous report assumed the Pd(OAc)₂-free oxidation of benzyl alcohol with *t*-BuOOH.⁶³



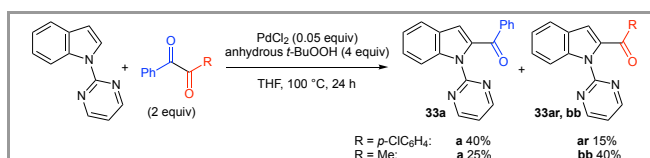
Scheme 40 C2-Arylation of *N*-(pyrimidin-2-yl) indole with benzylic alcohols

4.3. α -Diketones

The PdCl₂/*t*-BuOOH system led to the C2-acylation of *N*-(pyrimidin-2-yl)indoles with a variety of α -diketones (Scheme 41). Asymmetric α -diketones provided a mixture of the two acylated coupling products **33** (Scheme 42).⁶¹ Homolytic cleavage of OC-CO bond of the diketone by *t*-BuOOH would lead to acyl radicals which, as above, would add to **XV** (see Scheme 38). In agreement with this proposal, only traces of the acylated indole were produced in the presence of *p*-benzoquinone as a radical scavenger (Scheme 41).



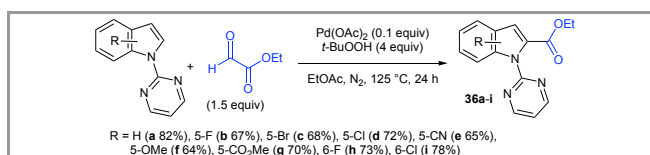
Scheme 41 Ketones from *N*-(pyrimidin-2-yl)indoles and symmetric α -diketones



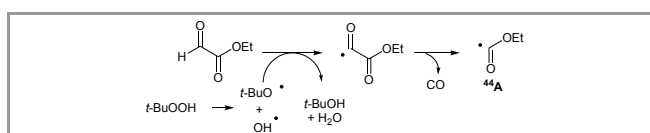
Scheme 42 Mixture of ketones from *N*-(pyrimidin-2-yl)indoles and asymmetric α -diketones

4.4. α -Oxo esters

Use of Pd(OAc)₂ catalysis and *t*-BuOOH at 125 °C in EtOAc allowed the coupling reaction of *N*-(pyrimidin-2-yl)indoles with ethyl glyoxylate to afford the corresponding ethyl 2-indole carboxylates **36a-i** (Scheme 43).⁵³ The CO₂Et radical **44A** *in situ* produced as depicted in Scheme 44 coordinates to a palladium chelate such as **38A** (see Scheme 38) to afford a Pd^{III} or Pd^{IV} intermediate which evolves towards the product.



Scheme 43 Indolyl carboxylates from *N*-(pyrimidin-2-yl)indoles and ethyl glyoxylate

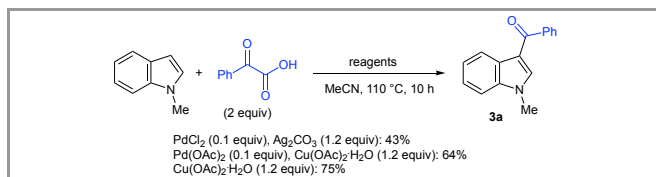


Scheme 44 Formation of the CO₂Et radical

4.5. α -Oxocarboxylic acids

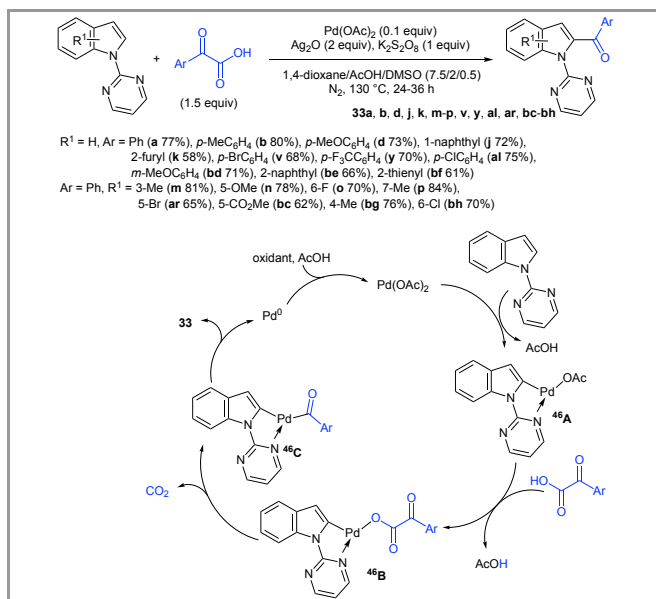
In the presence of a catalytic amount of PdCl₂ and a stoichiometric quantity of Ag₂CO₃, *N*-methylindole reacted with benzoylformic acid to afford 3-benzoyl-*N*-methylindole **3a** (Scheme 45).⁶⁴ Changing for Pd(OAc)₂ and Cu(OAc)₂ increased

the yield, but the best result was finally obtained using only the copper salt.



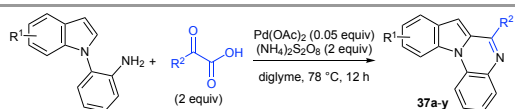
Scheme 45 3-Benzoyl-*N*-methylindole from *N*-methylindole and benzoylformic acid

$\text{Pd}(\text{OAc})_2$ catalysis was nevertheless used to prepare a number of 2-(hetero)aroyl-*N*-(pyrimidin-2-yl)indoles **33** from the corresponding indoles and α -oxocarboxylic acids in the presence of stoichiometric amounts of Ag_2O and $\text{K}_2\text{S}_2\text{O}_8$, at 130 °C in a 1,4-dioxane/AcOH/DMSO mixture (Scheme 46).⁶⁵ These syntheses could only involve the $\text{Pd}^{\text{II}}/\text{Pd}^0$ redox catalytic cycle (Scheme 46). The anion exchange affords **46A** from palladacycle **46A**. Subsequent decarboxylation leads to **46C**,⁶⁶ which suffers reductive elimination delivering the product and Pd^0 . The oxidative medium assumes the regeneration of Pd^{II} species. According to Zhu and co-workers, "the possibility of a $\text{Pd}^{\text{II}}-\text{Pd}^{\text{IV}}$ mechanism could not be thoroughly ruled out".⁶⁵



Scheme 46 C2-(Hetero)arylation of *N*-(pyrimidin-2-yl)indoles with α -oxocarboxylic acids and proposed mechanism

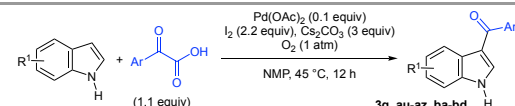
The Jiang and Ji team recently disclosed an efficient domino reaction leading to indolo[1,2-*a*]quinazolines **37a-y** via the palladium-catalyzed decarboxylative annulation of 2-(1*H*-indol-1-yl)anilines with 2-oxo-2-arylacetic acids (Scheme 47).⁶⁷ The best results were obtained in diglyme with $\text{Pd}(\text{OAc})_2$ as the catalyst and $(\text{NH}_4)_2\text{S}_2\text{O}_8$ as the oxidant. The reaction also occurred in 1,4-dioxane, but failed in DMSO, DMF and toluene or using 2-oxohexanoic acid instead of an aroylformic acid. The amine group of the substrate directs the C2-arylation, and then reacts with the carbonyl group to deliver water and the annulation product. The good yields of **37a** also isolated in the presence of radical scavengers (Scheme 47) agree with the mechanism of the arylation depicted in Scheme 46.



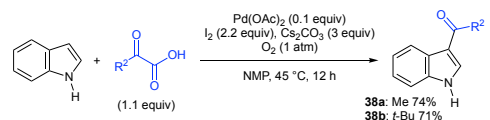
$\text{R}^2 = \text{Ph}$, $\text{R}^1 = \text{H}$ (**a** 81%^{a,b}), 3- Me (**b** 79%), 4- Cl (**c** 75%), 4- F (**d** 72%), 4- OMe (**e** 80%), 4- OBn (**f** 78%), 5- CN (**g** 54%), 5- F (**h** 74%), 5- OMe (**i** 78%), 6- F (**j** 73%), 6- OMe (**k** 82%), 7- F (**l** 35%^c)
 $\text{R}^1 = \text{H}$, $\text{R}^2 = o\text{-MeC}_6\text{H}_4$ (**m** 83%), *o*- FC_6H_4 (**n** 79%), *o*- BrC_6H_4 (**o** 63%), *m*- BrC_6H_4 (**p** 74%), *m*- FC_6H_4 (**q** 82%), *m*- MeOC_6H_4 (**r** 85%), *p*- MeC_6H_4 (**s** 80%), *p*- ClC_6H_4 (**t** 72%), *p*- BrC_6H_4 (**u** 67%), *p*- MeOC_6H_4 (**v** 82%), 1-naphthyl (**w** 73%), 2-furyl (**x** 66%), benzothiophen-2-yl (**y** 75%), *n*- Bu (**z** 0%)
^aOther solvents: 1,4-dioxane (69%), DMSO (0%), DMF (0%), PhMe (0%).
^b76-80% in the presence of TEMPO or BHT (3 equiv).
^cWith 4 equiv of the ketoacid.

Scheme 47 Decarboxylative annulations of 2-(1*H*-indol-1-yl)anilines

The $\text{Pd}(\text{OAc})_2$ -catalyzed C3-acylation of (NH)-indoles with α -oxocarboxylic acids was carried out using over-stoichiometric amounts of both I_2 and Cs_2CO_3 at 45 °C in *N*-methylpyrrolidone under oxygen (Scheme 48).⁶⁸ Gu and co-workers proposed the formation of 3-iodoindole as intermediate (see Section 2.2). Palladation of the latter would afford the iodopalladium complex. Subsequent exchange of I^- for $\text{R}^2\text{COCO}_2^-$ is followed by decarboxylation and reductive elimination to give the product. Thus, the proposed mechanism has strong similarities with that of Scheme 46. Nevertheless, the authors attributed the oxidation state IV to the indolylpalladium intermediates.



$\text{R}^1 = \text{H}$, $\text{Ar} = \text{Ph}$ (**g** 82%^a), *o*- MeC_6H_4 (**au** 79%), *m*- BrC_6H_4 (**av** 73%), *p*- MeOC_6H_4 (**aw** 77%), *p*- ClC_6H_4 (**ax** 76%), *p*- $\text{O}_2\text{NC}_6\text{H}_4$ (**ay** 80%), 2-thienyl (**az** 81%)
 $\text{Ar} = \text{Ph}$, $\text{R}^1 = 5\text{-OMe}$ (**ba** 81%), 5- F (**bb** 75%), 5- NO_2 (**bc** 62%), 7- Me (**bd** 84%)
^aOther solvents: DMF (77%), DMAc (58%), CH_2Cl_2 (23%).

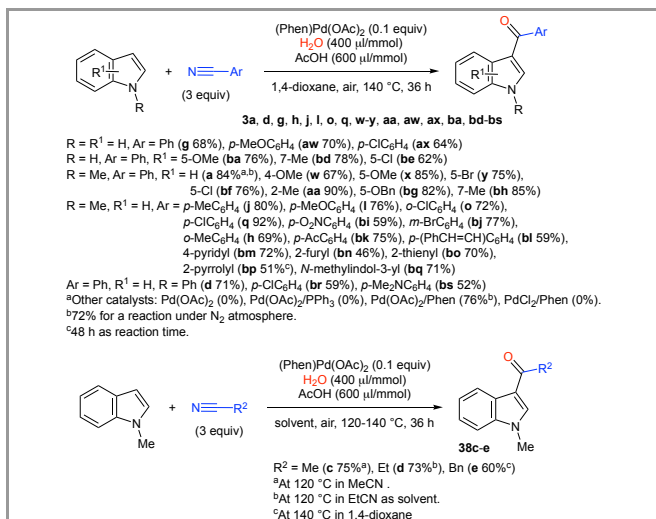


Scheme 48 C3-Acylation of indole with α -oxocarboxylic acids

4.6. Nitriles

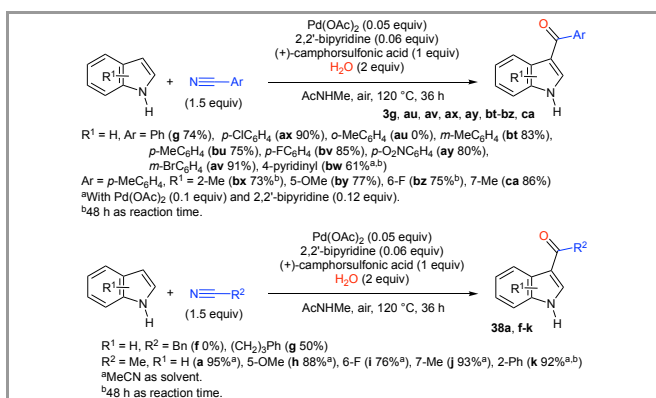
Under air atmosphere, indoles without directing *N*-substituent have been C3-acylated using nitriles and

- (1,10-phenanthroline) $\text{Pd}(\text{OAc})_2$ as the catalyst, at 140 °C in 1,4-dioxane containing water and acetic acid (Scheme 49),⁶⁹



Scheme 49 (1,10-Phenanthroline)Pd(OAc)₂-catalyzed C3-acylation of indoles with nitriles

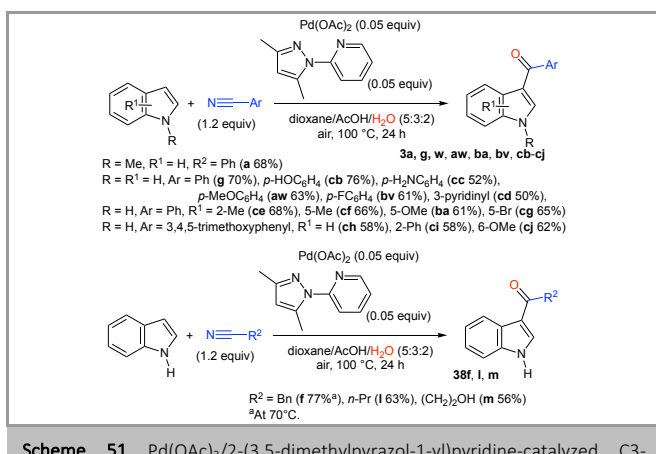
- Pd(OAc)₂/2,2'-bipyridine as the catalyst, at 120 °C in *N*-methylacetamide containing camphorsulfonic acid and water (Scheme 50),⁷⁰



Scheme 50 Pd(OAc)₂/2,2'-bipyridine-catalyzed C3-acylation of indoles with nitriles

or

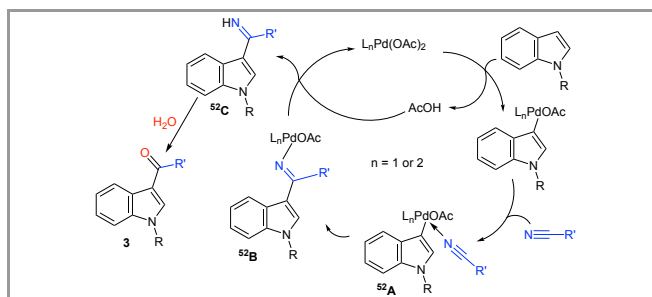
- Pd(OAc)₂/2-(3,5-dimethylpyrazol-1-yl)pyridine as the catalyst, at 100 °C in a dioxane/AcOH/H₂O mixture (Scheme 51).⁷¹



Scheme 51 Pd(OAc)₂/2-(3,5-dimethylpyrazol-1-yl)pyridine-catalyzed C3-

acylation of indoles with nitriles

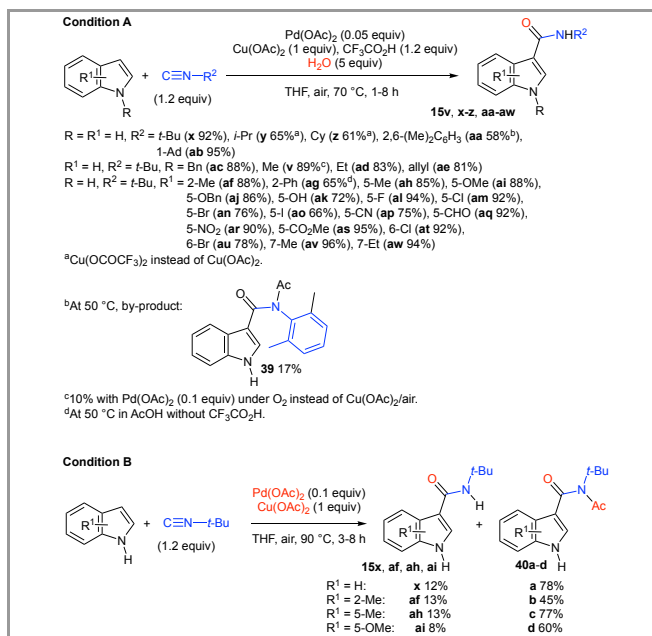
The similar outcome of the reactions performed under air and nitrogen of the reaction with benzonitrile (Scheme 49)⁶⁹ indicates that water provides the oxygen atom of the acylindole, hence the possible reaction mechanism depicted in Scheme 52. Palladation of the indole, followed by coordination of the nitrile leads to ⁵²A. Carbopalladation of the CN unit gives the ketamine complex ⁵²B, which, in the acid medium, evolves to ⁵²C. Hydrolysis of the latter affords 3-acylindole **3**. It was proposed that palladium intermediates are cationic species.⁷⁰



Scheme 52 Proposed mechanism for the acylation of indoles with nitriles

4.7. Isocyanides

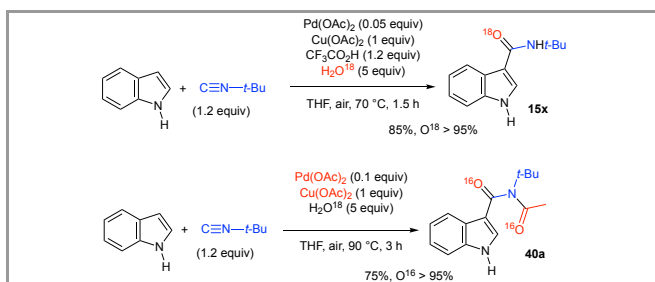
The C3-carboamidation of indoles with isocyanides, reported by Zhu's team, using Pd(OAc)₂ catalysis and air atmosphere, at 70 °C in THF containing copper acetate, trifluoroacetic acid and water, afforded secondary amides **15v, x-z, aa-aw** (Conditions A, Scheme 53).⁷² In the absence of trifluoroacetic acid and water (Conditions B), the reaction furnished tertiary *N*-acetyl amides **40a-d** as the main compounds (Scheme 53).



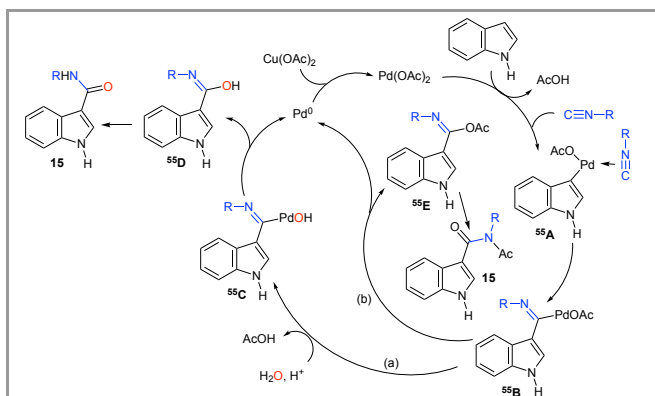
Scheme 53 C3-Carboamidation of indoles with isocyanides

Insights into the reaction were obtained using H₂O¹⁸. With CF₃CO₂H as co-reagent, fully O¹⁸ was incorporated into the secondary amide **15x** (Scheme 54). In contrast, without the acid, none of the oxygens of the tertiary *N*-acetyl amide **40a** was O¹⁸ labeled, suggesting to the authors that both oxygen atoms "were

derived from acetate" (Scheme 54). They also noted the absence of oxygen exchange between carbonyl oxygen of the secondary amide and H₂O¹⁸. Given these observations, a plausible mechanism involves the Pd^{II}-mediated C3-H activation and the coordination of isocyanide to afford **55A** (Scheme 55). Insertion of N=C unit into the C-Pd bond leads to **55B**. The presence of the acid favors quick ligand exchange of the acetate with water to yield **55C** (path *a*). From **55C**, reductive elimination of Pd⁰ delivers **55D** which furnishes the secondary amide **15** by tautomerization. Reductive elimination from **55B** is preferred in the absence of acid and water (path *b*). That results in the formation of the unstable imidic anhydride **55E**. Tautomerization of the latter leads to the tertiary *N*-acetyl amide **15**. Regeneration of the active Pd^{II} species is assumed by Cu(OAc)₂.

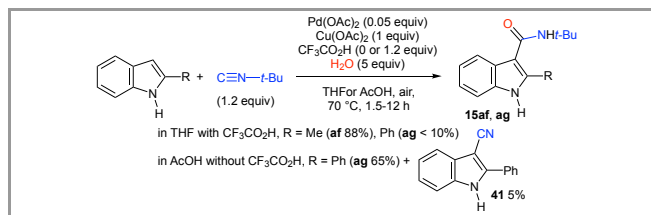


Scheme 54 Labelled experiments

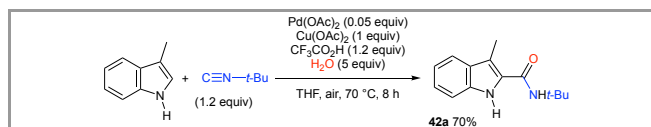


Scheme 55 Proposed mechanism for the carboamidation of indoles with isocyanides

Conditions A were effective for the C3-carboamidation of 2-methylindole,⁷² but led to only 10% yield of **15ag** from 2-phenylindole⁷³ (Scheme 56). The use of AcOH as the solvent at 50 °C without CF₃CO₂H improved the yield to 65% and led to 5% of 2-phenyl-1*H*-indole-3-carbonitrile **41** as side-product (Scheme 56).⁷³ This intriguing cyanation has been studied in detail by Zhu and co-workers.⁷³ Under Conditions A, 3-methylindole underwent C2-carboamidation in a fair yield (Scheme 57).⁷²



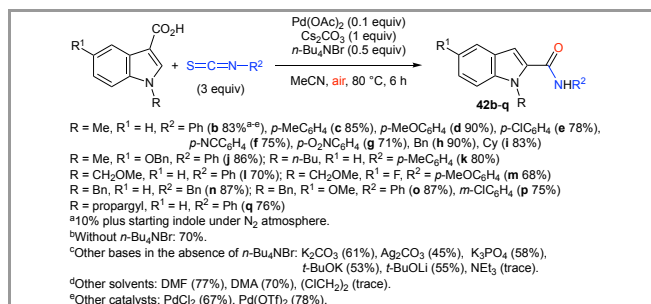
Scheme 56 C3-Carboamidation of 2-methylindoles with isocyanides



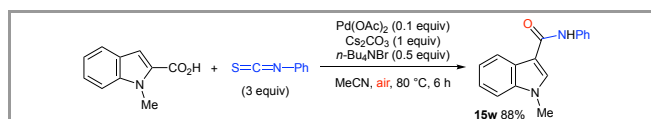
Scheme 57 C2-Carboamidation of 3-methylindoles with isocyanides

4.8. Isothiocyanates and Isocyanates

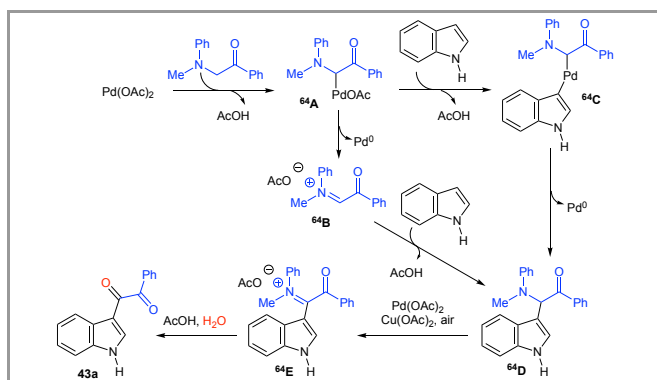
Recently, Swamy's team disclosed the Pd^{II}-catalyzed decarboxylative C2-amidation of indole-3-carboxylic acids with isothiocyanates.⁷⁴ The most optimal conditions were attained with Pd(OAc)₂, Cs₂CO₃ and *n*-Bu₄NBr in MeCN at 80 °C under air atmosphere (Scheme 58). C3-amidation arose from *N*-methylindole-2-carboxylic acid (Scheme 59). Reaction of *N*-methylindole-3-carboxylic acid with phenyl isocyanate instead of phenyl isothiocyanate gave a complex mixture containing only trace of the C2-amidation product. That could be due to the higher moisture sensitivity of the isocyanate.⁷⁴



Scheme 58 C2-Amidation of indole-3-carboxylic acids with isothiocyanates

Scheme 59 C3-Amidation of *N*-methylindole-2-carboxylic acid with phenylisocyanate

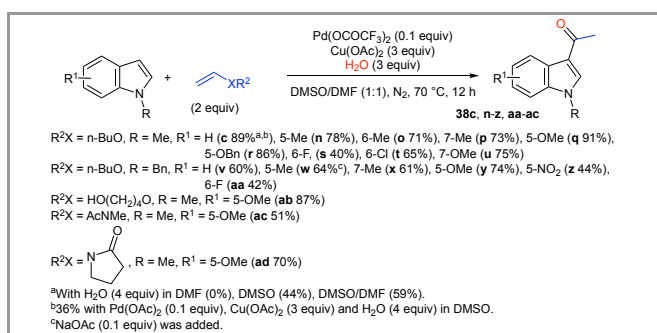
The amidation of indole and *N*-methylindole did not occur under Swamy's conditions. The authors proposed the formation of the cesium indole-3-carboxylic carboxylate **60A**, C(sp²)-H activation via η²-coordination of the cesium carboxylate unit to Pd(OAc)₂ leading to **60B**, and a mechanism preserving the initial oxidation state of palladium all along the catalytic cycle (Scheme 60).⁷⁴ Coordination of the isothiocyanate to **60B** followed by insertion of the C=N double bond into the Pd-C bond would result in the seven membered palladacycle **60C**. Protonation at the amidic nitrogen of **60C** with AcOH would regenerate the catalyst and would afford **60D**. Protodecarboxylation of the latter with *in situ* generated CsHCO₃ would lead to indole-2-thioamide **60E** which would be oxidized with O₂ into the corresponding amide **42**. The



Scheme 64 Proposed mechanism for the reaction of indoles with α -amino carbonyl compounds

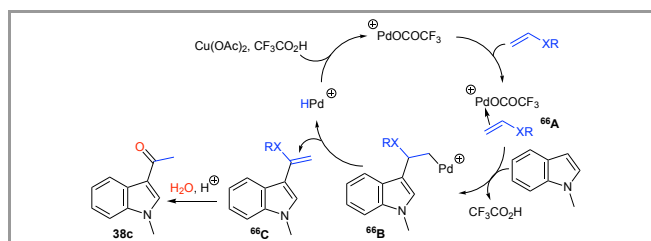
4.10. Vinyl ethers or vinyl amides

The teams of Xue and Xiao reported the synthesis of 3-acetylindoles **38c**, **n-z**, **aa-ad** from *N*-methyl- or *N*-benzylindoles and vinyl ethers or tertiary vinyl amides using $\text{Pd}(\text{OCOCF}_3)_2$ as catalyst, $\text{Cu}(\text{OAc})_2$ to regenerate the catalyst and H_2O in a 1:1 mixture of DMF and DMSO.⁷⁸ The yields depend on the solvent and the amount of water. The use of 3 equivalents of water was found to be the most optimal (Scheme 65). Increase or decrease of this ratio led to dropping of the yield up to 0% (Scheme 65).



Scheme 65 3-Acetylindoles from *N*-substituted indoles and vinyl derivatives

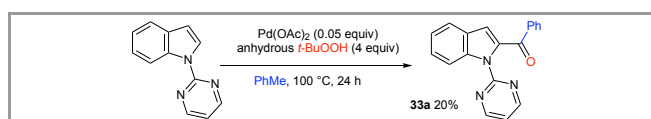
The authors suspect that H_2O promotes the dissociation of the anion from $\text{Pd}(\text{OCOCF}_3)_2$ leading to a cationic Pd^{II} which catalyzes the dehydrogenative Heck reaction between the indole and the electron-rich olefin.⁷⁹ Coordination of the vinylic compound to the cationic catalyst would produce **66A** (Scheme 66). That coordination was preferred because new resonances arose at room temperature in the ¹H NMR spectrum of a mixture of 1-(vinyloxy)butane and $\text{Pd}(\text{OCOCF}_3)_2$, while spectrum modification was not observed using *N*-methylindole and $\text{Pd}(\text{OCOCF}_3)_2$. Reaction of the indole with **66A** would afford **66B**, which would suffer β -H elimination leading to **66C**. Subsequent hydrolysis of **66C** gives 3-acetylindole **38c**. The catalytic cycle could nevertheless involve the reaction with indole rather than with the vinyl ether, because the 3 position of *N*-methylindole is deuterated by heating at 70 °C in the presence of $\text{Pd}(\text{OCOCF}_3)_2$ (0.1 equiv) and D_2O (3 equiv).



Scheme 66 Proposed mechanism for the acylation of *N*-methylindole with alkenes

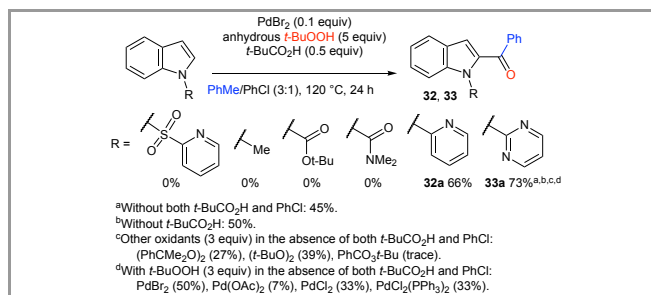
4.11. Toluene

In 2015, Wu, Liu and co-workers who studied different agents for the C2-acylation of *N*-(pyrimidin-2-yl)indole (Scheme 40-42), obtained the benzoylation adduct **33a** in 20% yield, using toluene with $\text{Pd}(\text{OAc})_2$ as catalyst and anhydrous *t*-BuOOH as the oxidant (Scheme 67).⁶¹

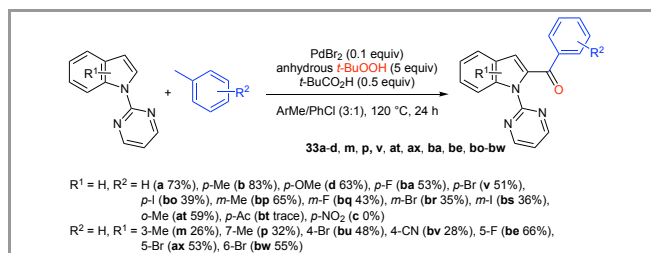


Scheme 67 C2-Benzoylation of *N*-(pyrimidin-2-yl)indole with toluene

The efficiency greatly increased under conditions subsequently reported by Van der Eycken's team:⁸⁰ PdBr_2 as catalyst and pivalic acid as additive at 120 °C in a PhMe/PhCl mixture (Scheme 68).⁸¹ Tested for the benzoylation of indoles variously *N*-substituted, these conditions have been revealed also effective for the functionalization of *N*-(pyridin-2-yl) indole (Scheme 68). They were also efficient with toluene derivatives except those with an electron withdrawing group such as acetyl and nitro (Scheme 69).



Scheme 68 C2-Benzoylation of *N*-substituted indoles with toluene



Scheme 69 C2-Benzoylation of *N*-(pyrimidin-2-yl)indole with toluene derivatives

The above reactions involve the oxidation of ArMe into the corresponding aldehyde, a reaction with *t*-BuOOH occurring even in the absence of any metal catalyst.⁸² Then, the

benzoylation would proceed as above depicted in Scheme 39. Recently, a different reaction leading to isatin was reported by Luo's team using Pd(OAc)₂ and aqueous *t*-BuOOH in toluene (Scheme 39).⁵⁹

4.12. Bromodichloromethane

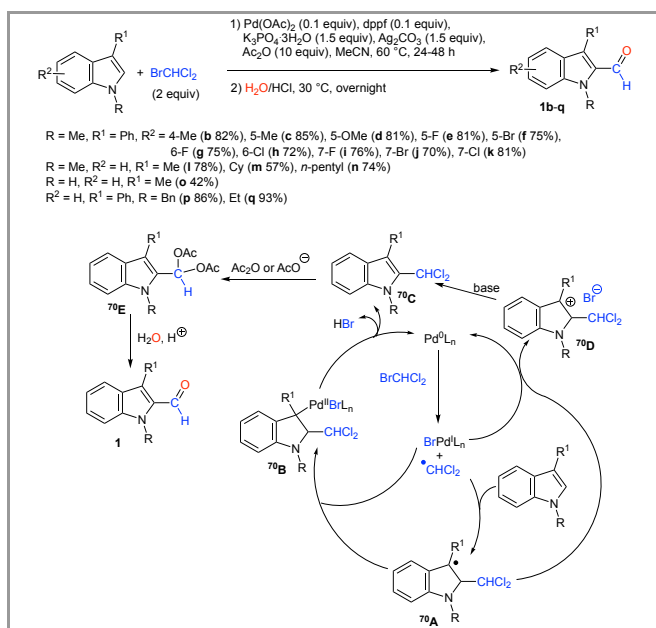
Recently, Wang's team disclosed the C2-formylation of 3-substituted indoles via hydrolysis of the C2-methylene diacetates obtained from the Pd-catalyzed reaction with bromodichloromethane and acetic anhydride (Scheme 70).⁸³ The homolytic cleavage of the C-Br bond has been demonstrated, hence the Pd⁰/Pd^{II} and unusual Pd⁰/Pd^I catalytic cycles proposed in Scheme 70. Addition of the dichloromethyl radical to the substrate leads to radical intermediate **70A** which may evolve through two pathways:

- reaction with Pd^I complex providing the Pd^{II} intermediate **70B** which gives the methylene dichloro compound **70C** and the active catalytic species,

or

- oxidation by Pd^I leading to Pd⁰ and ionic species **70D**, reaction of the latter with base giving **70E**.

The experimental conditions mediated the transformation of **70C** into acetal **70E** which was isolated, or hydrolyzed to afford the formylation product **1**.



Scheme 70 C2-Formylation of 3- and N-substituted indoles with bromodichloromethane and proposed mechanism

5. Conclusion

The development of palladium catalytic systems for the substitution of the indole core with a carbonylated tether has grown considerably over the last years. The number of papers devoted to this rather restricted topic demonstrates that indole, more than 150 years after its discovery,⁸⁴ remains the subject of intensive studies. Particularly interesting in the context of the green chemistry are the procedures avoiding preliminary functionalization. After Pd^{II}-mediated selective C2-H or C3-H activation of the indole, the acylation occurs via carbonylation,

or using a variety of carbonylated or non carbonylated species, to afford coupling products open to further reactions.

References

- (1) (a) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199-1222. (b) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673-714. (c) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608-9644. (e) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449-4465. (d) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508-3549. (e) Lancianesi, S.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2014**, *114*, 7108-7149. (f) Dalpozzo, R. *Chem. Soc. Rev.* **2015**, *44*, 742-778. (g) Petrini, M. *Chem. Eur. J.* **2017**, *23*, 16115-16151. (h) Ziarani, G. M.; Moradi, R.; Ahmadi, T.; Lashgari, N. *RSC Adv.* **2018**, *8*, 12069-12103. (i) Pirovano, V. *Eur. J. Org. Chem.* **2018**, 1925-1945. (j) Ieronimo, G.; Palmisano, G.; Maspero, A.; Marzorati, A.; Scapinello, L.; Masciocchi, N.; Cravotto, G.; Barge, A.; Simonetti, M.; Ameta, K. L.; Nicholas, K. M.; Penoni, A. *Org. Biomol. Chem.* **2018**, *16*, 6853-6859.
- (2) (a) Norman, M. H.; Navas, F. III; Thompson, J. B.; Rigdon, G. C. *J. Med. Chem.* **1996**, *39*, 4692-4703. (b) Thurmond, R. L.; Desai, P. J.; Dunford, P. J.; Fung-Leung, W.-P.; Hofstra, C. L.; Jiang, W.; Nguyen, S.; Riley, J. P.; Sun, S.; Williams, K. N.; Edwards, J. P.; Karlsson, L. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 404-413. (c) Pedras, M. S. C.; Yaya, E. E.; Glawischnig, E. *Nat. Prod. Rep.* **2011**, *28*, 1381-1405. (d) Sravanthi, T. V.; Manju, S. L. *Eur. J. Pharm. Sci.* **2016**, *91*, 1-10. (e) Chadha, N.; Silakari, O. *Eur. J. Med. Chem.* **2017**, *134*, 159-184. (f) Ciulla, M. G.; Kumar, K. *Tetrahedron Lett.* **2018**, *59*, 3223-3233.
- (3) (a) Cacchi, S.; Fabrizi, G.; *Chem. Rev.* **2005**, *105*, 2873-2920. (b) Lang, R.; Xia, C.; Li, F. *New J. Chem.* **2014**, *38*, 2732-2738. (c) Wu, X.-F. *Chem. Eur. J.* **2015**, *21*, 12252-12265. (d) Yao, S.-J.; Ren, Z.-H.; Guan, Z.-H. *Tetrahedron Lett.* **2016**, *57*, 3892-3901. (e) Sharma, S.; Mishra, N. K.; Shin, Y.; Kim, I. S. *Current Org. Chem.* **2016**, *20*, 471-511. (f) Wei, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev.* **2017**, *117*, 8864-8907. (g) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. *Chem. Rev.* **2017**, *117*, 9163-9227. (h) Wegmann, M.; Henkel, M.; Bach, T. *Org. Biomol. Chem.* **2018**, *16*, 5376-5385. (i) Shah, T. A.; De, P. B.; Pradhan, S.; Punniyamurthy, T. *Chem. Commun.* **2019**, *55*, 572-587.
- (4) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3185-3189.
- (5) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072-12073.
- (6) Joucla, L.; Batail, N.; Djakovitch, L. *Adv. Synth. Catal.* **2010**, *352*, 2929-2936.
- (7) Pi, J.-J.; Lu, X.-Y.; Liu, J.-H.; Lu, X.; Xiao, B.; Fu, Y.; Guimond, N. *J. Org. Chem.* **2018**, *83*, 5791-5800.
- (8) Moncea, O.; Poinsot, D.; Fokin, A. A.; Schreiner, P. R.; Hierso, J.-C. *ChemCatChem* **2018**, *10*, 2915-2922.
- (9) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676-14681.
- (10) Li, Y.; Wang, W.-H.; He, K.-H.; Shi, Z.-J. *Organometallics* **2012**, *31*, 4397-4400.
- (11) Tokuyama, H.; Kaburagi, Y.; Chen, X.; Fukuyama, T. *Synthesis* **2000**, 429-434.
- (12) Zhao, M.-N.; Ran, L.; Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *ACS Catal.* **2015**, *5*, 1210-1213.
- (13) Karpov, A. S.; Merkul, E.; Rominger, F.; Müller, T. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6951-6956.
- (14) Herbert, J. M.; McNeill, A. H. *Tetrahedron Lett.* **1998**, *39*, 2421-2424.
- (15) Buscemi, G.; Miller, P. W.; Kealey, S.; Gee, A. D.; Long, N. J.; Passchier, J.; Vilar, R. *Org. Biomol. Chem.* **2011**, *9*, 3499-3503.
- (16) Kumar, K.; Zapf, A.; Michalik, D.; Tillack, A.; Heinrich, T.; Böttcher, H.; Arlt, M.; Beller, M. *Org. Lett.* **2004**, *6*, 7-10.
- (17) Takács, A.; Marosvölgyi-Haskó, D.; Kabak-Solt, Z.; Damas, L.; Rodrigues, F. M. S.; Carrilho, R. M. B.; Pineiro, M.; Pereira, M. M.; Kollár, L. *Tetrahedron* **2016**, *72*, 247-256.
- (18) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 13577-13586.

- (19) Lang, R.; Shi, L.; Li, D.; Xia, C. G.; Li, F. W. *Org. Lett.* **2012**, *14*, 4130-4133.
- (20) Li, D.; Shan, S.; Shi, L.; Lang, R.; Xia, C. G.; Li, F. W. *Chin. J. Catal.* **2013**, *34*, 185-192.
- (21) Xing, Q.; Shi, L.; Lang, R.; Xia, C. G.; Li, F. W. *Chem. Commun.* **2012**, *48*, 11023-11025.
- (22) Tu, D.; Luo, J.; Jiang, C. *Chem. Commun.* **2018**, *54*, 2514-2517.
- (23) Ishikura, M.; Terashima, M. *J. Org. Chem.* **1994**, *59*, 2634-2637.
- (24) Ishikura, M.; Imaizumi, K.; Katagiri, N. *Heterocycles* **2000**, *53*, 2201-2220.
- (25) Ishikura, M.; Uchiyama, H.; Matsuzaki, N. *Heterocycles* **2001**, *55*, 1063-1070.
- (26) Ishikura, M.; Matsuzaki, Y.; Agata, I. *Chem. Commun.* **1996**, 2409-2410.
- (27) Itahara, T. *Chem. Lett.* **1982**, 1151-1152.
- (28) Lang, R.; Wu, J.; Shi, L.; Xia, C.; Li, F. *Chem. Commun.* **2011**, *47*, 12553-1255.
- (29) Zhang, H.; Liu, D.; Chen, C.; Liu, C.; Lei, A. *Chem. Eur. J.* **2011**, *17*, 9581-9585.
- (30) (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298-5300. (b) Muzart, J. In *Comprehensive Organic Synthesis* G. A. Molander, P. Knochel, Eds, 2nd Edition, Vol. 7, Oxford: Elsevier; 2014, pp 295-301.
- (31) Tjutrins, J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2015**, *137*, 12050-12054.
- (32) Bis(indolyl)arylmethanes have been obtained using formic acid as CO source: Qi, X.; Ai, H.-J.; Zhang, N.; Peng, J.-B.; Ying, J.; Wu, X.-F. *J. Catal.* **2018**, *362*, 74-77.
- (33) Nadres, E. T.; Lazareva, A.; Daugulis, O. *J. Org. Chem.* **2011**, *76*, 471-483.
- (34) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047-1060.
- (35) Liu, J.; Wei, Z.; Jiao, H.; Jackstell, R.; Beller, M. *ACS Cent. Sci.* **2018**, *4*, 30-38.
- (36) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451-5457.
- (37) Zeng, F.; Alper, H. *Org. Lett.* **2013**, *15*, 2034-2037.
- (38) The positive charge of intermediate ²¹D is missing in the original paper.
- (39) For the formation of η³-allyl palladium complexes from allyl alcohols and their reactivity, see: Muzart, J. *Tetrahedron* **2005**, *61*, 4179-4212.
- (40) (a) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592-4593. (b) Tseng, Y.-L.; Liang, M.-C.; Chen, I.-C.; Wu, Y.-K. *Synlett* **2018**, *29*, 609-612.
- (41) Wang, Z.; Yin, Z.; Wu, X.-F. *Chem. Commun.* **2018**, *54*, 4798-4801.
- (42) Hegedus, L. S.; Sestrick, M. R.; Michaelson, E. T.; Harrington, P. J. *J. Org. Chem.* **1989**, *54*, 4141-4146.
- (43) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657-2662.
- (44) Larock, R. C.; Bernhardt, J. C. *J. Org. Chem.* **1978**, *43*, 710-719.
- (45) (a) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109-1117. (b) Hodson, F. M.; Madge, D. J.; Slawin, A. N. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899-1906.
- (46) Labadie, S. S.; Teng, E. *J. Org. Chem.* **1994**, *59*, 4250-4254.
- (47) Soley, R.; Albericio, F.; Álvarez, M. *Synthesis* **2007**, 1559-1565.
- (48) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129-6137.
- (49) Kianmehr, E.; Kazemi, S.; Foroumadi, A. *Tetrahedron* **2014**, *70*, 349-354.
- (50) Yan, X.-B.; Shen, Y.-W.; Chen, D.-Q.; Gao, P.; Li, Y.-X.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *Tetrahedron* **2014**, *70*, 7490-7495.
- (51) Li, D.; Wang, M.; Liu, J.; Zhao, Q.; Wang, L. *Chem. Commun.* **2013**, *49*, 3640-3642.
- (52) Zhang, H.-J.; Wu, Z.; Lin, W.; Wen, T.-B. *Chin. J. Chem.* **2015**, *33*, 517-521.
- (53) Wang, W.; Liu, J.; Gui, Q.; Tan, Z. *Synlett* **2015**, *26*, 771-778.
- (54) Sharma, U. K.; Gemoets, H. P.; Schröder, F.; Noël, T.; Van der Eycken, E. V. *ACS Catal.* **2017**, *7*, 3818-3823.
- (55) Manna, M. K.; Bairy, G.; Jana, R. *Org. Biomol. Chem.* **2017**, *15*, 5899-5903.
- (56) Kumar, G.; Sekar, G. *RSC Adv.* **2015**, *5*, 28292-28298.
- (57) Jiang, H.; Gao, S.; Xu, J.; Wu, X.; Lin, A.; Yao, H. *Adv. Synth. Catal.* **2016**, *358*, 188-194.
- (58) Hu, Q.; Liu, X.; Huang, F.; Wang, F.; Li, Q.; Zhang, W. *Catal. Commun.* **2018**, *113*, 27-31.
- (59) Luo, J.; Gao, S.; Ma, Y.; Ge G. *Synlett* **2018**, *29*, 969-973.
- (60) Kothandapani, J.; Reddy, S. M. K.; Thamotharan, S.; Kumar, S. M.; Byrappa, K.; Ganesan, S. S. *Eur. J. Org. Chem.* **2018**, 2762-2767.
- (61) Li, C.; Zhu, W.; Shu, S.; Wu, X.; Liu, H. *Eur. J. Org. Chem.* **2015**, 3743-3750.
- (62) Pd-catalyzed C3-alkylation of indoles with alcohols has been reported under non-oxidative conditions: Putra, A. E.; Takigawa, K.; Tanaka, H.; Ito, Y.; Oe, Y.; Ohta, T. *Eur. J. Org. Chem.* **2013**, *28*, 6344-6354.
- (63) Park, J.; Kim, A.; Sharma, S.; Kim, M.; Park, E.; Jeon, Y.; Lee, Y.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Biomol. Chem.* **2013**, *11*, 2766-2771.
- (64) Yu, L.; Li, P.; Wang, L. *Chem. Commun.* **2013**, *49*, 2368-2370.
- (65) Pan, C.; Jin, H.; Liu, X.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 2933-2935.
- (66) The decarboxylation could be mediated by the Ag₂O/K₂S₂O₈ association: Mandal, S.; Bera, T.; Dubey, G.; Saha, J.; Laha, J. K. *ACS Catal.* **2018**, *8*, 5085-5144.
- (67) Jiang, G.; Wang, S.; Zhang, J.; Yu, J.; Zhang, Z.; Jia, F. *Adv. Synth. Catal.* In press
- (68) Gu, L.-J.; Liu, J.-Y.; Zhang, L.-Z.; Xiong, Y.; Wang, R. *Chin. Chem. Lett.* **2014**, *25*, 90-92.
- (69) Ma, Y.; You, J.; Song, F. *Chem. Eur. J.* **2013**, *19*, 1189-1193.
- (70) Jiang, T. S.; Wang, G. W. *Org. Lett.* **2013**, *15*, 788-791.
- (71) Das, T.; Chakraborty, A.; Sarkar, A. *Tetrahedron Lett.* **2014**, *55*, 7198-7202.
- (72) Peng, J.; Liu, L.; Hu, Z.; Huang, J.; Zhu, Q. *Chem. Commun.* **2012**, *48*, 3772-3774.
- (73) Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 4966-4969.
- (74) Tulichala, R. N. P.; Shankar, M.; Swamy, K. C. K. *J. Org. Chem.* **2018**, *83*, 4375-4383.
- (75) Nandi, D.; Jhou, Y.-M.; Lee, J.-Y.; Kuo, B.-C.; Liu, C.-Y.; Huang, P.-W.; Lee, H. M. *J. Org. Chem.* **2012**, *77*, 9384-9390.
- (76) Tang, R. Y.; Guo, X. K.; Xiang, J. N.; Li, J. H. *J. Org. Chem.* **2013**, *78*, 11163-11171.
- (77) For an efficient procedure under Cu-catalysis, see: Wu, J.-C.; Song, R.-J.; Wang, Z.-Q.; Huang, X.-C.; Xie, Y.-X.; Li, J.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 3453-3457.
- (78) Li, Y.; Xue, D.; Lu, W.; Fan, X.; Wang, C.; Xiao, J. *RSC Adv.* **2013**, *3*, 11463-11466.
- (79) For a review on dehydrogenative Heck reactions, see: Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170-1214.
- (80) Zhao, Y.; Sharma, U. K.; Schröder, F.; Sharma, N.; Song, G.; Van der Eycken, E. V. *RSC Adv.* **2017**, *7*, 32559-32563.
- (81) Anhydrous *t*-BuOOH solution (5.5 M in decane over molecular sieves) was used, *Personal communication* from Dr U. K. Sharma, April, 19, 2018.
- (82) Song, H.; Chen, D.; Pi, C.; Cui, X.; Wu, Y. *J. Org. Chem.* **2014**, *79*, 2955-2962.
- (83) Bao, Y.; Wang, J.-Y.; Zhang, Y.-X.; Li, Y.; Wang, X.-S. *Tetrahedron Lett.* **2018**, *59*, 3147-3150.
- (84) (a) Baeyer, A. *Ann. Chem. Pharm.* **1866**, *140*, 295-296. (b) Baeyer, A.; Emmerling, A. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 679-685.

Biosketches



Jacques Muzart was born in 1946, in Vienne la Ville, a small village in the Argonne area, 200 km east of Paris. He studied chemistry at l'Université de Reims Champagne-Ardenne and received his degrees (Doctorat de 3^{ème} cycle in 1972, Doctorat d'Etat in 1976) for his work with J.-P. Pète on photochemical rearrangements of α,β -epoxyketones and α,β -diketones. He spent 15 months as a postdoctoral fellow of National Science Foundation working with Nobel Laureate E. J. Corey at Harvard University. Directeur de Recherche Emérite since 2011, his research interests concentrate on transition metal-catalysis.



Jean Le Bras obtained his PhD at UPMC in 1998 with Dr. Hani Amouri on the iridium-mediated phenols functionalization. He then joined the group of John A. Gladysz in Salt Lake City (USA) and in Erlangen (Germany). In 2000, he became a CNRS fellow at Université de Reims Champagne-Ardenne, and was promoted Directeur de Recherche in 2013. His current interests are concentrated on oxidative palladium cross-coupling reactions.