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Achievement of regioselectivity in transition metal-catalyzed direct C-H (hetero)arylation reactions of heteroarenes with one heteroatom through the use of removable protecting/blocking substituents or traceless directing groups

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Chemoselectivity
Regioselectivity
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Removable groups
Traceless directing groups
Deprotection

Contents

Abbreviations: Ac, acetyl; acac, acetylacetonate; 1-Ad, 1-adamantyl; AIBN, azobisisobutyronitrile; Ar, aryl; Boc, *tert*-butoxycarbonyl; BQ, 1,4-benzoquinone; *n*-Bu, *n*-butyl; *t*-Bu, *t*-butyl; *Cp, cyclopentadienyl; Cy, cyclohexyl; DBU, 1,5-diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; DFT, density functional theory; DMEDA, *N,N*-dimethylethylenediamine; dppb, 1,4-bis(diphenylphosphino)butane; DMA, *N,N*-dimetylacetamide; DMAP, 4-dimethylaminopyridine; DMF, *N,N*-dimethylformamide; DMSO, dimethylsulfoxide; dtbpy, 4,4'-di-*tert*-butyl-2,2'-dipyridyl; Et, ethyl; HetAr, heteroaryl; *n*-Hex, *n*-hexyl; LDA, lithium diisopropylamide; Me, methyl; JohnPhos, (2-di-*tert*-butylphosphino)biphenyl; LiTMP, lithium tetramethylpiperidide; MS, molecular sieves; NMP, *N*-methyl-2-pyrrolidone; *i*-Pr,

i-propyl; Py, pyridine; rt, room temperature; SEM, 2-(trimethylsilyl)ethoxymethyl; TBAB, tetra-*n*-butyl bromide; TBAF, tetra-*n*-butyl fluoride; TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; Tf, trifluoromethanesulfonyl; Tfa, trifluoroacetate; THF, tetrahydrofuran; TIPS, triisopropylsilyl; XPhos, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

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1. Introduction

The transition metal-catalyzed direct C-H (hetero)arylation reactions of heteroarenes are currently one of the hottest topics of synthetic organic chemistry. In fact, these reactions, which have been covered by several reviews,[1] have emerged as an increasingly viable alternative to traditional Pd- or Ni-catalyzed cross-coupling reactions, enabling step- and atom economical access to C-heteroaryl-substituted heteroarene derivatives including structural motifs of biologically and pharmacologically active compounds and naturally occurring substances.[2]
The main methodologies that have been developed in this research area include: (i) direct (hetero)arylation reactions of heteroarenes with (hetero)aryl halides or pseudohalides or (hetero)aryliodonium salts;[3] (ii) dehydrogenative C-H/C-H coupling between two heteroarenes or a heteroarene with an arene;[4] and (iii) (hetero)arylation reactions of heteroarenes with (hetero)aryl metals.[5] However, the regioselectivity is a general challenge of these methodologies. In fact, certain heterocyclic scaffolds may be suffering from severe regioselectivity problems especially when they possess multiple acidic C-H bonds or multiple nucleophilic centers. Furthermore, the electronic properties of certain heteroarenes can dominate reactivity, preventing C-H (hetero)arylation reactions at their specific sites and allowing to the exclusive formation of particular regioisomers.

In order to overcome these limitations, strategies have been developed that allow highly regioselective direct C-H (hetero)arylation reactions through the use of removable protecting/blocking substituents or traceless directing groups in the heteroarene rings. These strategies enable coupling reactions at C-H bonds in which the (hetero)arylations do not occur in the absence of these substituents/groups.

However, despite the synthetic importance of these strategies and that several reviews covering the transition metal-catalyzed direct arylation reactions assisted by directing groups have been published,[6] no review has been devoted so far to describe specifically and exhaustively the use of such directing groups in direct (hetero)arylation reactions of heteroarenes. Also, the achievement of regioselectivity in direct C-H arylations through the use of removable protecting/blocking substituents has never been specifically summarized and discussed in the reviews published so far.

In this article with 453 references, which covers the literature up to the end of April 2015, we aim to showcase the state of the art in the field of the transition metal-catalyzed direct C-H (hetero)arylation reactions of heteroarenes with one heteroatom in which high regioselectivity has been gained by the use of their removable protecting/blocking substituents or traceless directing groups. In particular, we wish to illustrate the typical features of these methods which have dramatically increased the synthetic utility of the direct C-H (hetero)arylation reactions of heteroarenes, and to summarize the synthetic procedures used for the introduction of their removable protecting/blocking groups in the heteroarene substrates and for their removal from the products. The limitations related to the use of removable protecting/blocking substituents and directing groups, which include an increase in synthetic steps, the issues related to the ease of installing and the subsequent removal of the protecting/blocking/directing groups will be also highlighted. It should be noted that, in many cases, the (hetero)arylation reactions assisted by directing groups involve only *ortho* C-H bonds due to the coordination of the transition metal catalyst to the same groups.

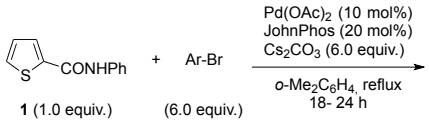
This review includes examples of regioselective direct (hetero)arylation reactions of heteroarenes containing directing groups which are also leaving groups. Therefore, in these cases, the achievement of regioselectivity through the use of these groups involves only a single synthetic step apart the coupling itself, that is the one to install the directing group.

As it will be shown on the following sections, the methodologies used in the described regioselective direct (hetero)arylations include reactions with (hetero)aryl (pseudo)halides, aryliodoniums salts, (hetero)arylcarboxylic acids, and (hetero)arylmetals as well as (hetero)arylations via oxidative C-H/C-H couplings. However, the review has been organized on the basis of the classes of heteroarenes used as substrates, but not of the methodologies. In particular, the review has been divided in two main sections which cover the (hetero)arylation reactions of five-membered and six-membered heteroarenes with one heteroatom and their benzocondensed derivatives, respectively. The first of these sections has been subdivided in the following two sub-sections: (i) (hetero)arylation reactions of thiophene, benzo[*b*]thiophene and furan ring systems; (ii) (hetero)arylation reactions of pyrrole, indole, carbazole, and indolizine ring systems. The second section covers the (hetero)arylation reactions of pyridine, quinoline, isoquinoline, phenanthridine, and benzo[*h*]quinoline ring systems. Recent advances into the mechanisms of the reactions that are illustrated in all these sections have also been briefly reported.

2. Direct (Hetero)arylation Reactions of Five-Membered Heteroarenes with One Heteroatom

2.1. Direct (hetero)arylation reactions of thiophene, benzo[*b*]thiophene and furan ring systems

Multiply arylated thiophenes are privileged structures with interesting biological[7a,b] and optoelectronic properties[7c,d] that, since the early 2000s, have attracted the attention of the research group of Miura. In 2002, this group developed an interesting one-step method for the Pd-catalyzed polyarylation of the thiophene ring that involved the use of the *N*-phenylcarboxyamide substituent as a removable *ortho*-directing group.[8] In particular, Miura and coworkers described that *N*-(2-thienoyl)aniline (**1**)[9] efficiently undergoes triarylation accompanied by formal decarbamoylation by treatment with a large molar excess of aryl bromide, 10 mol% $Pd(OAc)_2$, 20 mol% P(biphenyl-2-yl)(*t*-Bu)$_2$ (JohnPhos) and 6.0 equiv of Cs_2CO_3 in *o*-xylene under reflux to give 2,3,5-triarylthiophenes **2** in good isolated yields (Scheme 1).[8]

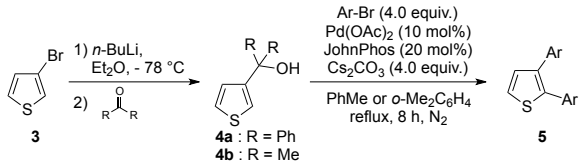


2	Ar	Yield %
a	Ph	83
b	4-$MeOC_6H_4$	68
c	4-FC_6H_4	71

Scheme 1. Synthesis of 2,3,5-triarylthiophenes **2** from *N*-(2-thenoyl)aniline (**1**)

The reaction was considered to proceed through coordination assisted arylation at the C-3 position of **1** followed by either arylation at the C-5 position or decarbamoylation at the C-2 position to provide both 2,4- and 2,3-diarylthiophenes as precursors to 2,3,5-triarylthiophenes **2**.[8] Major drawbacks of this reaction in terms of green chemistry were the lack of atom economy and the high loading of the catalyst system.

Four years later, Miura and coworkers[10] found that α,α-diphenylthien-3-ylmethanol (**4a**) and α,α-dimethylthien-3-ylmethanol (**4b**), which were prepared according to the literature by treatment of 3-bromothiophene (**3**) with *n*-BuLi in Et_2O at -78 °C followed by addition of benzophenone and acetone, respectively,[11a,b] underwent selective C-2 arylation accompanied by arylative C-C bond cleavage at the C-3 position by treatment with 4.0 equiv of aryl bromides, 10 mol% $Pd(OAc)_2$, 20 mol% JohnPhos, and 4.0 equiv of Cs_2CO_3 in toluene or *o*-xylene under reflux (Scheme 2). This protocol enabled the preparation of 2,3-diarylthiophenes **5** generally in good yields using both electron-rich and electron-deficient aryl bromides, but, unexpectedly, provided 2,3-di(4-methoxyphenyl)thiophene (**5b**) in only 12% yield by Pd-catalyzed reaction of **4b** with 4-bromoanisole.[10]

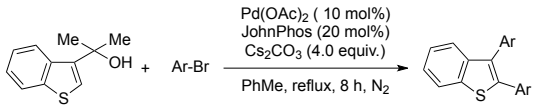


		Reaction products	
4	**5**	Ar	Yield %
b	**a**	Ph	62
b	**b**	4-$MeOC_6H_4$	12
b	**c**	4-ClC_6H_4	75
b	**d**	4-$EtOOCC_6H_4$	63
a	**b**	4-$MeOC_6H_4$	60
a	**e**	4-$CF_3C_6H_4$	64
a	**f**	4-ClC_6H_4	86
a	**d**	4-$EtOOCC_6H_4$	83
a	**a**	Ph	67

Scheme 2. Pd-catalyzed synthesis of 2,3-diarylthiophenes **5** from α,α-disubstituted thien-3-ylmethanols **4**

It is interesting to note that some 2,3-diarylthiophenes, which were found to be potent EP_1 receptor antagonists, had been previously synthesized via a three-step reaction sequence involving the use of 3-thienylboronic acid as the starting material and two Suzuki-type cross-coupling reactions.[12]

Notably, a protocol similar to that developed to prepare compounds **5** allowed the synthesis of 2,3-diarylbenzo[*b*]thiophenes **7** in satisfactory yields from α,α-dimethylbenzo[*b*]thien-3-ylmethanol (**6**) and aryl bromides (Scheme 3).[10]



7	Ar	Yield %
a	Ph	68
b	4-$MeOC_6H_4$	60
c	4-$EtOOCC_6H_4$	58

Scheme 3. Synthesis of 2,3-diarylbenzo[*b*]thiophenes **7** from compound **6**

However, the method was unsuitable for the preparation of 2,3-diarylbenzo[*b*]thiophenes **8** (Figure 1) bearing different aryl groups at positions 2 and 3.

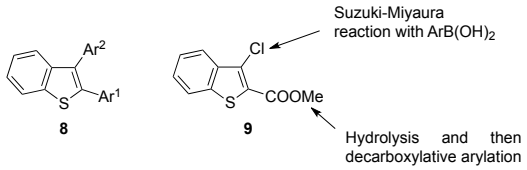
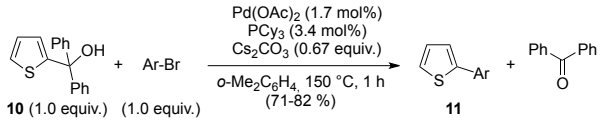


Figure 1. Chemical structures of compounds **8** and **9**

Compounds belonging to the latter class were most recently synthesized by Miura and coworkers from 3-chloro-2-methoxycarbonylbenzo[*b*]thiophene (**9**) (Figure 1) via Ni-

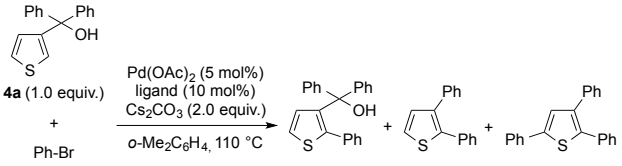
catalyzed Suzuki-Miyaura reaction with arylboronic acids and hydrolysis of the ester group followed by Pd-catalyzed decarboxylative arylation as the key transformations.[13]

In 2004, Miura and coworkers investigated the $Pd(OAc)_2/PCy_3$-catalyzed reaction of α,α-diphenylthien-2-ylmethanol (**10**) with aryl bromides[14] achieving a result significantly different from that of the $Pd(OAc)_2$/JohnPhos-catalyzed reaction of **4a** with aryl bromides.[10] In fact, the $Pd(OAc)_2/PCy_3$-catalyzed reaction of 1.0 equiv of **10**[15] with 1.0 equiv of aryl bromides in refluxing *o*-xylene in the presence of Cs_2CO_3 as the base gave 2-arylthiophenes **11** in good yields via *ipso*-substitution of the functional group of **10** (Scheme 4).[14]



Scheme 4. Pd-catalyzed *ipso*-arylation of compound **10**

In 2007, Biró and Kotschy reconsidered the Pd-catalyzed arylation of α,α-diphenylthien-3-ylmethanol (**4a**) with a series of aryl bromides by examining the influence of different phosphane ligands on the course of the reaction.[16] They found that treatment of **4a** with 2.0 equiv of bromobenzene, 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3 and 2.0 equiv of Cs_2CO_3 in *o*-xylene at 140 °C provided a mixture of the *ortho*-arylated starting material **12**, 2,3-diphenylthiophene (**5a**) and 2,3,5-triphenylthiophene (**2a**) (Scheme 5).[16]

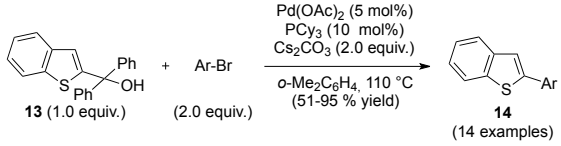


Ligand	Conversion	Product distribution		
		12	**5a**	**2a**
PPh_3	66	42%	20%	4%
PPh_3	100	6%	52%	42%
PCy_3	75	4%	52%	19%
PCy_3	90	6%	46%	38%

Scheme 5. Product distribution in the Pd-catalyzed reaction of **4a** with bromobenzene in the presence of PPh_3 or PCy_3 as the ligand

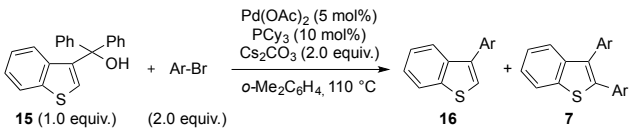
Compound **12** was the primary reaction product when the conversion of the reaction was 66% and this indicated the predominance of the *ortho*-directing effect of the functional group of **4a**. However, when the reaction was complete, compound **5a**, which derived from *ipso*-arylation of **12** at C-3, was the major component of the reaction mixture, but also the yield of **2a**, which presumably was obtained by direct arylation of **5a** at the C-5 position, significantly increased. Nevertheless, compound **5a** proved to be the main component of the reaction mixture when the conversion of the $Pd(OAc)_2/PCy_3$-catalyzed arylation of **4a** was 75 or 90%. It was also found that the $Pd(OAc)_2$-catalyzed arylation of **4a** occurred with poor selectivity for the *ipso*-arylation even when phosphines different from PCy_3 were used as ligands.[16]

On the contrary, the $Pd(OAc)_2/PCy_3$-catalyzed reaction of α,α-diphenylbenzo[*b*]thien-2-ylmethanol (**13**) with aryl bromides occurred with excellent selectivity providing the *ipso*-arylated compounds **14** in good to excellent yields (Scheme 6).[16]



Scheme 6. Synthesis of 2-arylbenzo[*b*]thiophenes **16** by $Pd(OAc)_2/PCy_3$-catalyzed *ipso*-arylation of compound **13** with aryl bromides

Biró and Kotschy also examined the arylation reaction of α,α-diphenylbenzo[*b*]thien-3-ylmethanol (**15**) with aryl bromides (Scheme 7) under experimental conditions similar to those used to prepare compounds **14**, but they observed a varying degree of selectivity, which decreased the yields of 3-arylbenzo[*b*]thiophenes **16** in most cases at the expense of the formation of 2,3-diarylbenzo[*b*]thiophenes **7**.[16]



Ar	**16**	GLC yield %	**7**	GLC yield %
2-ClC_6H_4	**a**	94	**d**	6
4-ClC_6H_4	**b**	89	**e**	11
2-MeC_6H_4	**c**	71	**f**	29
3-MeC_6H_4	**d**	55	**g**	45
4-MeC_6H_4	**e**	65	**h**	35
2-FC_6H_4	**f**	0	**i**	100
4-FC_6H_4	**g**	60	**p**	40
1-naphthyl	**h**	85	**k**	0
2-naphthyl	**i**	90	**l**	0
2-thienyl	**j**	47	**m**	53

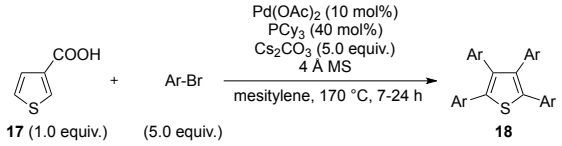
Scheme 7. $Pd(OAc)_2/PCy_3$-catalyzed reaction of α,α-diphenylbenzo[*b*]thien-3-ylmethanol (**15**) with aryl bromides

For example, while the reaction of **15** with 2-bromonaphthalene gave compound **16i** in 90% GLC yield and 55% isolated yield, the arylation of **15** with 1-bromo-2-fluorobenzene gave compound **7i** in 100% GLC yield and 51% isolated yield.[16]

The course of the arylation reactions of Scheme 7 was also followed by GLC-MS analyses and it was found that the **16**/**7** ratio varied only a little during the reactions, which suggested that *ortho*-arylation and *ipso*-arylation of **15** were competing processes.[16] Notably, this finding was in contrast

to that reported by Miura and coworkers for the $Pd(OAc)_2$/JohnPhos-catalyzed reaction of α,α-dimethylbenzo[*b*]thien-3-ylmethanol (**6**) with aryl bromides.[10] In fact, the latter authors reported that the arylation of **6** involves a C-2/C-3 arylation sequence.[10]

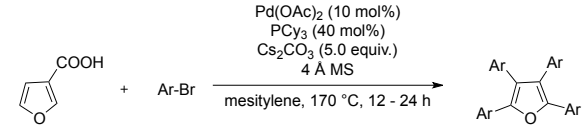
In 2008, Miura and coworkers investigated the multiple Pd-catalyzed arylation of commercially available 3-thienylcarboxylic acid (**17**) with aryl bromides bearing both electron-withdrawing and electron-donating groups at the *para*-position.[17] It was found that these reactions, which were carried out by treatment of 1.0 equiv of **17** with 5.0 equiv of aryl bromides, 10 mol% $Pd(OAc)_2$, 40 mol% PCy_3 and 5.0 equiv of Cs_2CO_3 in mesitylene at 170 °C for 7–24 h in the presence of 4 Å molecular sieves, involved cleavage of three C-H bonds and an *ipso*-arylation reaction providing 2,3,4,5-tetraarylthiophenes **18** in isolated yields ranging from 30 to 90% (Scheme 8).[17]



18	Ar	Yield %
a	4-MeC_6H_4	90
b	4-$CF_3C_6H_4$	86
c	4-*t*-BuC_6H_4	82
d	4-$EtOOCC_6H_4$	60
e	4-$MeOC_6H_4$	30
f	4-PhC_6H_4	79

Scheme 8. $Pd(OAc)_2$/PCy_3-catalyzed synthesis of symmetrical tetraarylthiophenes **18**

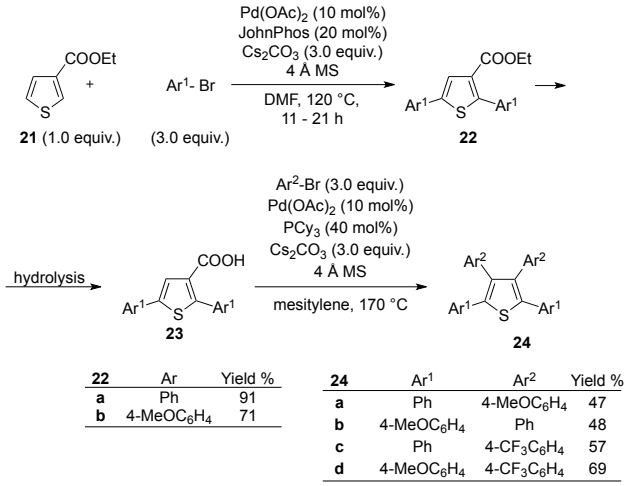
Commercially available 3-furoic acid (**19**) proved able to undergo a similar perarylation reaction to give tetrasubstituted furans **20** possessing four identical aryl rings in modest to satisfactory yields (Scheme 9).[17] More recently, various tetraarylfurans **20** have been synthesized in high yields but less conveniently by $Pd(PPh_3)_4$-catalyzed Suzuki-Miyaura reaction of 2,3,4,5-tetrabromofuran, a very expensive starting material, with 4.4 equiv of arylboronic acids.[18]



20	Ar	Yield %
a	Ph	69
b	4-$MeOC_6H_4$	33
c	4-$CF_3C_6H_4$	77

Scheme 9. $Pd(OAc)_2$/PCy_3-catalyzed synthesis of symmetrical tetraarylfurans **20**

Miura and coworkers then used commercially available ethyl 3-thienylcarboxylate (**21**) as the starting material for the selective synthesis of tetrasubstituted thiophenes **24** having two different aryl groups in the 2,5- and 3,4-positions.[17] The first step of this synthesis (Scheme 10) involved the high yielding preparation of ethyl 2,5-diaryl-3-thienylcarboxylates **22** by $Pd(OAc)_2$/JohnPhos-catalyzed reaction of **21** with 3.0 equiv of aryl bromides in DMF at 120 °C in the presence of Cs_2CO_3 as the base.

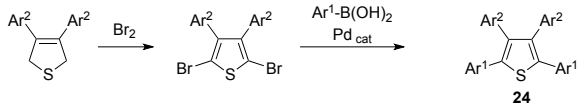


22	Ar	Yield %
a	Ph	91
b	4-$MeOC_6H_4$	71

24	Ar^1	Ar^2	Yield %
a	Ph	4-$MeOC_6H_4$	47
b	4-$MeOC_6H_4$	Ph	48
c	Ph	4-$CF_3C_6H_4$	57
d	4-$MeOC_6H_4$	4-$CF_3C_6H_4$	69

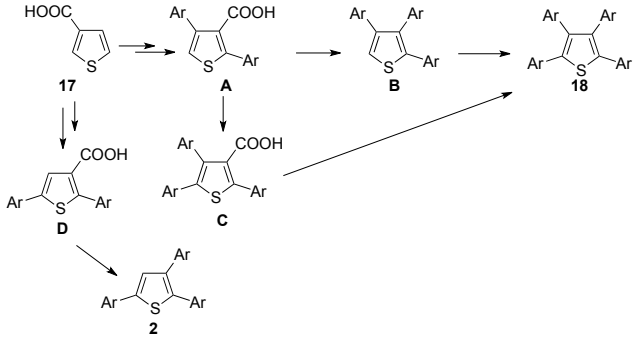
Scheme 10. Synthesis of tetraarylthiophenes **24** bearing two different aryl groups at the 2,5- and 3,4-positions

Hydrolysis of compounds **22** followed by treatment of the corresponding carboxylic acids **23** with 3.0 equiv of aryl bromides, 10 mol% $Pd(OAc)_2$, 40 mol% PCy_3 and 3.0 equiv of Cs_2CO_3 in mesitylene at 170 °C in the presence of molecular sieves then gave compounds **24** in moderate to good yields (Scheme 10). However, formation of a minor amount of a separable 2,3,5-triarylthiophene **2** could be detected by GLC-MS in each arylation reaction.[18] It is interesting to note that, in 2007, compounds of general formula **24** were synthesized by Suzuki-Miyaura couplings of 3,4-diaryl-2,5-dibromothiophenes, prepared by bromination of 3,4-diaryl-2,5-dihydrothiophenes (Scheme 11).[19]



Scheme 11. Synthesis of tetraarylthiophenes **24** via Suzuki arylation of 3,4-diaryl-2,5-dibromothiophenes

The details of the sequence of events leading to the formation of symmetrical tetraaryl-substituted thiophenes **18** from 3-thienylcarboxylic acid (**17**) were not elucidated. Nevertheless, Miura and coworkers proposed that the synthesis of compounds **18** involves the formation of intermediate 2,4-diaryl-3-thienylcarboxylic acids **A** through two direct C-H *ortho*-arylation reactions (Scheme 12).[17]



Scheme 12. Proposed sequence of events leading to the formation of compounds **18** from 3-thienylcarboxylic acid (**17**)

Decarboxylative arylation of **A** would then result in 2,3,4-triarylthiophenes **B** that would provide compounds **18** by direct C-H arylation. In addition, 2,3,5-triaryl-3-thienylcarboxylic acids **C**, which would be obtained by direct C-H arylation of **A**, might be converted to compounds **18** by *ipso*-arylation. Finally, a sequence of direct arylations of **17** would give 2,5-diaryl-3-thienylcarboxylic acids **D** that in turn might undergo decarboxylative arylation[20] to give 2,3,5-triarylthiophenes **2**, the by-products of the synthesis of **18**, and/or might undergo directed *ortho*-arylation providing compounds **C** (Scheme 12).[17]

In 2010, Liégault and coworkers developed innovative strategies for the regioselective synthesis of 2-aryl-3-hexylthiophenes **26** and 2-aryl-4-hexylthiophenes **27** (Figure 2),[21a] two classes of compounds previously inaccessible as single regioisomers via Pd-catalyzed direct C-H arylation of commercially available 3-hexylthiophene (**25**) (Figure 2) at positions 2 and 5, respectively.

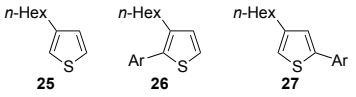
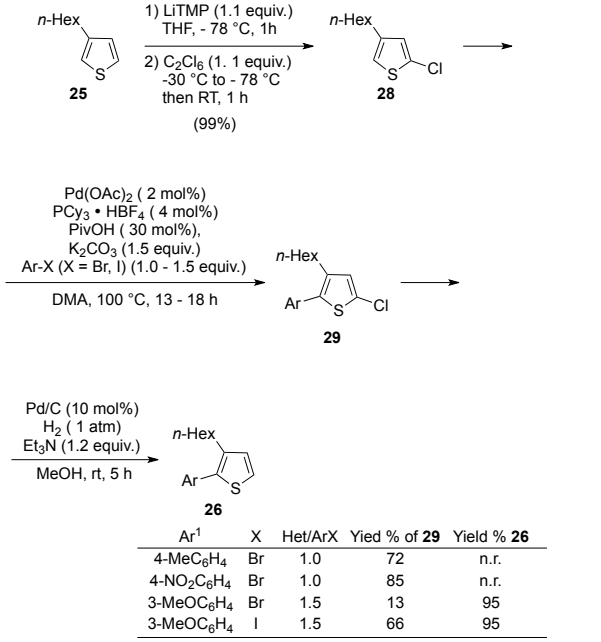


Figure 2. Chemical structures of compounds **25–27**

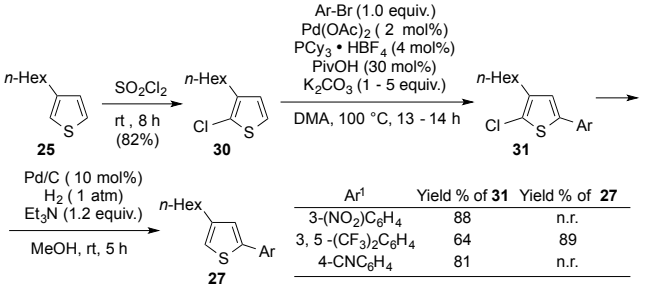
The strategies involved the use of a removable chloride substituent as an activating/blocking group in $Pd(OAc)_2/PCy_3$/pivalic acid-catalyzed direct arylations of the thiophene ring. Scheme 13 shows the reaction sequence used for the regioselective synthesis of compounds **26**. In the first step, 2-chloro-4-hexylthiophene (**28**) was prepared in 99% yield by deprotonation of **25** with lithium tetramethylpiperidide (LiTMP) followed by addition of hexachloroethane. Compound **28** was then reacted with 1.0 equiv of aryl halides, 2 mol% $Pd(OAc)_2$, 4 mol% $PCy_3{\cdot}HBF_4$, 30 mol% pivalic acid, and 1.5 equiv of K_2CO_3 in DMA at 100 °C providing 5-aryl-2-chloro-4-hexylthiophenes **29** as single regioisomers in good yields. Finally, removal of chlorine from **29** by treatment with a catalytic amount of Pd/C under a hydrogen atmosphere[21b] allowed to obtain 2-aryl-4-hexylthiophenes **26** in good yields.



Ar^1	X	Het/ArX	Yied % of **29**	Yield % **26**
4-MeC_6H_4	Br	1.0	72	n.r.
4-$NO_2C_6H_4$	Br	1.0	85	n.r.
3-$MeOC_6H_4$	Br	1.5	13	95
3-$MeOC_6H_4$	I	1.5	66	95

Scheme 13. Regioselective synthesis of 2-aryl-3-hexylthiophenes **26**

On the other hand, 2-aryl-4-hexylthiophenes **27** were synthesized using the reaction sequence depicted in Scheme 14.

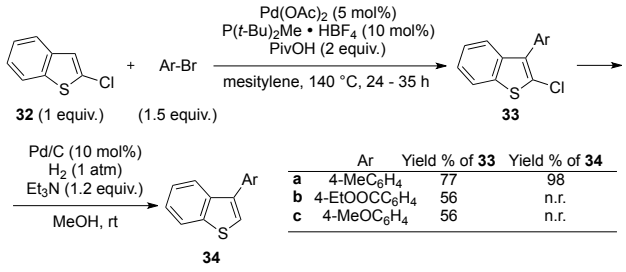


Ar^1	Yield % of **31**	Yield % of **27**
3-$(NO_2)C_6H_4$	88	n.r.
3, 5 -$(CF_3)_2C_6H_4$	64	89
4-CNC_6H_4	81	n.r.

Scheme 14. Regioselective synthesis of 2-aryl-4-hexylthiophenes **27**

Specifically, electrophilic chlorination of **25** with SO_2Cl_2 according to the literature[22] gave regioselectively compound **30** in 82% yield. The subsequent $Pd(OAc)_2/PCy_3{\cdot}HBF_4$/pivalic acid-catalyzed direct arylation of **30** with 1.0 equiv of aryl bromides provided compounds **31** as single regioisomers in good yields. Finally, the Pd-catalyzed removal of chlorine from compounds **31** gave the required 2-aryl-4-hexylthiophenes **27** in good yields. In an illustrative example compound **27**, in which Ar was 3,5-$(CF_3)_2C_6H_4$, was obtained in 89% yield.[20]

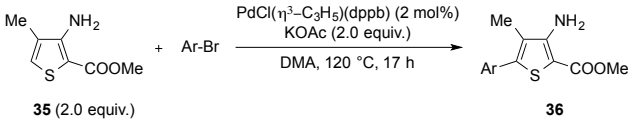
Liégault and coworkers also demonstrated that 3-arylbenzo[*b*]thiophenes **34**, which at that time were inaccessible by Pd-catalyzed direct arylation of benzo[*b*]thiophene,[23a–c] could be synthesized regioselectively and in high yields via a two-step protocol (Scheme 15) in which 2-chlorobenzo[*b*]thiophene (**32**)[23d] was reacted with 1.5 equiv of aryl bromides in mesitylene at 140 °C in the presence of a $Pd(OAc)_2/PCy_3{\cdot}HBF_4$/pivalic acid catalyst system and 2.0 equiv of Cs_2CO_3. Dechlorination of the resulting 3-aryl-2-chlorobenzo[*b*]thiophenes **33** by treatment with a catalytic amount of Pd/C under a hydrogen atmosphere may provide compounds **34**, as illustrated in the synthesis of compound **34a** in which Ar is *p*-tolyl (Scheme 15).[20] Interestingly, both electron-poor and electron-rich aryl bromides could be employed for the C-3 arylation of compound **32**.



	Ar	Yield % of **33**	Yield % of **34**
a	4-MeC_6H_4	77	98
b	4-$EtOOCC_6H_4$	56	n.r.
c	4-$MeOC_6H_4$	56	n.r.

Scheme 15. Two-step regioselective synthesis of 3-arylbenzo[*b*]thiophenes **34**

In 2010, Doucet and coworkers reported preliminary results on the Pd-catalyzed direct arylation of methyl 3-amino-4-methylthiophene-2-carboxylate (**35**),[24a] a commercially available substrate bearing a free NH_2 substituent at C-3 with carbon C-2 blocked by the easily removable methoxycarbonyl group. In 2012, the same research group investigated the scope of this interesting chemoselective reaction using a wide variety of electronically and sterically different aryl bromides, and demonstrated that the reaction of 2.0 equiv of **35** with 1.0 equiv of aryl bromides and 2.0 equiv of KOAc in DMA at 120 °C for 17 h in the presence of 2 mol% $PdCl(\eta^3\text{-}C_3H_5)$(dppb) gave chemoselectively 3-amino-5-aryl-4-methylthiophene-2-carboxylic acid methyl esters **36** (Scheme 16).[24b] The arylation reactions with electron-poor and electron-rich *para-, meta-* or *ortho*-substituted aryl bromides generally occurred in good to excellent yields, but the arylation reactions of **35** with 4-bromo-*N,N*-dimethylaniline and 2-bromobenzaldehyde did not produce the required C-5 arylation products. It also deserves to be pointed out that even electron-poor and sterically congested aryl bromide such as 2-bromobenzonitrile, 2-bromo(trifluoromethyl)benzene and methyl 2-bromobenzoate were found to provide the required C-5 arylation products in high yields.



36	Ar	Yield %	**36**	Ar	Yield %	**36**	Ar	Yield %
a	4-$(CHO)C_6H_4$	87	**i**	4-ClC_6H_4	84	**q**	3-$F_3CC_6H_4$	92
b	4-AcC_6H_4	90	**j**	4-MeC_6H_4	81	**r**	3-$(NO_2)C_6H_4$	79
c	4-$EtCOC_6H_4$	86	**k**	4-*t*-BuC_6H_4	67	**s**	3-ClC_6H_4	74
d	4-$PhCOC_6H_4$	74	**l**	4-$MeOC_6H_4$	58	**t**	3-$(NH_2)C_6H_4$	69
e	4-$MeOOCC_6H_4$	74	**m**	4-$Me_2NC_6H_4$	0	**u**	2-$MeOOCC_6H_4$	87
f	4-$NC\text{-}C_6H_4$	87	**n**	3-$(CHO)C_6H_4$	83	**v**	2-$NC\text{-}C_6H_4$	90
g	4-$(NO_2)C_6H_4$	83	**o**	3-AcC_6H_4	74	**w**	2-$F_3CC_6H_4$	88
h	4-FC_6H_4	89	**p**	3-$NC\text{-}C_6H_4$	90	**x**	2-$(CHO)C_6H_4$	0

Scheme 16. $PdCl(\eta^3\text{-}C_3H_5)$(dppb)-catalyzed direct arylation of compound **35** with *p-, m-* and *o*-substituted aryl bromides

The reactivity of heteroaryl bromides in the Pd-catalyzed direct arylation of **35** was also investigated and it was found that the synthesis of compounds **37–40** (Figure 3) under the experimental conditions illustrated in Scheme 16 occurred in high yields.

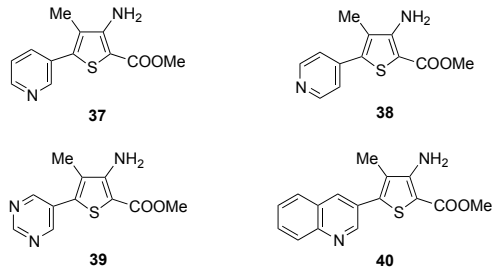
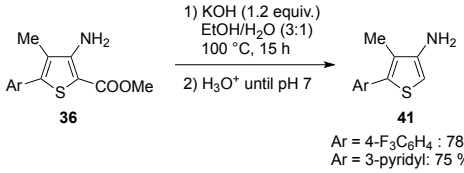


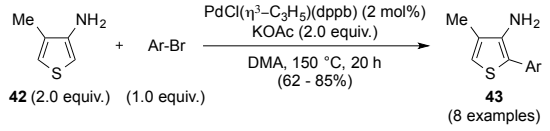
Figure 3. Chemical structures of compounds **37–40**

Doucet and coworkers then found that the methoxycarbonyl group could be removed efficiently from compounds **36** by treatment with KOH in a mixture of EtOH and water at 100 °C followed by acidification, providing 3-amino-5-aryl-4-methylthiophenes **41** in 75-78% yields (Scheme 17).[24b]



Scheme 17. Removal of the methoxycarbonyl group from compounds **36**

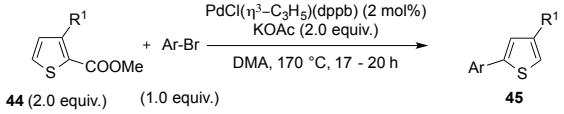
In this way it was possible to synthesize regioselectively compounds **41** which could not be prepared by Pd-catalyzed direct arylation of 3-amino-4-methylthiophene (**42**). Indeed, it was demonstrated that the $PdCl(\eta^3\text{-}C_3H_5)$(dppb)-catalyzed reaction of **42** with electron-rich or electron-poor aryl bromides in DMA at 150 °C in the presence of KOAc as base gave regioselectively 3-amino-2-aryl-4-methylthiophenes **43** in good yields (Scheme 18).[24b]



Scheme 18. Regioselective synthesis of 3-amino-2-aryl-4-methylthiophenes **43**

Doucet and coworkers suggested that the regioselectivity of these arylation reactions might be due either to electronic effects or to coordination of the free amino group to the palladium catalyst.[24b]

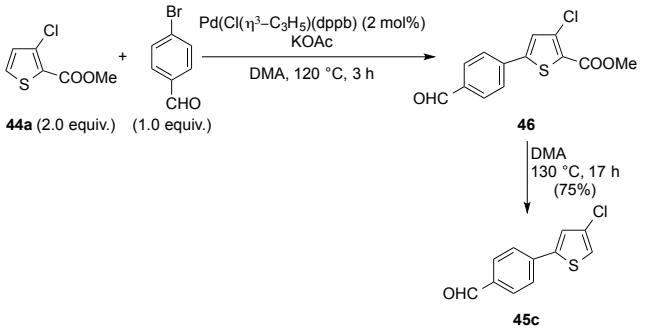
In 2012, Doucet and coworkers again illustrated the use of the methoxycarbonyl group as a removable blocking substituent at the C-2 position of thiophene derivatives in the regioselective synthesis of two 4-substituted 2-arylthiophenes of general formula **45** by Pd-catalyzed direct arylation of the corresponding 3-substituted methyl thiophene-2-carboxylates **44** (Scheme 19).[25]



45	R^1	Ar	Yield %
a	Cl	4-$(CN)C_6H_4$	67
b	MeO	4-$(NO_2)C_6H_4$	61

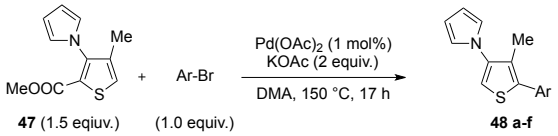
Scheme 19. Regioselective synthesis of 4-substituted 2-arylthiophenes **45**

In fact, they observed that treatment of 2.0 equiv of compounds **44** with 1.0 equiv of aryl bromides, 2 mol% $PdCl(\eta^3\text{-}C_3H_5)(dppb)$ and 2.0 equiv of KOAc in DMA at 170 °C provided compounds **45** in satisfactory yields. This process thus involved the one-pot regioselective C-H arylation at C-5 of the thiophene ring of the substrate accompanied by removal of the methoxycarbonyl group. However, the Pd-catalyzed reaction of **44a** with 4-bromobenzaldehyde in DMA at 120 °C in the presence of KOAc gave 4-(4-chlorothiophen-2-yl)benzaldehyde (**46**) in 70% yield, which by heating in DMA at 130 °C for 17 h provided 4-chloro-2-(4-formylphenyl)thiophene (**45c**) in 75% yield (Scheme 20).[25]



Scheme 20. Two-step regioselective synthesis of compound **45c**

Very recently, in continuation of their studies on the use of the methoxycarbonyl group as a removable blocking group in direct arylation reactions of thiophene derivatives, Doucet and coworkers investigated the ligand-free $Pd(OAc)_2$-catalyzed direct arylation of methyl 4-methyl-3-pyrrol-1-yl)thiophene-2-carboxylate (**47**) and found that the reaction of 1.5 equiv of this compound with 1.0 equiv of aryl bromide, 1 mol% $Pd(OAc)_2$ and 2.0 equiv of KOAc in DMA at 150 °C for 17 h under ligandless conditions gave 2-aryl-3-methyl-4-(pyrrol-1-yl)thiophenes **48** (Scheme 21).[46]



48	Ar	Yield %
a	4-$(CN)C_6H_4$	90
b	4-$EtCOC_6H_4$	72
c	4-ClC_6H_4	66
d	2-$(CN)C_6H_4$	79
e	3-CF_3 , 4-$(NO_2)C_6H_3$	70
f	4-$MeOC_6H_4$	0

Scheme 21. Pd-catalyzed direct arylation of compound **47** with aryl bromides under ligandless conditions

The reaction, which involved a C-5 arylation followed by removal of the methoxycarbonyl group, gave high yield of compounds **48** when aryl bromides bearing an electron-withdrawing group were used as arylating reagents. However, no formation of the desired arylation product **48f** was obtained using 4-bromoanisole as the electrophile and the reaction provided compound **49a** (Figure 4) in 68% yield.

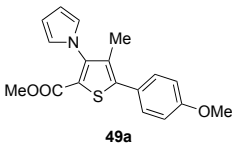
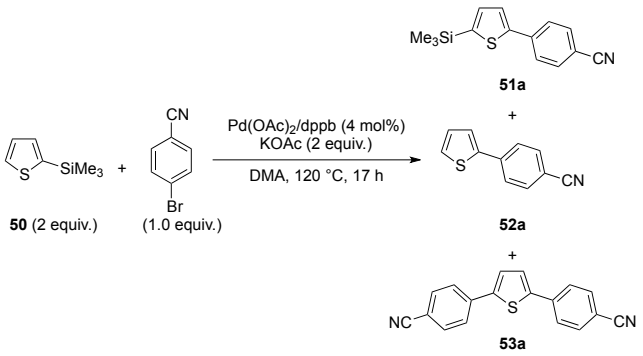


Figure 4. Chemical strcture of compound **49a**

Interestingly, good yields of 2-aryl-3-methyl-4-(pyrrol-1-

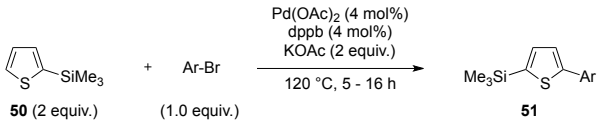
yl)thiophenes **48** were also obtained in Pd-catalyzed reactions at 150 °C involving the use of bromides of electron-deficient heteroarenes such as 3-bromopyridine, 5-bromonicotinonitrile, and 5-bromopyridine.[26] It was also found that the $Pd(OAc)_2$-catalyzed arylation reactions of compound **47** at 130 °C in the presence of KOAc occurred at the C-5 position of this substrate, but the reactions occurred without removal of the methoxycarbonyl group.[26] Unfortunately, the preparation of compound **47** was not reported.

Three years earlier, Doucet and coworkers had demonstrated that even the trimethylsilyl group could be used as a removable blocking group in Pd-catalyzed regioselective direct arylation reactions of the thiophene ring.[27] In fact, they found that the $Pd(OAc)_2$/dppb-catalyzed coupling of commercially available 2-(trimethylsilyl)thiophene (**50**) with 4-bromobenzonitrile in DMA at 120 °C in the presence of KOAc as the base gave a mixture of 4-(5-trimethylsilylthiophen-2-yl)benzonitrile (**51a**), 4-(thiophen-2-yl)benzonitrile (**52a**) and 2,5-diarylthiophene **53a** in a 11 : 78 : 11 ratio, respectively (Scheme 22).[27] Compound **52a**, which was the main component of the reaction mixture, derived from the regioselective C-H arylation of **50** accompanied by removal of the trimethylsilyl group and compound **53a** was formed by C-5 arylation of **52a**.



Scheme 22. $Pd(OAc)_2$/dppb-catalyzed reaction between thiophene **50** and 4-bromobenzonitrile at 120 °C for 17 h

It was also observed that the desilylation reaction leading to compounds **52a** and **53a** could be minimized by using reduced reaction times. Doucet and coworkers then identified the optimal reaction conditions outlined in Scheme 22 to prepare regioselectively and in satisfactory to good yields a variety of 2-aryl-5-trimethylsilylthiophenes **51** from compound **50** and aryl bromides.[27]

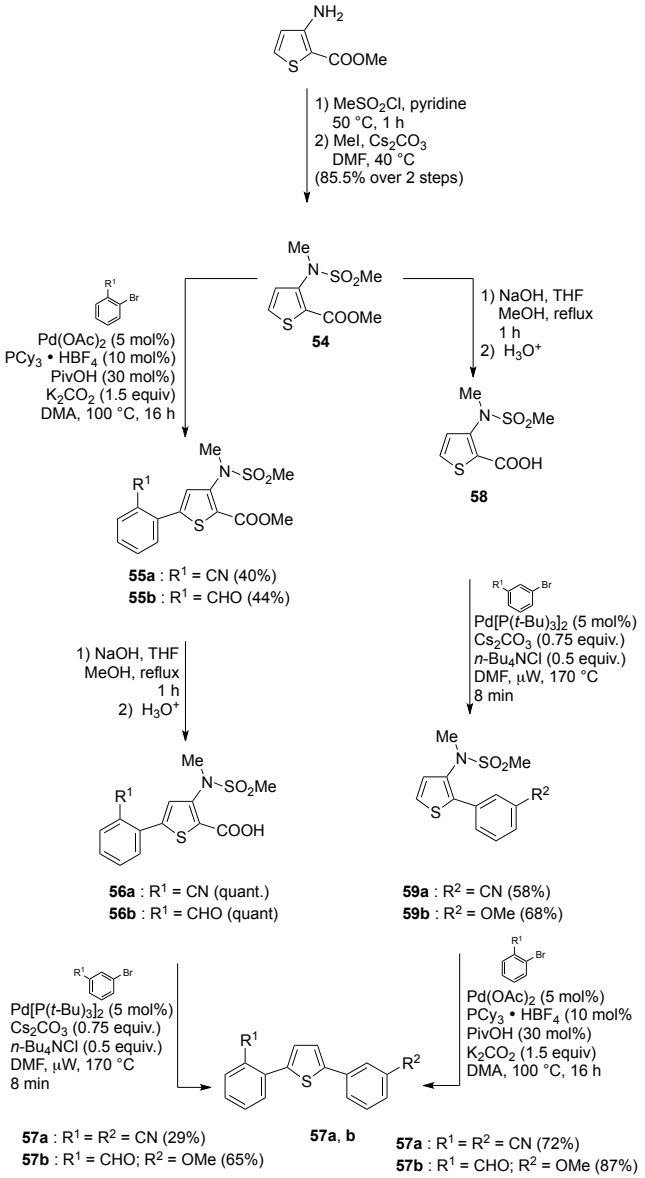


51	Reaction time (h)	Ar	Yield%
a	5	4-(CN)C_6H_4	65
b	7	4-EtCOC_6H_4	75
c	6	4-AcC_6H_4	70
d	6	4-(CHO)C_6H_4	72
e	5	4-MeOOCC_6H_4	79
f	11	4-$CF_3C_6H_4$	52
g	4	4-ClC_6H_4	78
h	5	3-NC-C_6H_4	64
i	7	2-NC-C_6H_4	73
j	7	2-(CHO)C_6H_4	84
k	16	2-$CF_3C_6H_4$	70

Scheme 23. Regioselective synthesis of 2-aryl-5-trimethylsilylthiophenes **51**

Unfortunately, Doucet and coworkers did not describe the conversion of compounds **51** into the corresponding 2-arylthiophenes **9**, but it was already known that 2-trimethylsilylthiophene derivatives undergo efficient desilylation by treatment with TBAF in THF at 60-70°C.[28]

In 2014, in the context of a study on the synthesis of ligands able to modulate islet amyloid polypeptide amyloidogenesis and cytotoxicity on β-pancreatic cells, Bourgault, Forgione and coworkers synthesized 2,5-diaryl-substituted thiophenes **57a** and **57b** from methyl 3-(*N*-methylmethylsulfonamido)thiophene-2-carboxylate (**54**) by using the methoxycarbonyl group of this reagent as a removable blocking group in Pd-catalyzed regioselective direct arylation reactions.[29a] Compound **54** was synthesized by treatment of methyl 3-aminothiophene-2-carboxylate with 1.5 equiv of methanesulfonyl chloride in pyridine at 50 °C for 1 h according to a modification of the procedure described by Tondi and coworkers,[29b] followed by treatment of the resulting methyl 3-(methylsulfonamido)thiophene-2-carboxylate with 2.5 equiv of methyl iodide and 1.0 equiv of Cs_2CO_3 in DMF at 40 °C for 2 h (Scheme 24).

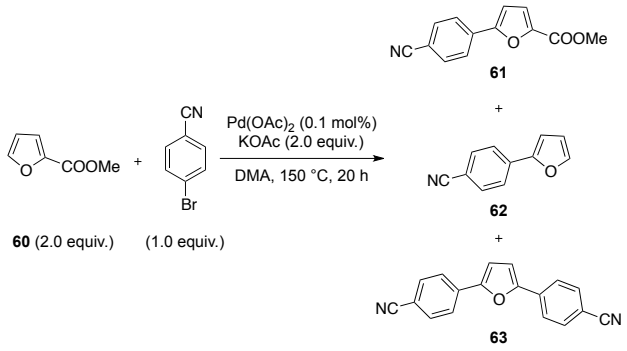


Scheme 24. Synthesis of 2,5-diarylthiophenes **57a** and **57b** starting from thiophene **54** via two different routes

As depicted in Scheme 24, two different pathways were used to prepare compounds **57a** and **57b**. In the first route, the Pd-catalyzed direct C-5 arylations of **54** with 2-bromobenzonitrile and 2-bromobenzaldehyde were carried out using the procedure developed by Fagnou and coworkers[30] with slight modifications providing compounds **55a** and **55b** in 40 and 44% yield, respectively. These compounds were then saponified and the resulting carboxylic acids, **56a** and **56b**, were subjected to microwave-induced Pd-catalyzed decarboxylative arylation according to the procedure described by Forgione and coworkers with slight modifications.[20a] In this way compounds **57a** and **57b** were synthesized in 29 and 65% yield, respectively.

The second route developed for the preparation of the target compounds proved more efficient than the first route. It began with the saponification of **54**. The resulting carboxylic acid **58** was subjected to decarboxylative arylation reactions with 3-bromobenzonitrile and 3-bromoanisole, which provided compounds **59a** and **59b** in 58 and 68% yield, respectively. Finally, C-5 arylation of these substances by $Pd(OAc)_2/PCy_3{\cdot}HBF_4$/pivalic acid-catalyzed reactions with 2-bromobenzonitrile and 2-bromobenzaldehyde gave the required unsymmetrically substituted 2,5-diarylthiophenes **57a** and **57b** in 72 and 87% yield, respectively.[29a]

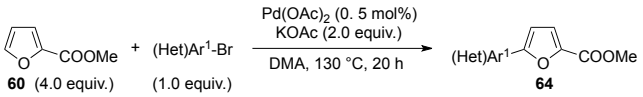
The removable methoxycarbonyl group was also used by Doucet and coworkers in the regioselective arylation of methyl 2-furoate (**60**). In 2009, they found that the coupling of 2.0 equiv of **60** with 1.0 equiv of 4-bromobenzonitrile in DMA at 150 °C for 20 h in the presence of 0.1 mol% $Pd(OAc)_2$ and 2.0 equiv of KOAc gave a mixture of 5-arylated methyl 2-furoate **61**, 2-arylfuran **62** and 2,5-diarylfuran **63** from which **61** was isolated in 26% yield (Scheme 25).[31]



Scheme 25. Ligand-free $Pd(OAc)_2$-catalyzed reaction of methyl 2-furoate (**60**) with 4-bromobenzonitrile

The low yield of **61** in this ligand-free direct arylation was caused by the partial removal of its methoxycarbonyl group with formation of **62**, which was in turn the direct precursor to **63**. Nevertheless, it was found that when the arylation reaction of Scheme 25 was carried out at 130 °C instead at 150 °C and using 4.0 equiv of **60**, a smaller amount of **62** was formed allowing the isolation of **61** in 70% yield.[31]

A slight modification of this protocol involving the use of 0.5 mol% $Pd(OAc)_2$ instead of 0.1 mol% was then employed to prepare a wide variety of methyl 5-(hetero)aryl-2-furoates **64** from **60** and (hetero)aryl bromides. Representative examples of these ligand-free direct arylations, which were found to tolerate a wide range of functional groups, such as acetyl, ester, formyl, nitrile, nitro, chloro, fluoro and trifluoromethyl, are illustrated in Scheme 26.



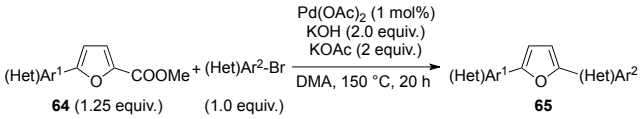
60 (4.0 equiv.) (1.0 equiv.) **64**

64	(Het)Ar^1	Yield %	**64**	(Het)Ar^1	Yield %
a	4-AcC_6H_4	77	**j**	3-ClC_6H_4	80
b	4-(CHO)C_6H_4	73	**k**	2-(CN)C_6H_4	83
c	4-(COOMe)C_6H_4	78	**l**	2-(CF_3)C_6H_4	64
d	4-(CF_3)C_6H_4	69	**m**	1-naphthyl	80
e	4-(NO_2)C_6H_4	79	**n**	3-pyridyl	69
f	4-ClC_6H_4	73	**o**	4-pyridyl	72
g	4-FC_6H_4	66	**p**	quinolin-3-yl	33
h	4-*t*-BuC_6H_4	9	**q**	isoquinolin-4-yl	14
i	4-MeC_6H_4	35	**r**	4-MeOC_6H_4	8

Scheme 26. Ligand-free $Pd(OAc)_2$-catalyzed arylation reactions of methyl 2-furoate (**60**) with (hetero)aryl bromides at 130 °C

Good yields were generally obtained, but the reactions with 1-bromo-4-(*t*-butyl)benzene, 4-bromotoluene and 4-bromoanisole gave the required coupling products in low yields. It was also found that the low yields obtained using 3-bromoquinoline and 4-bromoisoquinoline as arylating reagents could be significantly improved by using a reaction temperature of 150 °C instead of 130 °C.[31]

Fu and Doucet also investigated the synthesis of 2,5-di(hetero)aryl-substituted furans **65** through a one-pot process involving the conversion of compounds **64** into the corresponding furoic acids followed by decarboxylative arylation.[31] Thus, 1.25 equiv of compounds **64** were reacted with 1.0 equiv of (hetero)aryl bromides, 2.0 equiv of KOAc, 2.0 equiv of KOH and 1 mol% $Pd(OAc)_2$ at 150 °C for 20 h. The yields of the resulting compounds **65** were found to strongly depend on the nature of the substituents on compounds **64**. Illustrative examples of the results obtained in these couplings are shown in Scheme 27. The couplings of **64** with 4-bromobenzaldehyde and 4-bromobenzonitrile were carried out by using 4.0 equiv of KOAc and 2.0 equiv of K_2CO_3 because the formyl and cyano groups were unstable under the basic conditions illustrated in Scheme 27.[31]

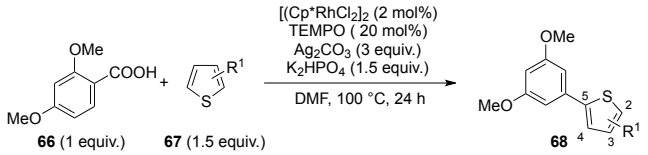


64 (1.25 equiv.) (1.0 equiv.) **65**

65	(Het)Ar^1	(Het)Ar^2	Yield %
a	3-$CF_3C_6H_4$	3-pyridyl	65
b	3-pyridyl	3-$CF_3C_6H_4$	35
c	1-naphthyl	3-pyridyl	70
d	3-pyridyl	1-naphthyl	87
e	1-naphthyl	4-(NO_2)C_6H_4	51
f	1-naphthyl	4-F-C_6H_4	78
g	4-*t*-BuC_6H_4	4-(OH)C_6H_4	41
h	3-$CF_3C_6H_4$	4-(CN)C_6H_4	52
i	3-pyridyl	4-*t*-BuC_6H_4	70

Scheme 27. Synthesis of 2,5-di(hetero)arylfurans **65** from methyl 5-(hetero)aryl-2-furoates **64**

In concluding this section it must also be mentioned that, in March 2015, Su and coworkers used the carboxylic group of the *ortho*-substituted benzoic acid **66** as traceless directing group for the rhodium(III)-catalyzed decarboxylative *ortho* C-H arylation of thiophenes of general formula **67**.[33] In particular, they reported that, under optimized conditions, the reaction of 1.0 equiv of carboxylic acid **66** with 1.5 equiv of thiophenes **67**, 2 mol% $[Cp^*RhCl_2]_2$, 2.0 equiv of Ag_2CO_3, 1.5 equiv of K_2HPO_4 and 20 mol% TEMPO in DMF or NMP at 100 °C for 24 h produced 2-arylthiophenes **68** in good yields with complete regioselectivity (Scheme 28).



66 (1 equiv.) **67** (1.5 equiv.) **68**

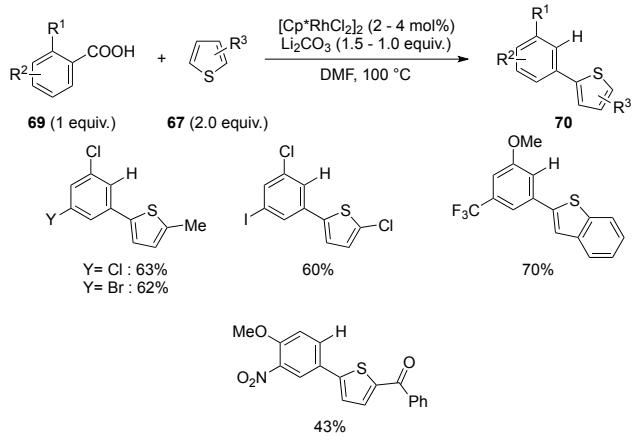
Rapresentative results:

68	R^1	Yield %
a	2-*n*-Bu	76
b	2-Me	81
c	2-Ph	84
d	2-PhCO	83
e	2-CHO	73
f	2-Cl	83
g	2-Br	82
h	2-CN	72
i	2-EtOOC	81
j	3-Me	51

Scheme 28. Rh-catalyzed decarboxylative arylation of thiophenes **67** with 2,4-dimethoxybenzoic acid (**66**)

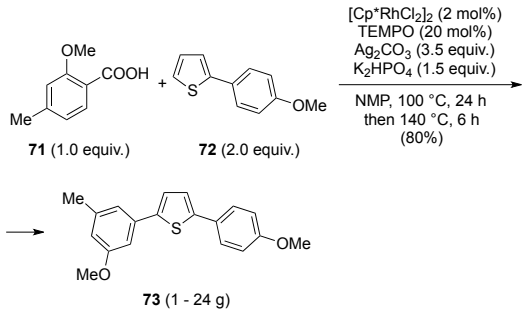
TEMPO, which was used as additive, was found to have a positive effect on the reaction outcome by accelerating the oxidation of Rh(I) to Rh(III) as an electron transfer intermediate.[34] Interestingly, thiophenes bearing functional groups such as chloro, bromo, formyl, keto, ester, and cyano proved to be suitable substrates and gave high yields in the Rh-catalyzed decarboxylative arylations with 2,4-dimethoxybenzoic acid (**66**).

Satisfactory to good yields were also obtained in the Rh-catalyzed C-2 arylation of benzo[*b*]thiophene and 3-bromo benzo[*b*]thiophene.[33] However, the reaction conditions used to prepare compounds **68** proved to be unsuitable for the high yielding arylation of thiophenes with benzoic acids bearing methyl, chloro, trifluoromethyl or nitro substituents. Nevertheless, the reactions involving a variety of *ortho*-substituted carboxylic acids **69** different from **66** and thiophenes **67** gave the required arylation products **70** in good yields when Li_2CO_3 instead of K_2HPO_4 was used as the base and the reactions were carried out in the absence of Ag_2CO_3 and TEMPO. Scheme 29 illustrates the conditions used for the Rh-catalyzed arylation reactions of thiophenes **67** with carboxylic acids **69** in the presence of Li_2CO_3 as well as some illustrative results.[33]



Scheme 29. Rh-catalyzed decarboxylative arylation reaction of thiophenes **67** with *ortho*-substituted benzoic acids **69** in the presence of Li_2CO_3

It should be noted that a modification of the protocol developed for the synthesis of compounds **68** involving the use of NMP instead of DMF as the solvent and a higher reaction temperature allowed the high yielding synthesis of 2-(3-methoxy-5-methylphenyl)-5-(4-methoxyphenyl)thiophene (**73**) on a gram scale from 2-methoxy-4-methylbenzoic acid (**71**) and 2-(4-methoxyphenyl)thiophene (**72**) (Scheme 30).[33] Compound **73** in a precursor to a 17β-hydroxysteroid dehydrogenase inhibitor.[35]



Scheme 30. Synthesis of compound **73**

It was also found that experimental conditions similar to those illustrated in Scheme 29 allowed Rh-catalyzed decarboxylative arylation reactions of thiophenes with heteroaryl-3-carboxylic acids thereby providing compounds such as heteroarylthiophenes **74** and **75** (Figure 5) in good yields.

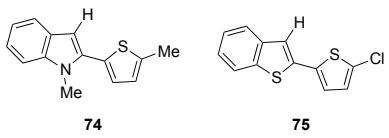
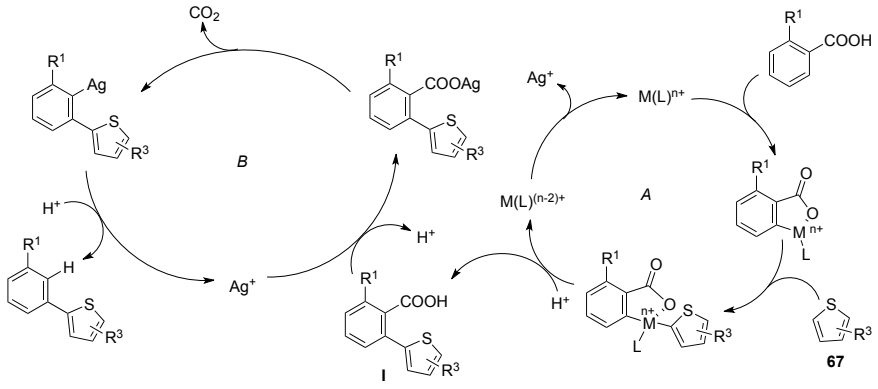


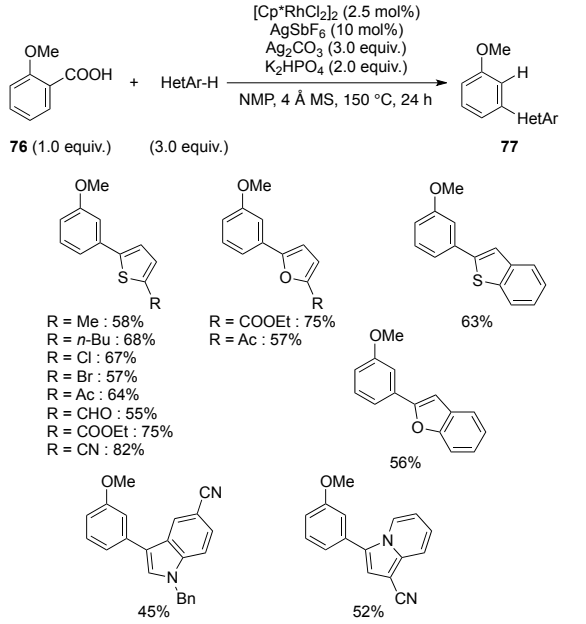
Figure 5. Chemical structures of compounds **74** and **75**

Finally, Su and coworkers proposed a mechanism involving two catalytic cycles for the developed Rh-catalyzed decarboxylative arylation reaction of thiophenes with *ortho*-substituted benzoic acids in the presence of Ag_2CO_3, (Scheme 31). The first cycle (cycle *A*) involved a metal-catalyzed arylcarboxylic acid directed *ortho*-arylation that gave rise to the *ortho*-thienyl-substituted arylcarboxylic acid **I**. The second cycle (cycle *B*) involved a silver-catalyzed protodecarboxylation of **I**.[33]



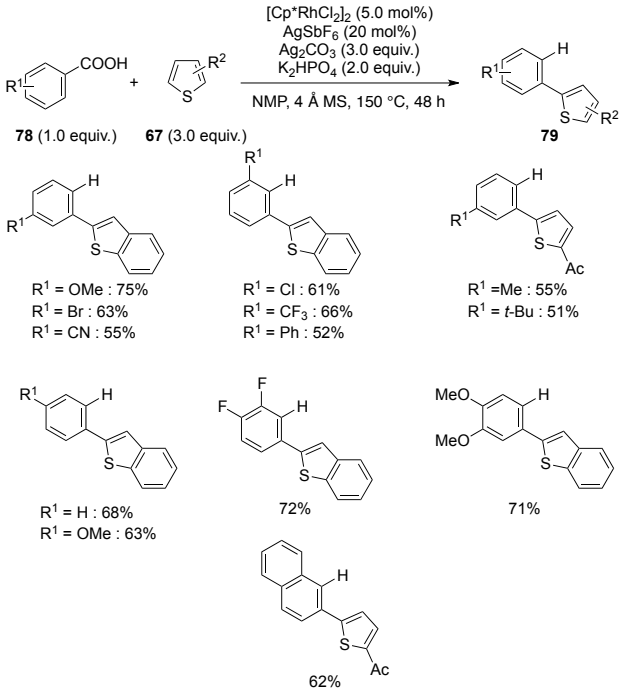
Scheme 31. Proposed mechanism for the Rh-catalyzed decarboxylative arylation of thiophenes with *ortho*-substituted arylcarboxylic acids in the presence of Ag_2CO_3

Still in March 2015, Lan, You and coworkers developed a highly regioselective Rh-catalyzed decarboxylative *ortho*-heteroarylation of arylcarboxylic acids with heteroarenes such as thiophenes, furans, benzo[*b*]thiophenes, indoles and indolizines by using the carboxylic acid as a traceless directing group.[36] The reactions, which exhibited a substrate scope of both the arylcarboxylic acids and the heteroarenes wider than that reported by Su and coworkers,[33] in the case of the reactions of 2-methoxybenzoic acid (**76**) involved treatment of 1.0 equiv of this carboxylic acid with 3.0 equiv of heteroarenes, 2.5 mol% $[Cp^*RhCl_2]_2$, 3.0 equiv of Ag_2CO_3, 10 mol% $AgSbF_6$, and 2.0 equiv of K_2HPO_4 in NMP at 150 °C for 24 h (Scheme 32). The resulting *meta*-heteroarylated products **77** were obtained in synthetically useful yields. Remarkably, functional groups such as Cl, Br, CN, CHO, Ac and COOEt were found to be compatible with this protocol.



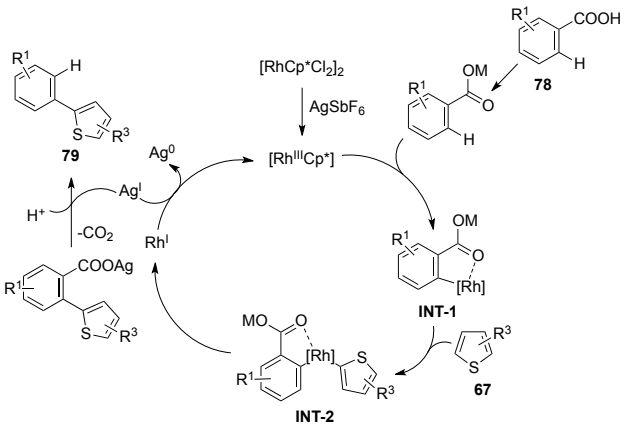
Scheme 32. Rh-catalyzed decarboxylative *ortho*-heteroarylation of 2-methoxybenzoic acid (**76**)

Lan, You and coworkers then examined the scope of the arylcarboxylic acids and found that the reaction of *ortho*- and *para*-substituted benzoic acids **78** bearing both electron-donating and electron-withdrawing substituents with benzo[*b*]thiophene and 2-substituted thiophenes provided the *meta*-heteroarylated products **79** in moderate to good yields (Scheme 33). However, the protocol used for the synthesis of compounds **79** differed from that employed to prepare compounds **77** as concerned the catalyst loading, which was higher in the case of the synthesis of compounds **79**.



Scheme 33. Rh-catalyzed decarboxylative heteroarylation of *ortho*- and *para*-substituted benzoic acids with benzo[*b*]thiophene and 2-substituted thiophenes

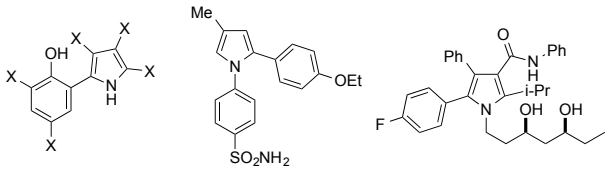
In the mechanism proposed for these reactions (Scheme 34),[36] which was not very different from the one formulated by Su and coworkers,[33] the intermediate rhodacycle **INT-1** would react with thiophenes **67** to give the heteroaryl-rhodacycle intermediate **INT-2** that by means of reductive elimination and subsequent protodecarboxylation would provide the *ortho*-heteroarylated products **79**.



Scheme 34. Possible mechanism for the *ortho*-heteroarylation of arylcarboxylic acids **78**

2.2. Direct (hetero)arylation reactions of pyrrole, indole, carbazole and indolizine ring systems

In the last few decades the synthesis of 2-arylated pyrroles via Pd-catalyzed intermolecular direct arylation reactions of *N*-protected pyrroles or free NH-pyrrole has been the subject of several studies.[37–47] In fact, 2-arylpyrroles are important structures that serve as key components of naturally-occurring compounds such as pentabromopseudiin (**80a**)[48] and pentachloropseudiin (**80b**),[49] the novel inhibitor of COX-2 apricoxib (**81**),[50], the cholesterol-lowering drug atovarstatin (**82**)[51] (Figure 6), and some Cdc7 kinase inhibitors.[52]



80a : X = Br
80b : X = Cl

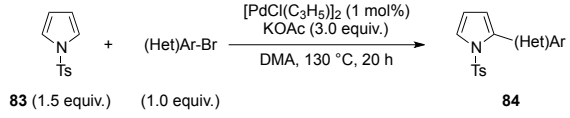
81

82

Figure 6. Chemical structures of compounds **80a**, **80b**, **81** and **82**

However, few of the various Pd-catalyzed direct C-H arylation reactions of the pyrrole ring that have been reported in the literature relate to the acquisition of high C-2 regioselectivity through the use of removable protecting groups.

In 2012, Doucet and coworkers investigated the use of the removable *N*-tosyl group in Pd-catalyzed reactions of commercially available *N*-tosylpyrrole (**83**) with (hetero)aryl bromides and found that under optimized conditions the reaction of 1.5 equiv of **83** with 1.0 equiv of (hetero)aryl bromides, 1 mol% $[PdCl(C_3H_5)]_2$ and 3.0 equiv of KOAc in DMA at 130 °C for 20 h produced 2-(hetero)aryl-*N*-tosylpyrroles **84** in moderate to good yields (Scheme 35).[44] The aryl bromides that were used as arylating reagents possessed electron-withdrawing or electron-neutral substituents and the heteroaryl bromides were nitrogen-containing six-membered derivatives. Interestingly, the reactions proved to be chemoselective and even substituents on the aryl bromides such as the CHO or Cl group were well tolerated.

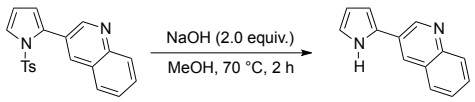


83 (1.5 equiv.) (1.0 equiv.) **84**

84	(Het)Ar	Yield %
a	4-(CHO)C_6H_4	62
b	4-(EtCO)C_6H_4	61
c	4-MeOOC-C_6H_4	63
d	4-$CF_3C_6H_4$	55
e	4-FC_6H_4	64
f	4-ClC_6H_4	62
g	4-*t*-BuC_6H_4	41
h	4-MeC_6H_4	47
i	3-(CN)C_6H_4	68
j	2-(CN)C&H_4	60
k	3-pyridyl	40
l	4-pyridyl	58
m	3-quinolinyl	40
n	4-isoquinolinyl	47
o	5-pyrimidyl	46

Scheme 35. Pd-catalyzed direct C-2 (hetero)arylation of *N*-tosylpyrrole (**83**) with (hetero)aryl bromides

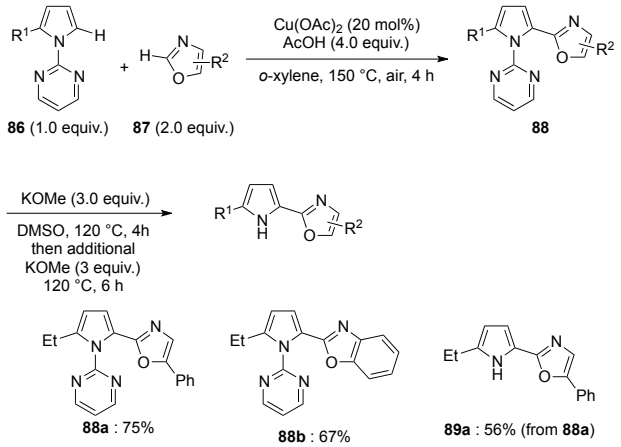
Compounds **84** were then efficiently *N*-deprotected by treatment with NaOH in MeOH at 70 °C. For instance, under these conditions compound **84m** gave free NH-pyrrole **85** in 89% yield (Scheme 36).[44]



84m **85**

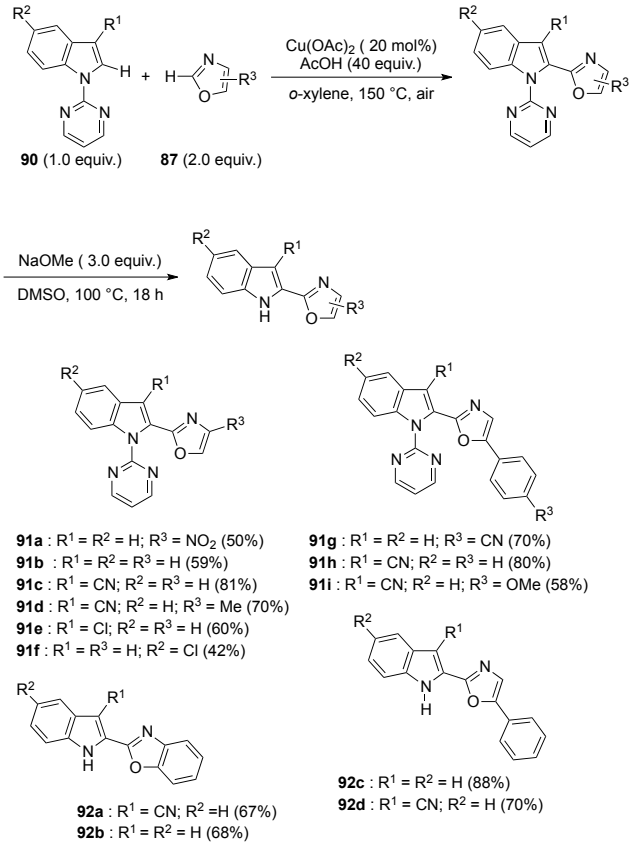
Scheme 36. *N*-Deprotection of *N*-tosylpyrrole **84m**

Also in 2012, Hirano, Miura and coworkers developed an effective two-step method for the regioselective synthesis of free NH 2-[(benz)oxazol-2-yl]pyrroles **89** in which the *N*-2-pyrimidyl group was used as a removable directing group.[53] The first step involved the copper-catalyzed dehydrogenative cross-coupling reaction of 1-(pyrimidin-2-yl)-1*H*-pyrroles **86** with (benz)oxazoles **87**, which was carried out in *o*-xylene at 150 °C using atmospheric oxygen as the sole oxidant (Scheme 37). The resulting *N*-2-pyrimidin-2-yl protected cross-coupling products **88** were obtained in good yields. In the second step, the 2-pirimidyl group was efficiently removed from compounds **88** by treatment with a large molar excess of KOMe in DMSO at 100-120 °C (Scheme 37).[53] Compound **86** were in turn prepared in high yields by treating the corresponding free NH-pyrroles with 1.1 equiv of NaH (60% dispersion in mineral oil) in DMF at 0 °C for 0.5 h, followed by the reaction with 1.2 equiv of 2-chloropyrimidine at 130 °C for 24 h.[53]



Scheme 37. $Cu(OAc)_2$-catalyzed dehydrogenative cross-coupling of pyrroles **86** with (benzo)oxazoles **87** followed by removal of the 2-pyrimidyl group from the resulting products **88**

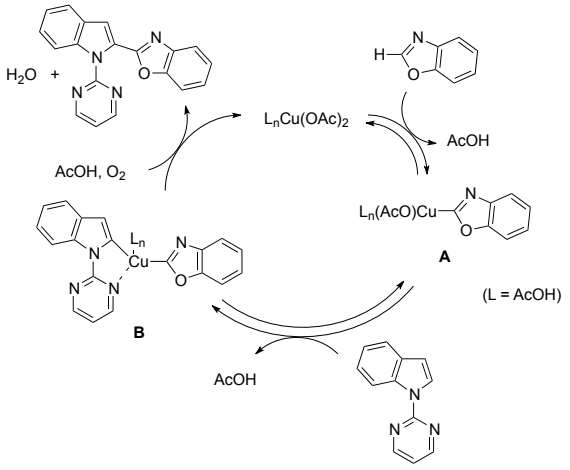
The copper-catalysis also proved applicable to the dehydrogenative cross-coupling reaction of *N*-2-pyrimidyl-substituted indoles **90** and (benz)oxazoles **87** (Scheme 38).[53]



Scheme 38. $Cu(OAc)_2$-catalyzed dehydrogenative cross-coupling of indoles **90** with (benz)oxazoles **87** followed by removal of the 2-pyrimidyl group from the resulting reaction products **91**

The resulting 2-[1-(pyrimidin-2-yl)-1*H*-indol-2-yl](benz)oxazoles **91**, which were obtained in moderate to good yields, could be *N*-deprotected by treatment with 3.0 equiv of NaOMe in DMSO at 100 °C for 18 h providing compound **92** in good yields (Scheme 38).[53] Compounds **90**, the starting materials of this process, were prepared by the reaction of the corresponding free NH-indoles with 1.5 equiv of NaH (60% dispersion in mineral oil) in DMF at room temperature for 0.5 h followed by treatment with 1.5 equiv of 2-chloropyrimidine at 150 °C for 12 h.[53]

Hirano, Miura and coworkers also proposed a plausible reaction mechanism for the dehydrogenative cross-coupling of *N*-(2-pyrimidyl)indole with benzoxazole (Scheme 39). It included *i)* formation of heteroarylcopper intermediates **A**; *ii)* coordination of the pyrimidyl nitrogen atom of *N*-(2-pyrimidyl)-1*H*-indole to the copper center of **A**; and *iii)* the reaction of the resulting intermediate **B** with dioxygen and acetic acid with the consequent formation of the desired cross-coupling product and regeneration of the catalyst system.



Scheme 39. Plausible mechanism for the dehydrogenative Cu-catalyzed cross-coupling reaction of *N*-(2-pyrimidyl)-1*H*-indole with benzoxazole

However, an alternative mechanism was not ruled out. It included *i)* formation of an indolylcopper species through a chelation-assisted C-H cupration of *N*-(2-pyrimidyl)-1*H*-indole; *ii)* insertion of the C-N bond of benzoxazole to the C-Cu bond to give complex **C** (Figure 7); and *iii)* oxidation leading to rearomatization of the benzoxazole core.[53]

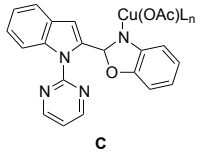
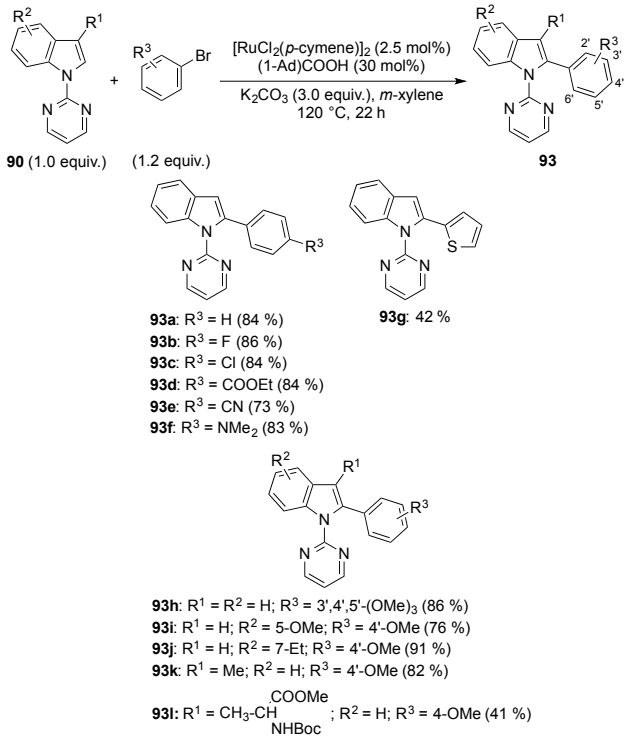


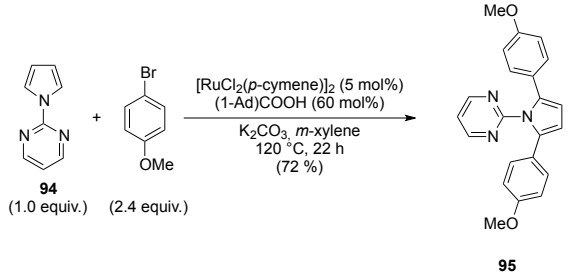
Figure 7. Chemical structure of complex **C**

Many other methods for the regioselective synthesis of 2-(hetero)arylindoles via transition metal-catalyzed direct arylation reactions have been reported in the literature.[54–56] In fact, these heteroarene derivatives are recurrent molecular scaffolds in various biologically active compounds including estrogen antagonists,[57] nitric oxide synthase and NF-kB inhibitors,[58] selective high-affinity antagonists for the h5-HT_{2A} receptor,[59] CDK (cyclin-dependent kinase) inhibitors and cytotoxic agents,[60] and ligands for several G-protein-coupled receptors.[61] In several cases, suitable removable NH protecting groups or traceless directing substituents have been used to achieve high C-2 regioselectivity in direct arylation reactions of the indole ring systems. In 2011, the readily installable and removable *N*-(2-pyrimidyl) group was used by Ackermann and Lygin in the Ru-catalyzed direct C-2 arylation reactions of indoles and pyrroles with aryl halides.[55a] It was found that, under optimized conditions, the reaction of 1.0 equiv of *N*-2-pyrimidyl-substituted indoles **90** with 1.2 equiv of aryl bromides, 2.5 mol% $[RuCl_2(p\text{-cymene})]_2$, 30 mol% 1-adamantylcarboxylic acid [(1-Ad)COOH], and 3.0 equiv of K_2CO_3 in *m*-xylene at 120 °C for 22 h produced 2-aryl-1-(2-pyrimidyl)-1*H*-indoles **93** in good yields (Scheme 40).



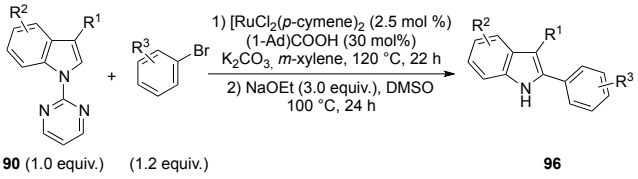
Scheme 40. Ru-catalyzed direct C-2 arylation of indoles **90** with aryl bromides

Aryl chlorides could also be used as arylating reagents, but the most efficient catalysis in this case was achieved using $(1\text{-Ad})_2P(O)H$ as the preligand.[55a] It was also found that a protocol similar to that developed for the synthesis of compounds **93** was applicable to the direct α-arylation of 2-(1-pyrrol-1-yl)pyrimidine (**94**). For instance, treatment of 1.0 equiv of **94** with 2.4 equiv of 4-bromoanisole, 5 mol% $[RuCl_2(p\text{-cymene})]_2$, and 60 mol% (1-Ad)COOH in *m*-xylene at 120 °C in the presence of K_2CO_3 as the base gave 2-[2,5-bis(4-methoxyphenyl)-1*H*-pyrrol-1-yl]pyrimidine (**95**) in 72% yield (Scheme 41).[55a]



Scheme 41. Synthesis of 2,5-diarylpyrrole **95**

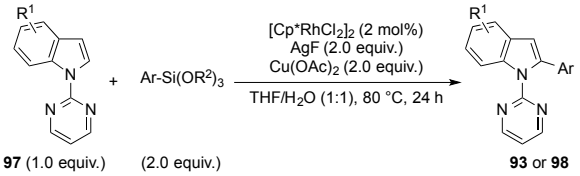
Finally, taking into account that the *N*-2-pyrimidyl group of *N*-2-pyrimidylindoles could be readily removed under basic conditions, Ackermann and Lygin developed a one-pot synthesis of free NH 2-aryl-1*H*-indoles **96** that involved the Ru-catalyzed C-2 arylation of compounds **90** with aryl bromides followed by removal of the 2-pyrimidyl protecting group from the resulting arylated derivatives by treatment with NaOEt in DMSO at 100 °C (Scheme 42). This protocol allowed the synthesis of compounds **96** in good yields.[55a]



96	R^1	R^2	R^3	Yield %
a	H	H	4'-OMe	77
b	H	5-OMe	H	72
c	H	7-Et	H	68
d	Me	H	H	73

Scheme 42. One-pot synthesis of free NH 2-aryl-1*H*-indoles **96**

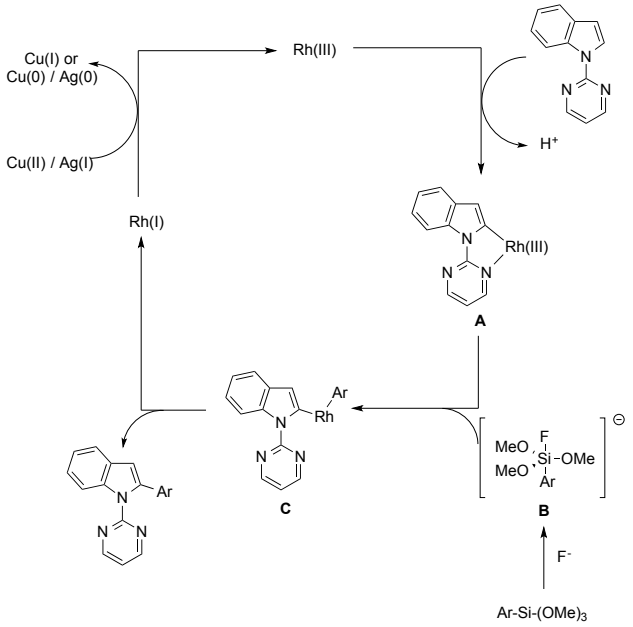
More recently, Xu, Loh and coworkers used the 2-pyrimidyl group as a directing NH protecting group in the regioselective synthesis of 2-aryl-1-(2-pyrimidyl)-1*H*-indoles **98** by Rh catalyzed reaction of 1-(2-pyrimidyl)-1*H*-indoles **97** with aryltrialkoxysilanes.[56b] The C-2 acylation reactions, which were carried out in a mixture of THF and water at 80 °C in the presence of 2 mol% $[Cp^*RhCl_2]_2$, 2.0 equiv of AgF and 2.0 equiv of $Cu(OAc)_2$ as the oxidant, exhibited excellent functional group compatibility and gave the coupling products **93a**, **93c**, and **98a-t** in good to excellent yields (Scheme 43).[56b] Unfortunately, the removal of the *N*-(2-pyrimidyl) protecting group from compounds **98** was not described.



93 or **98**	R^1	Ar	R^2	Yield%
93a	H	Ph	Me	92
98a	H	3-MeC_6H_4	Et	60
98b	H	4-MeC_6H_4	Et	79
98c	H	4-$CF_3C_6H_4$	Et	81
93c	H	4-ClC_6H_4	Et	93
98d	H	4-$MeOC_6H_4$	Me	92
98e	H	1-naphthyl	Me	80
98f	H	2-thienyl	Et	67
98g	3-Me	Ph	Me	81
98h	3-Cl	Ph	Me	86
98i	3-Br	Ph	Me	83
98j	4-Me	Ph	Me	95
98k	4-MeOOC	Ph	Me	85
98l	4-Cl	Ph	Me	91
98m	5-Me	Ph	Me	90
98n	5-MeO	Ph	Me	94
98o	5-F	Ph	Me	87
98p	5-Br	Ph	Me	91
98q	5-CN	Ph	Me	88
98r	6-F	Ph	Me	88
98s	6-Br	Ph	Me	96
98t	7-Me	Ph	Me	88

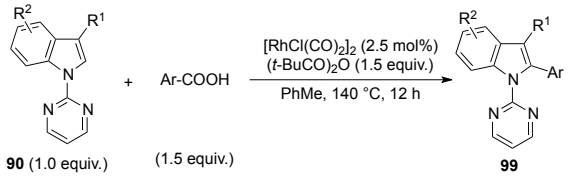
Scheme 43. Rh-catalyzed Ag-mediated direct C-2 arylation of 1-(2-pyrimidyl)-1*H*-indoles **97** with aryltrialkoxysilanes

The results of preliminary isotope experiments suggested that the C-H bond cleavage was not the rate-determining step of the catalytic cycle of these reactions for which, on the basis of previous reports,[62] Xu, Loh and coworkers proposed the plausible mechanism shown in Scheme 44. In this mechanism the catalytic cycle would begin by the coordination of the nitrogen atom of the 2-pyrimidyl group of the substrate to the rhodium catalyst. Subsequent cyclometalation reaction via C-H bond cleavage would give rhodacycle **A**. This intermediate would react with the pentavalent arylsilicate **B** to afford the Rh(III) intermediate **C**. Finally, reductive elimination would provide the required cross-coupling product and Rh(I) species, which would be reoxidized to Rh(III) species by AgF or $Cu(OAc)_2$ to complete the catalytic cycle.[56b]



Scheme 44. Plausible mechanism for the Rh-catalyzed direct C-2 arylation of 1-(2-pyrimidyl)-1*H*-indole with aryltrialkoxysilanes

Also in 2014, the 2-pyrimidyl group was used by Xu, Li, Shi and coworkers as a removable directing group in the Rh-catalyzed decarbonylative C-2 arylation of 1-(2-pyrimidyl)-1*H*-indoles **90** with diversely substituted arylcarboxylic acids.[56c] The reactions (Scheme 45), which were carried out by treatment of 1.5 equiv of arylcarboxylic acids with 1.0 equiv of indoles **90**, 2.5 mol% $[RhCl(CO)_2]_2$ and 1.5 equiv of pivalic anhydride in toluene at 140 °C for 12 h, provided the corresponding C-2 arylated indoles **99** in good to excellent yields and with complete regioselectivity regardless the electronic properties of the carboxylic acids. Notably, the arylation reactions proved also to be tolerant to a number of substituents on the benzene ring of the indole substrate. Investigations were also undertaken to study the mechanism of the arylation reactions and evidence was obtained suggesting that the reactions involved a decarbonylative step and that the carboxylic acids could form mixed anhydrides by treatment with pivalic anhydride.[56c]



99	R^1	R^2	Ar	Yield %	99	R^1	R^2	Ar	Yield %
a	H	H	Ph	95	**q**	H	H	2-thienyl	87
b	H	H	4-$MeOC_6H_4$	96	**r**	H	5-Me	Ph	89
c	H	H	4-MeC_6H_4	96	**s**	H	6-Me	Ph	93
d	H	H	3-$MeOC_6H_4$	87	**t**	H	4-Me	Ph	95
e	H	H	2-$MeOC_6H_4$	85	**u**	H	7-Me	Ph	92
f	H	H	3,5-$Me_2C_6H_3$	86	**v**	H	5-MeO	Ph	95
g	H	H	4-ClC_6H_4	95	**w**	H	5-Cl	Ph	96
h	H	H	2-ClC_6H_4	90	**x**	H	5-Br	Ph	93
i	H	H	4-BrC_6H_4	95	**y**	H	5-F	Ph	95
j	H	H	4-FC_6H_4	85	**z**	H	5-NO_2	Ph	87
k	H	H	4-$CF_3C_6H_4$	83	**aa**	H	5-MeOOC	Ph	91
l	H	H	4-CNC_6H_4	90	**ab**	Me	H	Ph	86
m	H	H	4-$(NO_2)C_6H_4$	75	**ac**	Br	H	Ph	78
n	H	H	2-naphthyl	91	**ad**	COOMe	H	Ph	85
o	H	H	3-Cl, 4-MeC_6H_3	88	**ae**	CN	H	Ph	72
p	H	H	2,4-$(MeO)_2C_6H_3$	82					

Scheme 45. Rh(I)-catalyzed decarbonylative direct C-2 arylation of *N*-(2-pyrimidyl)-1*H*-indoles **90** with arylcarboxylic acids

The removal of the 2-pyrimidyl group from compounds **99** was then easily achieved by treatment with EtONa in DMSO at 100 °C, namely by using the same protocol previously used by Miura and coworkers[53] to prepare 2-heteroaryl-1H-indoles **92** from the corresponding *N*-2-pyrimidyl-substituted indoles **91**. In this way **99a** was converted to 2-phenyl-1*H*-indole (**100**) (Figure 8) in 89% yield.

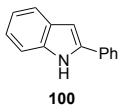
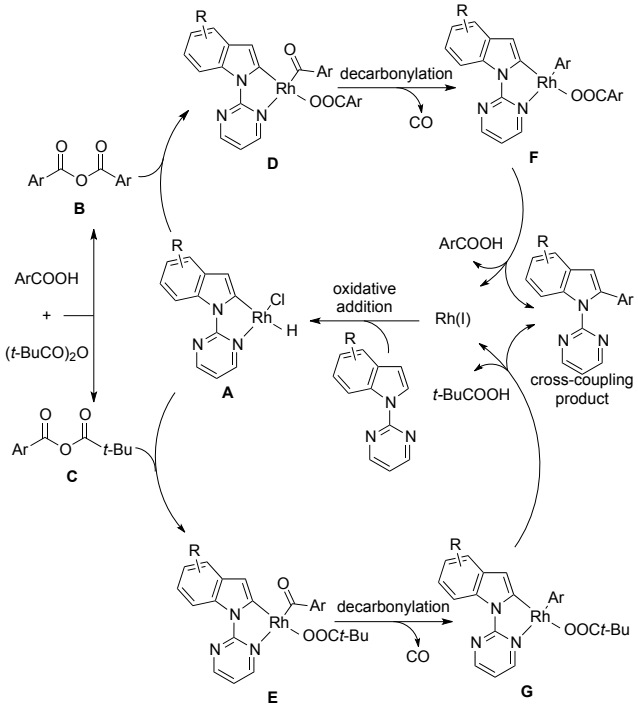


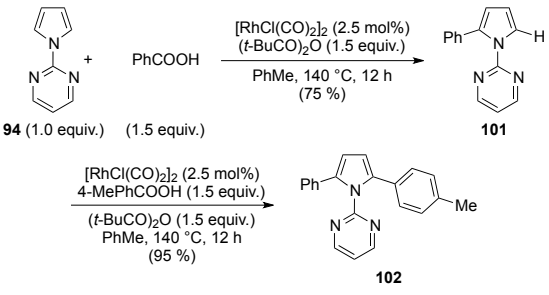
Figure 8. Chemical structure of compound **100**

The mechanism of the Rh(I)-catalyzed arylation reactions of compounds **90** with arylcarboxylic acids was also investigated and, on the basis of the obtained results and of previous reports,[63] the plausible mechanism shown in Scheme 46 was suggested. The first step of this mechanism would involve the reaction of the substrate with the catalytic Rh(I) species to produce the cyclorhodium intermediate **A** by C-H oxidative addition assisted by the pyrimidyl nitrogen atom. Anhydrides **B** and **C** that would arise from the reaction of pivalic anhydride with arylcarboxylic acids would react with **A** to give intermediates **D** and **E**, which would provide intermediates **F** and **G**. The latter complexes would then undergo reductive elimination to give the desired arylation products also regenerating Rh(I) to complete the catalytic cycle.[56c]



Scheme 46. Plausible mechanism for the Rh-catalyzed direct C-2 arylation of 1-(2-pyrimidyl)-1*H*-indoles with arylcarboxylic acids

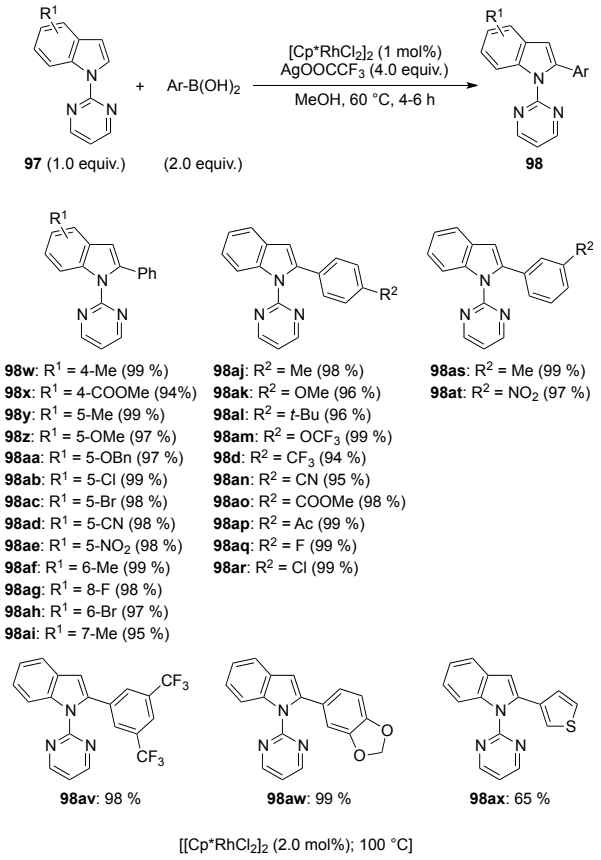
Xu, Li, Shi and coworkers also explored the $[Rh(CO)_2Cl]_2$/(*t*-$BuCO)_2O$-catalyzed reaction of 2-(1*H*-pyrrol-1-yl)pyrimidine (**94**) with arylcarboxylic acids (Scheme 47) and found that **94** was mono-arylated with benzoic acid giving rise to 2-phenylimidazole **101** in 75% yield. It was then established that the latter compound was able to undergo further $[Rh(CO)_2Cl]_2$/(*t*-$BuCO)_2O$-catalyzed α-arylation reaction with *p*-tolylcarboxylic acid providing the 2,5-biarylated compound **102** in 95% yield (Scheme 47).[56c] However, the removal of the 2-pyrimidyl group from compounds **101** and **102** was not described.



Scheme 47. Regioselective $[Rh(CO)_2Cl]_2$/(*t*-$BuCO)_2O$-catalyzed arylation of pyrrole **94** with arylcarboxylic acids

More recently, Wang, Peng and coworkers developed a highly efficient Rh-catalyzed direct C-2 arylation of *N*-2-pyrimidyl-substituted indoles **97** with a large variety of boronic acids bearing both electron-withdrawing and

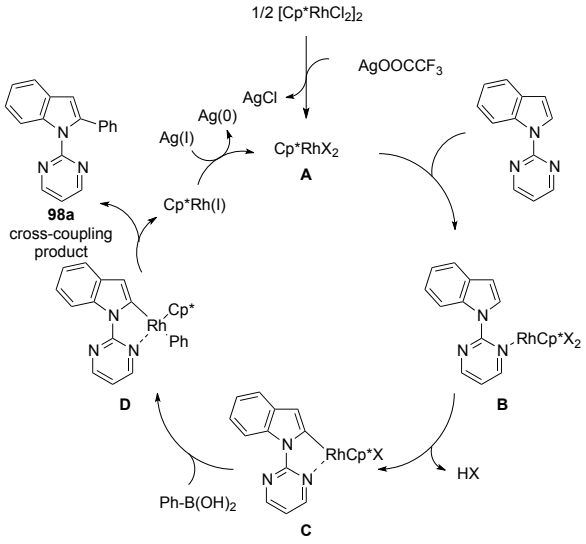
electron-donating substituents.[56d] The reaction (Scheme 48), which was carried out by treating 1.0 equiv of compounds **97** with 2.0 equiv of boronic acids, 1.0 mol% $[Cp^*RhCl_2]_2$ and 4.0 equiv of $AgOOCF_3$ in MeOH at 60 °C for 4–6 h under argon, exhibited excellent functional group compatibility and gave the cross-coupling products **98** with excellent regioselectivity and yields.



Scheme 48. Rh-catalyzed direct C-2 arylation of indoles **97** with arylboronic acids

Under optimized conditions, the synthesis of 2-phenyl-1-(2-pyrimidyl)-1*H*-indole (**98a**) was performed on a gram scale in 96% yield.

A preliminary study was also carried out to gain insight into the mechanism of the arylation reaction and competition experiments involving differently substituted indoles indicated that electron-rich indoles were better substrates than electron-poor indoles. Based on this result, the data obtained in kinetic isotope effects and literature data,[64] a plausible mechanism was then proposed (Scheme 49) in which the Rh catalyst precursor would be activated by $AgOOCF_3$ to generate the electrophilic complex **A**.

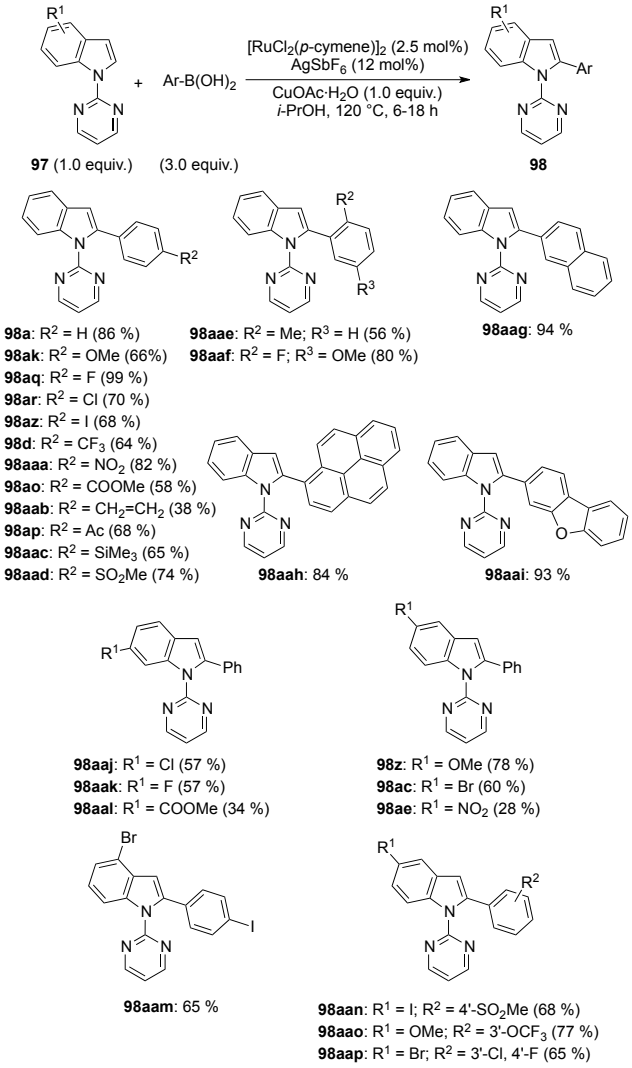


Scheme 49. Plausible mechanism for the Rh-catalyzed direct C-2 arylation of 1-(2-pyrimidyl)-1*H*-indole with phenylboronic acid

Coordination of the pyrimidyl group of the substrate to **A** resulting in the formation of complex **B** and subsequent regioselective C-H activation would then provide rhodacycle **C**. Reaction of **C** with phenylboronic acid would then give the new Rh(III) intermediate **D**, which by reductive elimination would provide the cross-coupling product **98a** and Rh(I) species. Finally, the catalytic cycle would be completed by oxidation of Rh(I) to complex **A**.[56d]

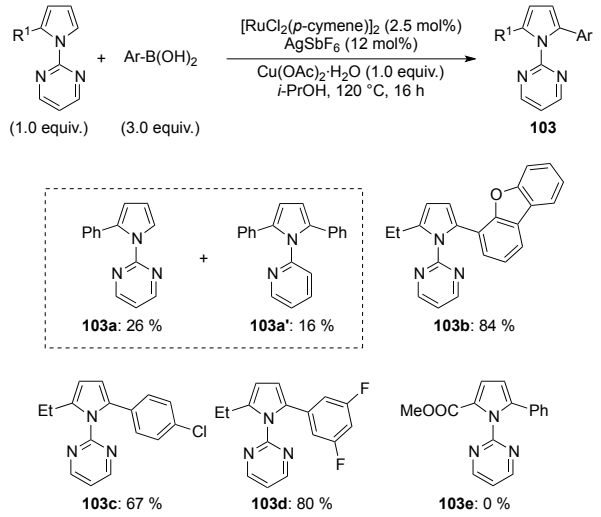
Interestingly, Wang, Peng and coworkers also reported the removal of the 2-pyrimidyl group from **98a** in 99% yield by treatment with NaOEt in DMSO at 110 °C for 2 h.[56d]

Again in 2015, several 2-aryl-1-(2-pyrimidyl)-1*H*-indoles **98** were also synthesized by Pilarski and coworkers by regioselective Ru-catalyzed C-2 arylation of 1-(2-pyrimidyl)-1*H*-indoles **97** with arylboronic acids under oxidative conditions.[55c] The arylation reactions were carried out by treatment of 1.0 equiv of compounds **97** with 3.0 equiv of arylboronic acids, 2.5 mol% $[RuCl_2(p\text{-cymene})]_2$, 12 mol% $AgSbF_6$, and 1.0 equiv of $Cu(OAc)_2{\cdot}H_2O$ in *i*-PrOH at 120 °C for 18 h (Scheme 50). Compounds **98**, which included derivatives bearing halogen substituents on the C-2 aryl moiety as well as on the benzene ring of the indole system, were obtained in yields ranging from 28 to 99%.



Scheme 50. Ru-catalyzed direct C-2 arylation of indoles **97** with arylboronic acids under oxidative conditions

Pilarski and coworkers also found that even 1-(2-pyrimidyl)-1*H*-pyrroles **86**[55a,d] were amenable to Ru-catalyzed *ortho*-arylation with arylboronic acids under condition similar to those used to prepare indoles **98**.[55c] The arylation reactions (Scheme 51) furnished 2-aryl-1-(2-pyrimidyl)-1*H*-pyrroles **103** generally in good yields, but the Ru-catalyzed reaction of 1-(2-pyrimidyl)-1*H*-pyrrole (**86**: R^1 = H) with phenylboronic acid gave a separable mixture of 2-phenyl- and 2,5-diphenyl-1-(2-pyrimidyl)-1*H*-pyrroles in 26 and 16% yield, respectively. Moreover, the Ru-catalyzed reaction between 2-methoxycarbonyl-1-(2-pyrimidyl)-1*H*-pyrrole with phenylboronic acid did not furnish the required C-5 arylation product.



Scheme 51. Ru-catalyzed direct α-arylation of 1-(2-pyrimidyl)-1*H*-pyrroles with arylboronic acids under oxidative conditions

Pilarski and coworkers then proposed that cyclometalated complex **CycRu** (Figure 9) acts as a precursor rather than as a true catalytic intermediate in the direct *ortho*-arylation reactions of indoles **97** and pyrroles **86** and that, under the catalytic conditions, the pyrimidine group of the substrates **97** or **86** displace the *p*-cymene ligand of this cyclometalated complex. They also suggested that the intermediates of the reactions may have more than one pyrimidyl heteroarene ligand in the Ru coordination sphere.[55c]

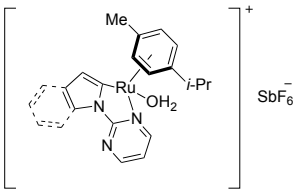
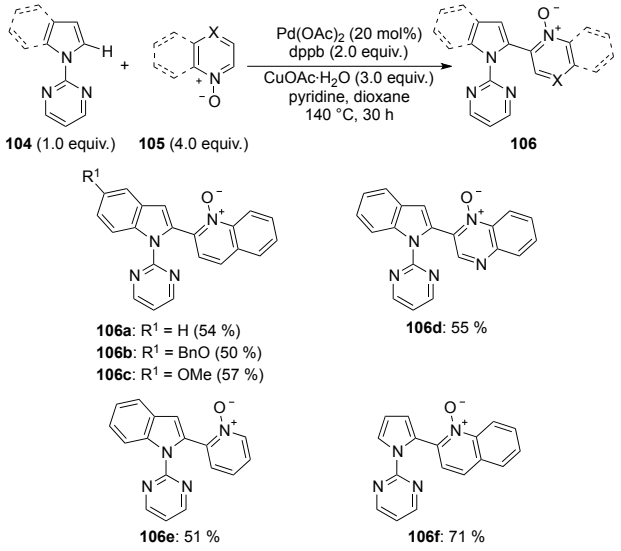


Figure 9. Chemical structure of cyclometalated complex **CycRu**

Prior to the studies mentioned above on the Rh and Ru-catalyzed direct C-2 arylation reactions of indole and pyrrole derivatives, the pyrimidyl group had also been shown to be a good *ortho*-directing group in the regioselective Pd-catalyzed oxidative cross-coupling of 1-(2-pyrimidyl)-1*H*-indoles/pyrroles **104** with *N*-heteroarene *N*-oxides such as quinoline *N*-oxide, quinoxaline *N*-oxide, and pyridine *N*-oxide.[54s] You and coworkers carried out these highly selective reactions by treating 1.0 equiv of the indole or pyrrole derivative with 4.0 equiv of a *N*-heteroarene *N*-oxide **105**, 20 mol% $Pd(OAc)_2$, 2.0 equiv of dppb, and 3.0 equiv of $Cu(OAc)_2{\cdot}H_2O$ in a mixture of pyridine and dioxane at 140 °C for 30 h (Scheme 52). The resulting compounds **106** were so obtained in yields ranging from 50 to 71%.[54s]

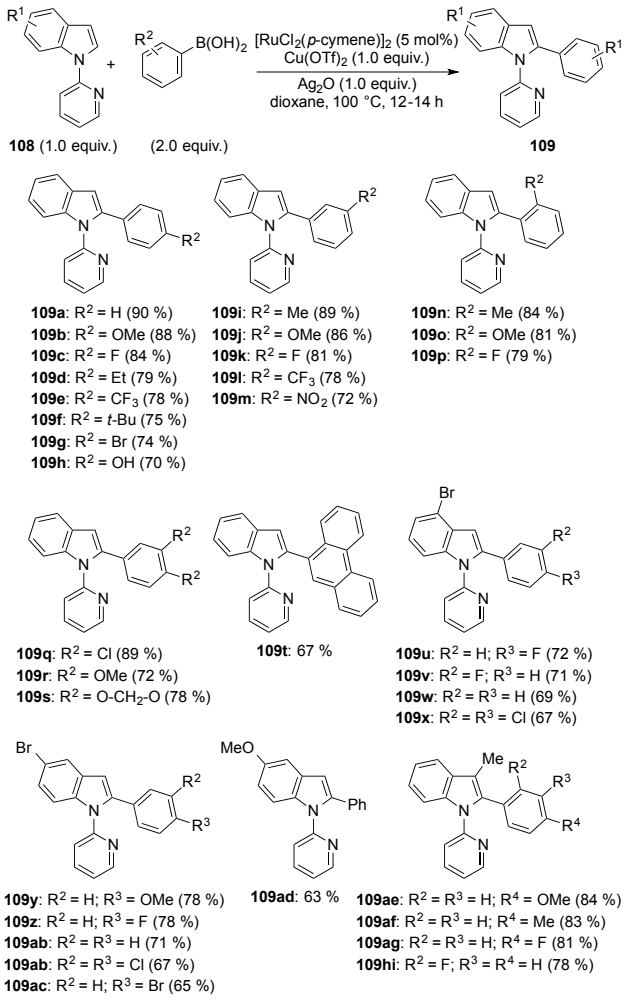


Scheme 52. Pd-catalyzed oxidative cross-coupling of indoles/pyrroles **104** with *N*-heteroarene *N*-oxides **105**

You and coworkers then found that the 2-pyrimidyl group could be removed from 2-[1-(2-pyrimidyl)indolyl]-quinoline *N*-oxide (**106a**) by treatment with NaOEt in DMSO at 120 °C to give the corresponding free-NH biheteroarene **107** in 68% yield (Scheme 53).[53s]

Scheme 53. Deprotection of the 2-pyrimidyl group tethered to the nitrogen atom of indole **106a**

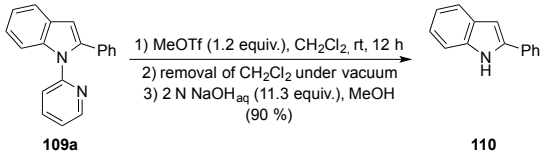
In 2015, Kapur and coworkers employed another removable directing group, the azole NH protecting 2-pyridyl group, in the regioselective Ru-catalyzed direct C-2 arylation reactions of indoles with arylboronic acids.[55b] The reactions were carried out by treating 1.0 equiv of 1-(pyridine-2-yl)-1*H*-indoles **108** with 2.0 equiv of arylboronic acids, 5 mol% $[RuCl_2(p\text{-cymene})]_2$, 1.0 equiv of $Cu(OTf)_2$ and 1.0 equiv of Ag_2O in dioxane at 100 °C for 12–14 h (Scheme 54). The resulting 2-aryl-1-(pyridin-2-yl)-1*H*-indoles **109** were obtained in high yields using arylboronic acids bearing both electron-withdrawing and electron-donating substituents. The starting materials, compounds **108**, were synthesized in high yields by the reaction of the corresponding free-NH indoles with 2.5 equiv of NaH (60% dispersion in mineral oil) in DMF at 0 °C for 0.5 h followed by treatment with 1.2 equiv of 2-bromopyridine at 130 °C for 24 h.



Scheme 54. Ru-catalyzed direct C-2 arylation of 1-(pyridin-2-yl)-1*H*-indoles **108** with arylboronic acids

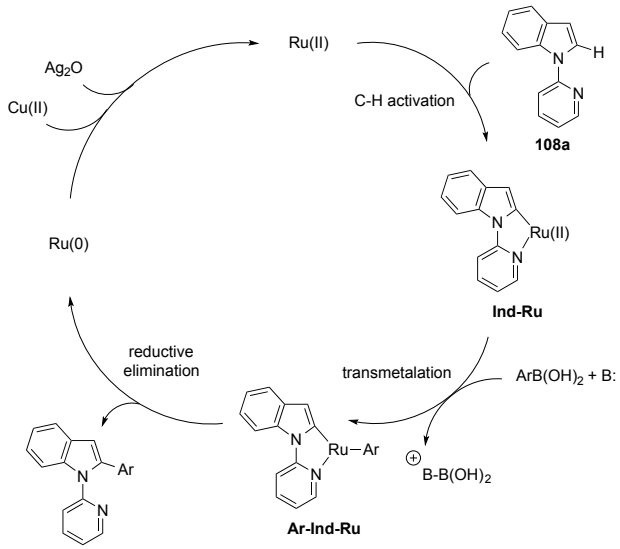
It was also observed that the catalyst system used to prepare compounds **109** did not work with 1-methyl- and 1-phenyl-1*H*-indoles, this showing the importance of the role played by the pyridin-2-yl directing group.

Kapur and coworkers also found that this protecting group could be removed from compounds **109** by treatment with MeOTf followed by addition of 2N NaOH. For instance, the reaction of **109a** with 1.2 equiv of MeOTf in CH_2Cl_2 at room temperature for 12 h followed by removal of the solvent, addition of 11.3 equiv of 2N NaOH and MeOH and heating the reaction mixture at 60 °C for 10 h provided free-NH 2-phenyl-1*H*-indole (**110**) in 90% yield (Scheme 55).[55b]



Scheme 55. Removal of the pyridin-2-yl group from indole **109a**

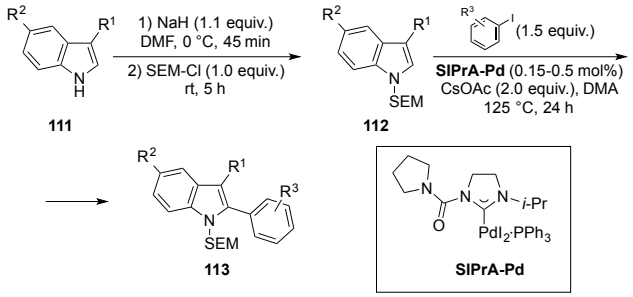
Finally, Kapur and coworkers formulated a plausible mechanism for the Ru-catalyzed heteroatom-directed C-2 arylation of compounds **108** with arylboronic acids (Scheme 56).



Scheme 56. Plausible mechanism for the Ru-catalyzed direct C-2 arylation of 1-(pyridin-2-yl)-1*H*-indole (**108a**) with arylboronic acids

The first step of this mechanism involved the coordination of the Ru catalyst to the *N*-pyridyl group of **108a** (R^1 = H) followed by C-H activation at C-2 of the substrate that would provide ruthenacycle **Ind-Ru**. Transmetalation of **Ind-Ru** with an arylboronic acid would provide complex **Ar-Ind-Ru**, which by reductive elimination would provide the required C-2 arylated indole and Ru(0). Oxidation of Ru(0) by Cu(II) then would give Ru(II) thus completing the catalytic cycle. In this reaction mechanism Ag_2O would act not only as a base, but would also assist the reoxidation step.[55b]

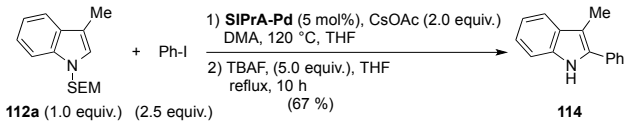
Removable azole NH protecting groups, structurally different from the 2-pyrimidyl and 2-pyridyl groups, have also been used in transition metal-catalyzed direct C-2 arylation reactions of indoles. In 2006, Sames and coworkers[54d] employed the 2-(trimethylsilyl)ethoxymethyl (SEM) group, a protecting group for azoles that can be removed under a variety of conditions,[65] in an efficient protocol for the C-2 arylation of *N*-SEM-protected indoles **112** with aryl iodides. Compounds **112** were prepared by the reaction of the corresponding free-NH indoles **111** with NaH in DMF at 0 °C for 45 min followed by treatment of the resulting sodium derivatives with SEM-Cl at room temperature. Compounds **112** were then reacted with 1.5 equiv of aryl iodides, 2.0 equiv of CsOAc and 0.15–0.5 mol% *N*-heterocyclic carbene Pd complex **SIPrA-Pd** in DMA at 125 °C for 24 h providing the C-2 arylated derivatives **113** in yields ranging from 22 to 82% (Scheme 57).[54d]



113	SIPrA-Pd mol%	R^1	R^2	R^3	Yield %
a	0.15	H	H	H	91
b	1.5	H	CN	H	82
c	2.0	H	NO_2	H	68
d	3.5	H	H	2-Me	52
e	5.0	COOMe	H	H	22

Scheme 57. Pd-catalyzed C-2 arylation of *N*-SEM-protected indoles **112** with aryl iodides

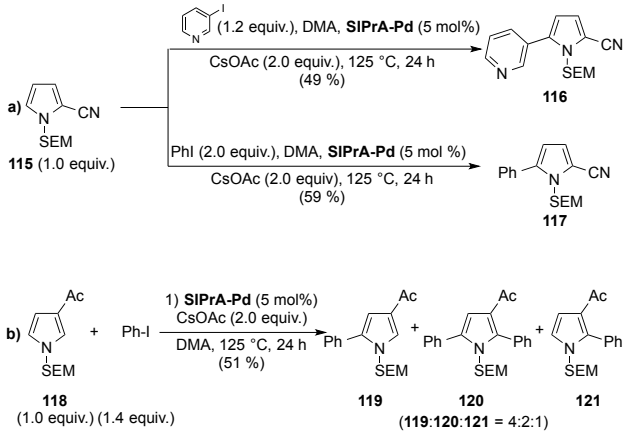
In many cases the arylation reaction was found to occur with a C-2/C-3 ratio of the products higher than 10 : 1, but the reaction of 1-SEM-1*H*-indole (**112a**; R^1 = R^2 = H) with 2-iodotoluene provided a mixture of 2-(2-tolyl)- and 3-(2-tolyl)-1-SEM-1*H*-indole in a 3.5 : 1 ratio with a 52% yield. It was also found that 3-methyl-2-phenyl-1*H*-indole (**114**) could be synthesized in 65% overall yield in a one-pot process involving the **SIPrA-Pd**-catalyzed reaction of 1-SEM-1*H*-indole (**112a**) with iodobenzene followed by *N*-deprotection of the resulting crude cross-coupling product with TBAF in refluxing THF (Scheme 58).[54d]



Scheme 58. One-pot synthesis of free-NH indole **114** from 1-SEM-1*H*-indole (**112a**) and iodobenzene

A protocol similar to that developed for the synthesis of compounds **113** was then tested for the direct C-5 arylation reactions of 1-SEM-1*H*-pyrrole-2-carbonitrile (**115**) with 3-iodopyridine and 3-iodobenzene and it was found that the resulting pyrroles **116** and **117**, respectively, were so obtained in good yields (Scheme 59, eq. a). However, the **SIPrA-Pd**-catalyzed reaction of 3-acetyl-1-SEM-1*H*-pyrrole (**118**) with iodobenzene gave a

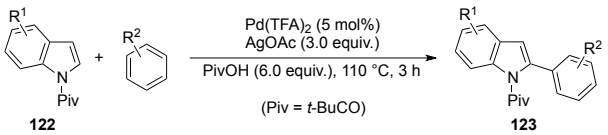
mixture of 5-phenyl-, 2,5-diphenyl- and 2-phenyl-1-SEM-1*H*-pyrrole, **119**, **120** and **121**, in a 4 : 2 : 1 ratio, respectively, and 51% yield (Scheme 59, eq. b).[54d]



Scheme 59. SIPrA-Pd-catalyzed direct arylation reactions of 1-SEM-1*H*-pyrroles **115** and **118** with aryl iodides

Unfortunately, the removal of the SEM-protecting group from compounds **116** and **119–121** was not reported.

In 2007, Fagnou and coworkers described that *N*-pivaloylindoles **122** undergo highly regioselective C-2 arylation reaction by treatment with a molar excess of arenes, 5 mol% $Pd(tfa)_2$, 3.0 equiv of AgOAc and 6.0 equiv of pivalic acid at 110 °C (Scheme 60).[54e] These oxidative coupling reactions, which were carried out by using the arenes as the solvent, provided 2-aryl-*N*-pivaloylindoles **123** in high yields with a C-2/C-3 selectivity ranging from 17 : 2 to 46 : 1. It was also noted that small quantities of diarylated derivatives were obtained in all cross-couplings. Compounds **122** were prepared by reacting a solution of the corresponding free-NH indoles in a mixture of CH_2Cl_2, 0.1 equiv of DMAP and 1.48 equiv of Et_3N with 1.17 equiv of pivaloyl chloride at 0 °C for 10 min and allowing the resulting stirred mixture to warm to room temperature overnight.[54e]

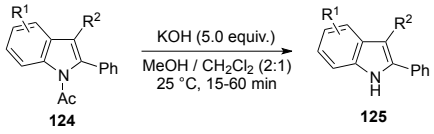


123	R^1	R^2	Yield %	C-2/C-3
a	H	H	84	25:1
b	5-MeO	H	90	46:1
c	5-Cl	H	86	31:1
d	6-MeO	H	76	26:1
e	6-Me	H	88	31:1
f	6-MeOOC	H	86	31:1
g	H	2',5'-$(Me)_2$	58	31:1
h	H	3',4'-$(Cl)_2$	55	17:2
i	H	3',4'-$(Me)_2$	75	30:1

Scheme 60. Pd-catalyzed C-2 oxidative arylation of *N*-pivaloylindoles **122** with arenes

Fagnou and coworkers did not investigate the *N*-deprotection of compounds **123**, but, more recently, it has been reported that the efficient removal of the *N*-pivaloyl group from *N*-pivaloylindoles can be achieved by hydrolysis with a DBU-water system[66a] or by treatment with an excess of LDA at 40-45 °C.[66a,b]

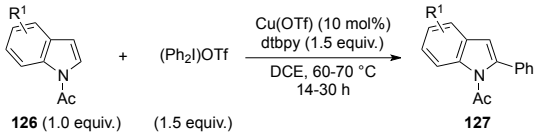
In 2008, it was reported that even the acetyl group can be easily removed under basic condition from 2-aryl-substituted 1-acetyl-1*H*-indoles **124** to provide the corresponding free-NH indoles in excellent yields (Scheme 61).[67]



125	R^1	R^2	Yield %
a	H	Me	90
b	H	Ph	97
c	5-OMe	Me	98

Scheme 61. Deacetylation of *N*-acetyl-1*H*-indoles **124**

In that same year, Gaunt and coworkers employed the acetyl group as an efficient directing group in the $Cu(OTf)_2$/2,6-di-*t*-butylpyridine (dtbpy)-catalyzed C-2 arylation of a range of electronically diverse *N*-acetylindoles **126** with diphenyliodonium triflate.[68a] The reactions (Scheme 62), which were carried out at 60-70 °C in 1,2-dichloroethane (DCE), gave 1-acetyl-2-phenyl-1*H*-indoles in 37–83% yield with a C-2/C-3 regioselectivity ranging from 6 : 1 to 9 : 1.[68] The *N*-acetyl substrates were efficiently prepared by reacting a mixture of 1.0 equiv of their parent free-NH indoles, 0.19 equiv of DMAP and 1.5 equiv of Et_3N in DCE with 1.9 equiv of acetic anhydride at 80 °C for 24 h.[68a,b]

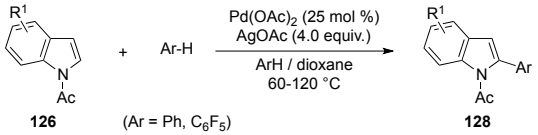


127	R^1	Yield %	C-2/C-3
a	H	83	9:1
b	5-Br	76	8:1
c	5-OMe	72	7:1
d	6-COOMe	81	7:1
e	5-CHO	61	6:1
f	5-NO_2	37	9:1

Scheme 62. Cu(II)-catalyzed C-2 arylation of *N*-acetylindoles **126** with diphenyliodonium triflate

Again in 2008, DeBoef and coworkers demonstrated that the Pd-catalyzed oxidative cross-coupling reactions of *N*-acetylindoles **126** with benzene and pentafluorobenzene using AgOAc as the stoichiometric oxidant produced selective arylation at C-2 position of the indole ring.[54h] As

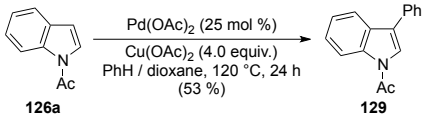
shown in Scheme 63, the reactions furnished compounds **128** in yields ranging from 22 to 56%.



128	R^1	Ar^1	Real temp. (°C)	Yield %
a	H	Ph	120	43
b	5-COOMe	Ph	100	33
c	4-CHO	Ph	100	22
d	4-COOMe	Ph	100	55
e	5-CHO	Ph	60	56
f	5-MeO	Ph	100	38
g	6-CHO	Ph	60	52
h	H	C_6F_5	100	38

Scheme 63. Pd-catalyzed oxidative C-2 arylation reactions of *N*-acetylindoles **126** with benzene and pentafluorobenzene

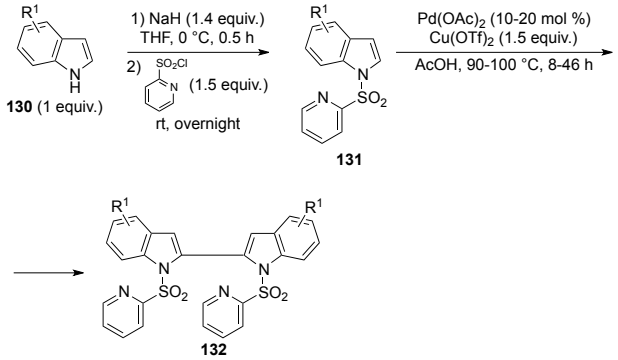
The oxidative cross-couplings were generally C-2 regioselective, but the Pd-catalyzed reaction of 5-methyl-1-acetyl-1*H*-indole with benzene using AgOAc as the oxidant gave a 1 : 1 mixture of 2- and 3-phenylated products.[54h] It was also demonstrated that the regioselectivity of the arylation of indoles **126** was controlled by the oxidant. In fact, the reaction of *N*-acetylindole (**126a**) with benzene in the presence of 4.0 equiv of $Cu(OAc)_2$ furnished 1-acetyl-3-phenyl-1*H*-indole (**129**) in 53% yield (Scheme 64).[54h,69]



Scheme 64. Pd-catalyzed C-3 phenylation of 1ndole **126a** with benzene using $Cu(OAc)_2$ as the oxidant

DeBoef and coworkers then proposed that the oxidant-controlled regioselectivity in the oxidative arylation of indoles **126** is a consequence of the formation of polymetallic, catalytically active clusters and hypothesized that the $Cu(OAc)_2$ oxidant forms a polymetallic cluster with $Pd(OAc)_2$[70] that selectively acrylates C-3 position of compounds **126**. On the other hand, the AgOAc oxidant would form either a different polymetallic cluster or "naked" $Pd(OAc)_2$ that selectively arylates C-2 position of compounds **126**.[54h] It is also worth noting that, in 2009, Larrosa and coworkers discovered that a $Pd(MeCN)_2Cl_2$-catalyzed C–H activation of *N*-pivaloylindoles **122** and an Ag_2CO_3-catalyzed decarboxylative C–C activation of *ortho*-substituted benzoic acid were synergistically combined to provide *N*-pivaloylindoles arylated exclusively at the C-3 position.[69g]

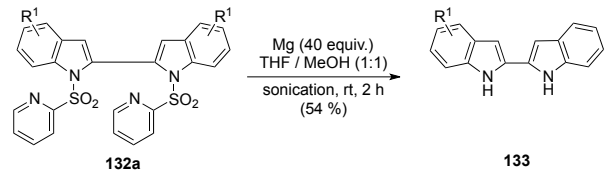
In 2010, Arrayás, Carretero and coworkers demonstrated that the readily installable and removable *N*-(2-pyridyl)sulfonyl group allowed the $Cu(OTf)_2$-mediated $Pd(OAc)_2$-catalyzed dehydrogenative intermolecular homocoupling of *N*-(2-pyridyl)sulfonylindoles **131** with complete regiocontrol providing *N,N'*-bis(2-pyridylsulfonyl)-2,2'-biindolyls **132** in satisfactory yields.[54k] Compounds **131** were in turn prepared by the reaction of free-NH indoles **130** with NaH in THF at 0 °C for 0.5 h and treatment of the resulting sodium derivatives with 2-pyridylsulfonyl chloride at room temperature overnight (Scheme 65). The dehydrogenative homocoupling of compounds **131** was carried out at 90-100 °C in AcOH in the presence of 10-20 mol% $Pd(OAc)_2$ and 1.5 equiv of $Cu(OTf)_2$ to give compounds **132** in yields ranging from 61 to 68%.[54k]



132	R^1	Mol % Pd	Yield %
a	H	10	68
b	5-MeO	10	64
c	6-F	10	66
d	5-Br	20	61

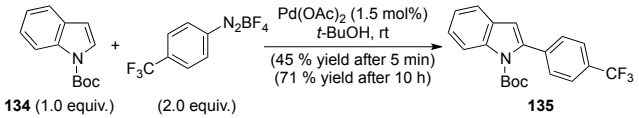
Scheme 65. Pd-catalyzed Cu-mediated dehydrogenative homocoupling of *N*-(2-pyridylsulfonyl)indoles **131**

Arrayás, Carretero and coworkers then demonstrated the feasibility of the removal of the two *N*-(2-pyridyl)sulfonyl groups of compounds **132** showing that treatment of compound **132a** with 40 equiv of Mg turnings in a 1 : 1 mixture of THF and MeOH at room temperature under sonication gave free-NH biindole **133** in 54% yield (Scheme 66).[54k,71] Compound **133** had previously been found to be a precursor to arcyriaflavin A, a potent inhibitor of CDK4/cyclin D1, as well as staurosporinone, an ATP competitive inhibitor of protein kinase C and protein kinase A.[71c]



Scheme 66. Removal of the (2-pyridyl)sulfonyl group from biindole **132a**

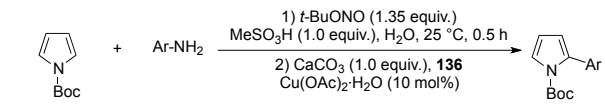
Protecting groups for the pyrrole and indole nitrogen atom such as the Boc and TIPS groups have also been employed to achieve regioselectivity in transition metal-catalyzed direct arylation reactions. However, although methods for the efficient removal of such groups have been reported in the literature,[72,73] their removal from the products of direct arylation reactions has not been described. Anyhow, we believe useful to report that, in 2012, Correia and coworkers used the *N*-Boc protecting group as a director in the $Pd(OAc)_2$-catalyzed regioselective C-2 arylation of *N*-Boc-1*H*-indole (**134**) with 4-trifluoromethylphenyldiazonium tetrafluoroborate in *t*-BuOH at room temperature.[54r] As shown in Scheme 67, the reaction gave compound **135** in 71% yield after 10 h and in 45% yield after 5 min.[54r,74a] Compound **134** was in turn prepared by treating a CH_2Cl_2 solution of free-NH indole with 1.2 equiv of Et_3N, 0.1 equiv of DMAP and 2.4 equiv of Boc anhydride in CH_2Cl_2 at room temperature.[74b]



134 (1.0 equiv.) (2.0 equiv.) **135**

Scheme 67. Direct C-2 arylation of *N*-Boc indole (**134**) with 4-trifluoromethylphenyldiazonium tetrafluoroborate

More recently, Felpin and coworkers developed a highly regioselective method for the synthesis of 2-aryl-1-Boc-1*H*-pyrroles **137** under mild and neutral conditions.[75] It involved the $Cu(OAc)_2{\cdot}H_2O$-catalyzed radical arylation of *N*-Boc-1*H*-pyrrole (**136**) with anilines through *in situ* generated aryldiazonium salts.[75] Anilines were converted into the corresponding diazonium salts by treatment with equimolar amounts of *t*-BuONO in $MeSO_3H$ and the Cu-catalyzed arylation reactions were carried out in the presence of $CaCO_3$ as a mild base to trap $MeSO_3H$ still present after the *in situ* diazotization reactions (Scheme 68). Remarkably, the process proved to be compatible with a variety of functional groups providing compounds **137** in yields ranging from 58 to 83%.[75]

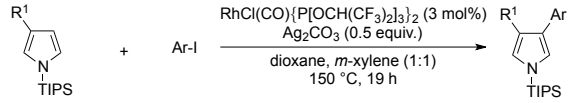


136 (4.0 equiv.) (1.0 equiv.) **137**

137	Ar	Yield %
a	4-$(NO_2)C_6H_4$	83
b	2-OMe, 4-$(NO_2)C_6H_3$	75
c	4-NCC_6H_4	70
d	4-$MeOOCC_6H_4$	69
e	2-$MeOOCC_6H_4$	59
f	4-$(PhCO)C_6H_4$	75
g	4-BrC_6H_4	76
h		58

Scheme 68. Cu-catalyzed C-2 arylation of *N*-Boc-1*H*-pyrrole (**136**) with aryldiazonium salts

Also in 2014, after extensive investigations, Itami, Yamaguchi and coworkers[76] found that commercially available *N*-TIPS-1*H*-pyrrole (**138a**) and 3-methyl-1-TIPS-1*H*-pyrrole (**138b**) underwent β-selective Rh(I)-catalyzed direct arylation with aryl iodides in a mixture of dioxane and *m*-xylene at 150 °C in the presence of Ag_2CO_3 by providing 3-aryl-1-TIPS-1*H*-pyrroles **139** in low to moderate yields and with high β-selectivity (Scheme 69).



138a: R^1 = H (1.5 equiv.) (1.0 equiv.) **139**
138b: R^1 = Me (1.5 equiv.)

139	R^1	Ar	Yield %	β–selectivity
a	H	4-$MeOOCC_6H_4$	46	> 99 %
b	H	4-$(NO_2)C_6H_4$	63	> 99 %
c	Me	4-$(NO_2)C_6H_4$	42	92 %
d	H	Ph	12	> 99 %

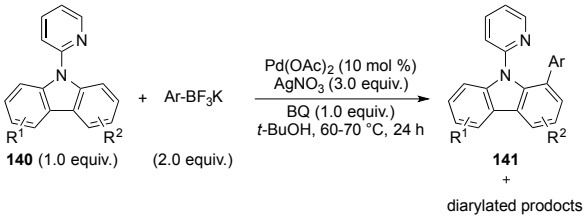
Scheme 69. Rh(I)-catalyzed β-selective direct arylation of *N*-TIPS-1*H*-pyrroles **138** with aryl iodides

The high β-selectivity of these reactions was believed to be closely related to the steric effect of the bulky triisopropylsilyl group.[76]

A β-selective direct arylation of a pyrrole derivative devoid of substituents at positions 2 and 5 had been previously observed only in the case of the $RhCl(CO)_2\{P[OCH(CF_3)_2]_3\}_2$-catalyzed reaction of 1-phenyl-1*H*-pyrrole with 4-iodoacetophenone in the presence of Ag_2CO_3 in *m*-xylene at 150–200 °C under microwave irradiation.[78]

In concluding the part of this section concerning the regioselective direct arylation reactions of azoles involving the use of removable *ortho*-directing NH-protecting groups, we want to mention that, recently, both the removable *N*-pyrimidin-2-yl and *N*-pyridin-2-yl groups have also been employed as directing groups in highly regioselective direct arylation reactions of carbazole derivatives.[79,80] In 2013, Chu, Wu and coworkers developed a one-pot synthesis of 1-aryl-9-(pyridine-2-yl)-9*H*-carbazoles **141** involving the Pd-catalyzed direct oxidative *ortho*-arylation of 9-(pyridine-2-yl)-9*H*-carbazoles **140** with potassium aryltrifluoroborates.[79] As shown in Scheme 70, compounds **141** were prepared by treatment of 1.0 equiv of substrates **140** with 2.0 equiv of potassium aryltrifluoroborates,[81] 10 mol% $Pd(OAc)_2$, 3.0 equiv of $AgNO_3$, and 1.0 equiv of benzoquinone (BQ) in *t*-BuOH at 60–70 °C for 24 h. Compounds **140** were in turn prepared on 80–88% yield by the reaction of 1.0 equiv of the corresponding 9*H*-carbazoles with 1.2 equiv of 2-iodopyridine, 0.30 equiv of Cu powder, and 1.5 equiv of K_2CO_3 in DMF at 130–140 °C for 30 h.[79] The direct

arylation reactions of compounds **140** produced the predominant compounds **141** in moderate to good yields along with small amounts of diarylated products.



141	R^1	R^2	Ar	GLC yield (%)
a	H	H	Ph	25
b	H	H	4-$(NO_2)C_6H_4$	73
c	H	H	3-$(NO_2)C_6H_4$	81
d	H	H	4-$(CHO)C_6H_4$	83
e	H	H	4-FC_6H_4	84
f	H	H	4-ClC_6H_4	84
g	H	H	4-BrC_6H_4	73
h	H	H	4-IC_6H_4	47
i	H	H	4-*t*-BuC_6H_4	79
j	H	H	4-MeC_6H_5	85
k	H	H	4-$MeOC_6H_4$	73
l	H	H	3-$MeOC_6H_4$	83
m	H	H	2-naphthyl	88
n	H	H	1-naphthyl	0
o	H	H	2-$MeOOCC_6H_4$	0
p	7-NO_2	H	Ph	64
q	6-NO_2	H	Ph	45
r	7-*t*-Bu	H	Ph	98
s	7-Ar	H	Ph	58
t	6-Br	3-Br	Ph	53
u	7-Br	2-Br	Ph	0

Scheme 70. Direct *ortho*-arylation of 9-(pyridin-2-yl)-9*H*-carbazoles **140** with potassium aryltrifluoroborates

However, the attempted arylation reactions of **140a** (R^1 = R^2 = H) with potassium 1-naphthyltrifluoroborate and potassium 2-(methoxycarbonyl)phenyltrifluoroborate as well as of 2,7-dibromo-9-(pyridine-2-yl)-9*H*-carbazole with potassium phenyltrifluoroborate did not produce the desired arylated products **141n**, **141o** and **141u**, respectively. It was also found that, in the case of carbazoles **140** containing a substituent such as NO_2, *t*-Bu or Ac, the monoarylation reactions were highly selective occurring on the aryl moiety that did not contain the functional group. Nevertheless, the arylation reactions of 7- and 8-methoxy-9-(pyridine-2-yl)-9*H*-carbazoles, **140h** and **140i** respectively (Figure 10), with potassium phenyltrifluoroborate produced mixtures of mono- and diarylated derivatives.

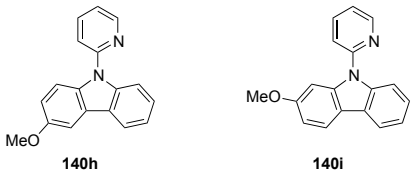
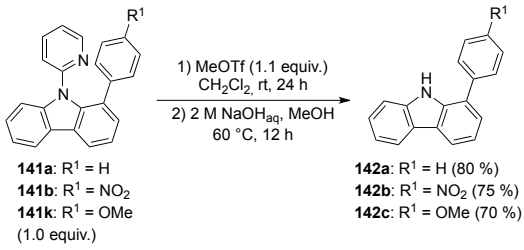


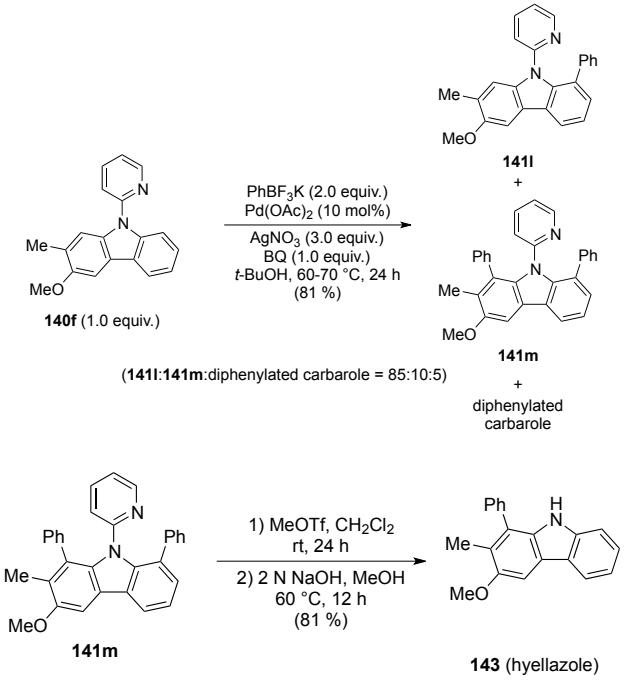
Figure 10. Chemical structures of compounds **140h** and **140i**

Chu, Wu and coworkers then investigated the removal of the *N*-(pyridin-2-yl) group from compounds **141** and found that compounds **141a**, **141b** and **141k** underwent depyridination by treatment with MeOTf in CH_2Cl_2 at room temperature followed by removal of the solvent and reaction with a 2N aqueous NaOH solution. The resulting free-NH carbazoles **142a–c** were obtained in high yields (Scheme 71).[79]



Scheme 71. Removal of the pyridin-2-yl group from compounds **141a**, **141b** and **141k**

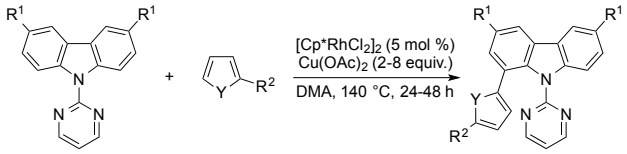
Finally, Chu, Wu and coworkers carried out the direct *ortho*-phenylation of 3-methoxy-2-methyl-9-(pyridine-2-yl)-9*H*-carbazole (**140j**) and employed the resulting compound **141m**, which was a minor component of the phenylation products, as precursor to hyellazole (**143**) (Scheme 72),[79] a carbazole derivative isolated in 1979 from the blue-green alga *Hyella caespitosa*.[8]



Scheme 72. Synthesis of hyellazole (**143**)

Again in 2013, Kambe and coworkers described a straightforward method for the Rh-catalyzed intermolecular oxidative cross-coupling of 9-(pyrimidin-2-yl)-9*H*-carbazoles **144** with thiophene derivatives and selenophene.[80] The reactions were carried out by

treatment of 1.0 equiv of compounds **144** with 3.0 equiv of chalcogenophenes, 5 mol% $[Cp^*RhCl_2]_2$ and 2.8 equiv of $Cu(OAc)_2$ in DMA at 140 °C for 24-48 h (Scheme 73). The resulting cross-coupling products **145** were regioselectively obtained in yields ranging from 30 to 46%.

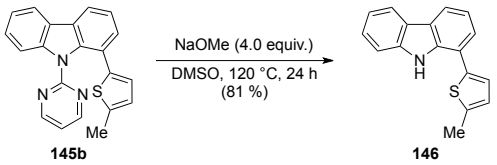


144 (1.0 equiv.) (Y = S, Se) (3.0 equiv.) **145**

145	R^1	R^2	Y	Yield (%)
a	H	H	S	43
b	H	Me	S	46
c	H	Ph	S	41
d	*t*-Bu	Me	S	37
e	*t*-Bu	H	S	35
f	*t*-Bu	H	Se	30
g	H	2-thienyl	S	35
h	H	2-(2'-bithienyl)	S	33

Scheme 73. Rh-catalyzed oxidative coupling of carbazoles **144** with chalcogenophenes

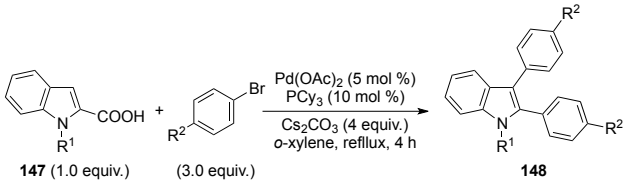
It was also established that the directing group could be removed from compounds **145** under basic conditions. For instance, the reaction of **145b** with 4.0 equiv of NaOMe in DMSO at 120 °C for 24 h produced 1-(5-methylthiophen-2-yl)-9*H*-carbazole (**146**) in 81% yield (Scheme 74).[80]



145b **146**

Scheme 74. Removal of the 2-pyrimidyl directing group from compound **145b**

In the past years, high regioselectivity in transition metal-catalyzed direct arylation reactions involving indole and indolizine derivatives was also gained through the use of the carboxyl group as a traceless directing group. In 2009, Miura and coworkers found that the $Pd(OAc)_2/PCy_3$-catalyzed reaction of 1.0 equiv of indole-2-carboxylic acids **147** with 3.0 equiv of electronically diverse aryl bromides in refluxing *o*-xylene for 4 h in the presence of Cs_2CO_3 as the base allowed the C-3 arylation reaction of the indole ring accompanied by decarboxylative arylation of the substrates (Scheme 75).[54j]

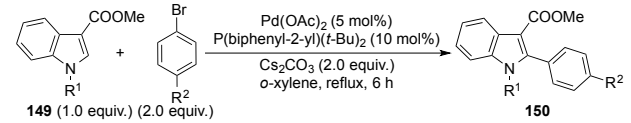


147 (1.0 equiv.) (3.0 equiv.) **148**

148	R^1	R^2	Yield (%)
a	Me	H	90
b	Me	Me	86
c	Me	MeO	93
d	Me	CF_3	78
e	Me	F	79
f	MOM	H	82
g	Ph	H	79

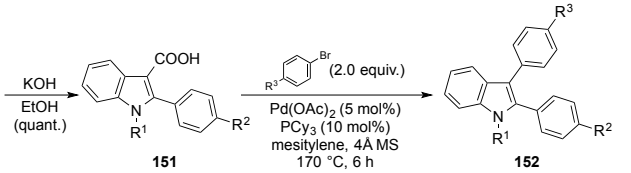
Scheme 75. $Pd(OAc)_2/PCy_3$-catalyzed diarylation of indole-2-carboxylic acids **147**

Miura and coworkers also found that carboxylic acids **151**, which were prepared by $Pd(OAc)_2$/P(biphenyl-2-yl)(*t*-Bu)$_2$-catalyzed reaction of 3-(methoxycarbonyl)indoles **149** with aryl bromides in *o*-xylene under reflux in the presence of Cs_2CO_3 as the base followed by hydrolysis of the resulting 2-arylated indoles **150**, underwent $Pd(OAc)_2/PCy_3$-catalyzed decarboxylative arylation by treatment with 2.0 equiv of aryl bromides and 2.0 equiv of Cs_2CO_3 in mesitylene at 170 °C in the presence of 4Å molecular sieves to give unsymmetrical 2,3-diaryl-1*H*-indoles **152** in good yields (Scheme 76).[54j]



149 (1.0 equiv.) (2.0 equiv.) **150**

150	R^1	R^2	Yield (%)
a	Me	H	82
b	Me	CF_3	79
c	MOM	H	73

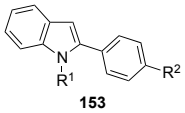


151 **152**

152	R^1	R^2	R^3	Yield (%)
a	Me	H	Me	84
b	Me	H	CF_3	60
c	Me	H	COOEt	89
d	Me	H	Ph	94
e	Me	CF_3	H	55
f	MOM	H	Me	70

Scheme 76. Synthesis of unsymmetrical 2,3-diaryl-1*H*-indoles **152**

It should also be noted that carboxylic acids **151** might be employed as direct precursors to the corresponding 2-arylindoles **153** (Figure 11).

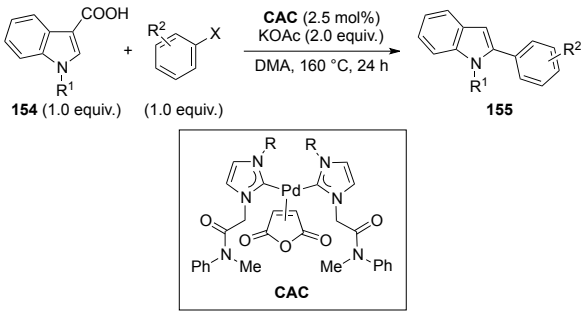


153

Figure 11. Chemical structure of compounds **153**

In fact, indole-3-carboxylic acids can undergo decarboxylation under acidic conditions[83] or by heating in quinoline in the presence of a catalytic amount of their copper salts.[84]

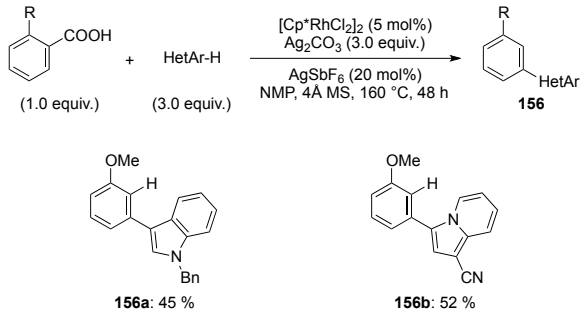
In 2012, Lee and coworkers synthesized *N*-substituted-2-arylindoles **155** in moderate to satisfactory yields by tandem C-H arylation and decarboxylation of 1-alkylindole-3-carboxylic acids **154** with aryl bromides in DMA at 160 °C for 24 h in the presence of KOAc as the base and a catalytic amount of the Pd(0) carbene complex **CAC** (Scheme 77).[54q] Thus, the carboxy group of indoles **154** proved to act in these reactions as an efficient traceless *ortho*-directing group.



155	X	R^1	R^2	Yield (%)
a	Br	Me	4-Ac	60
b	Br	Bn	4-Ac	58
c	Br	Me	4-CN	53
c	Cl	Me	4-CN	35
d	Br	Bn	4-CN	63
e	Br	Me	H	62
f	Br	Me	3,4,5-$(OMe)_3$	45
g	Br	Me	3-OMe	48
h	Br	Me	4-Me	45

Scheme 77. Synthesis of 2-arylindoles **155** from compounds **154** by tandem C-H arylation and decarboxylation

Finally, very recently, Lan You and coworkers described a highly regioselective Rh-catalyzed decarboxylative *ortho*-heteroarylation of aromatic carboxylic acids with heteroarenes and employed their procedure for the synthesis of 1-benzyl-3-(3-methoxyphenyl)-1*H*-indole-5-carbonitrile (**156a**) and 3-(3-methoxyphenyl)indolizine-1-carbonitrile (**156b**).[85] The decarboxylative *ortho*-heteroarylation reactions, which were carried out by the reaction of 1.0 equiv of arylcarboxylic acids with 3.0 equiv of heteroarene, 5.0 mol% $[Cp^*RhCl_2]_2$, 20 mol% $AgSbF_6$, 3.0 equiv of Ag_2CO_3, and 2.0 equiv of K_2HPO_4 in NMP at 160 °C for 48 h in the presence of 4Å molecular sieves, gave compounds **156a** and **156b**, in 45 and 52% yield, respectively (Scheme 78).[85]



Scheme 78. Synthesis of compounds **156a** and **156b** by Rh-catalyzed decarboxylative *ortho*-heteroarylation of arylcarboxylic acids

Notably, *ortho*- or *para*-substituted benzoic acids bearing both electron-donating and electron-withdrawing substituents could undergo similar Rh-catalyzed *ortho*-heteroarylation reactions also with heteroarenes such as thiophenes, benzo[*b*]thiophenes, furans, xanthines and thiazoles to produce *meta*-heteroarylated products in moderate to good yields.[85]

3. Direct (Hetero)arylation Reactions of Six-Membered Heteroarenes with One Heteroatom

3.1. Direct (hetero)arylation reactions of pyridine, quinoline, isoquinoline, phenanthridine, and benzo[*h*]quinoline ring systems

2-Arylpyridines are an important class of heterocyclic compounds that include pharmacologically and/or biologically active compounds such as atazanavir (**157**) (Figure 12), an antiretroviral drug of the protease inhibitor class,[86] etoricoxib (**158**) (Figure 12), a selective cyclooxygenase (COX)-2 inhibitor, [87] nemertelline (**159**) (Figure 12), a neurotoxic compound originally found in marine hoplonemertine worm *Amphiporus angulatus,*[88] vismodegib (**160**) (Figure 12), a hedgehog signaling antagonist that inhibits pancreatic cancer stem characteristics,[89] and 2-thienyl-4-furyl-6-arylpyridine derivatives such as compound **161** (Figure 12), which exhibits significant topoisomerase II inhibitory activity.[90]

The methods for the synthesis of 2-arylpyridines include Pd-catalyzed Suzuki-Miyaura couplings of 2-pyridyl-derived nucleophiles,[91] microwave- assisted Pd-catalyzed Suzuki-Miyaura couplings of 2-halopyridines in water using hydrophilic theophylline base compound as ligands,[92] reaction of 2-pyridyl halides with electron-rich arenes in the presence of $AlCl_3$,[93] electrochemical cross-coupling between 2-halopyridines and (hetero)aryl halides catalyzed by Ni-2,2'-bipyridine complexes,[94] and $NiBr_2$(2,2'-bipyridine)-catalyzed reaction of 2-

halopyridines with aryl halides in DMF in the presence of Mn powder and trifluoroacetic acid.[95]

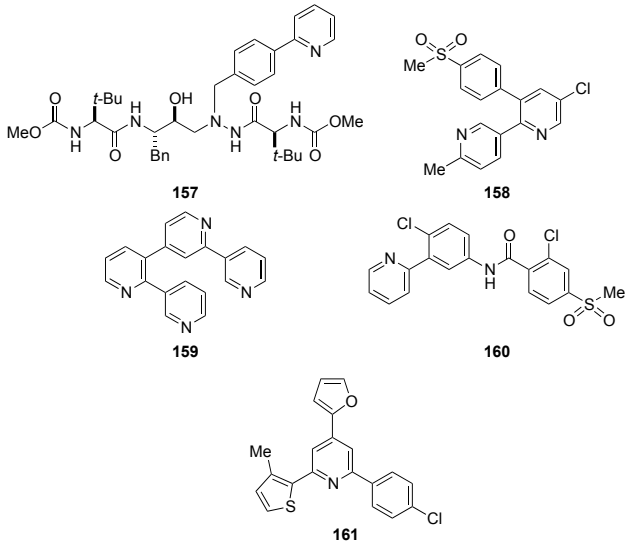
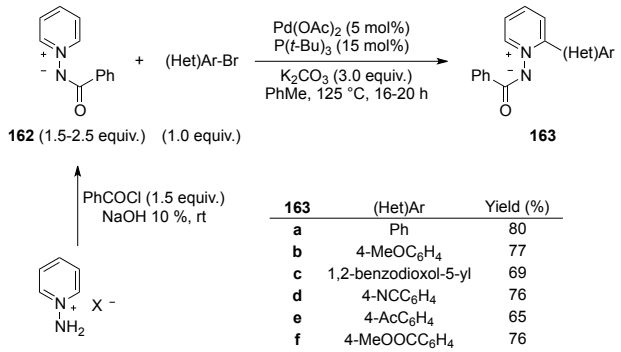


Figure 12. Chemical structures of compounds **157–161**

However, as far as we know, no method for the synthesis of 2-(hetero)arylpyridines via transition metal-catalyzed direct C-2 (hetero)arylation reactions of the unsubstituted pyridine ring with (hetero)aryl halides or pseudohalides has been reported so far.

Nevertheless, in 2008, Charette and coworkers demonstrated that 2-arylpyridines can be synthesized efficiently and regioselectively via a three-step reaction sequence involving the Pd-catalyzed *ortho*-(hetero)arylation of a *N*-iminopyridinium ylide.[97] The substrate used by these authors was *N*-benzoyliminopyridinium ylide (**162**),[98a,b] a compound in which the *N*-iminobenzoyl moiety acted as a removable directing group. It was synthesized by the reaction of 1.0 equiv of a *N*-aminopyridinium salt with 1.5 equiv of benzoyl chloride at room temperature in the presence of 10% aq NaOH (Scheme 79). The pyridinium salt was in turn prepared by direct *N*-amination of pyridine using hydroxylamine-O-sulfonic acid.[98c]

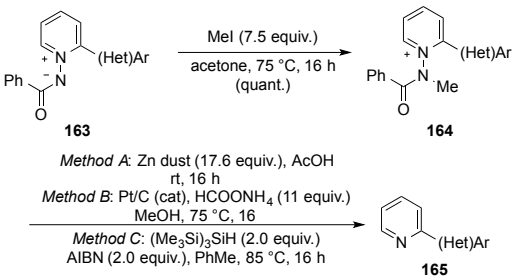
Under optimized conditions the (hetero)arylation reactions of **162** were carried out by treatment of 1.5–2.5 equiv of **162** with 1.0 equiv of (hetero)aryl bromides, 5 mol% $Pd(OAc)_2$, 15 mol% P(*t*-Bu)$_3$, 3.0 equiv of K_2CO_3 and 3Å molecular sieves in toluene at 125 °C for 16-20 h providing 2-(hetero)aryl-*N*-benzoyliminopyridinium ylides **163** in yields ranging from 50 to 83% (Scheme 79).[97]



163	(Het)Ar	Yield (%)
a	Ph	80
b	4-$MeOC_6H_4$	77
c	1,2-benzodioxol-5-yl	69
d	4-NCC_6H_4	76
e	4-AcC_6H_4	65
f	4-$MeOOCC_6H_4$	76
g	4-$F_3CC_6H_4$	56
h	3,5-$F_2C_6H_3$	53
i	2-MeC_6H_4	72
j	pyrimidin-5-yl	50
k	2-pyridyl	50
l	3-pyridyl	83

Scheme 79. $Pd(OAc)_2$/P(*t*-Bu)$_3$-catalyzed C-2 (hetero)arylation of *N*-benzoyliminopyridinium ylide **162**

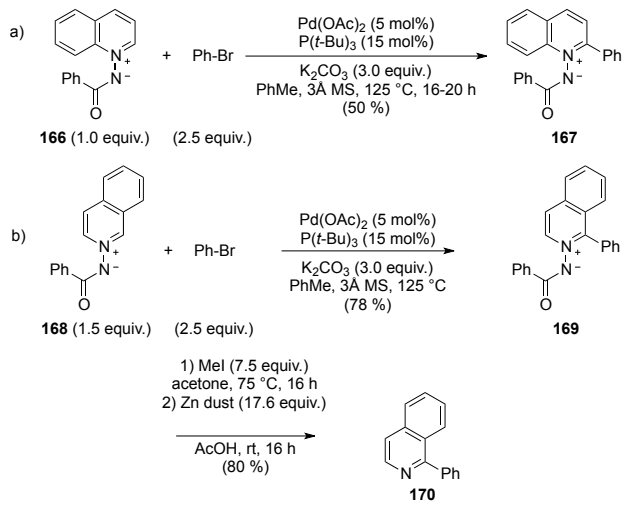
Both electron-rich and electron-poor (hetero)aryl bromides could be used as arylating reagents although the use of a large molar excess of **162** was necessary for the latter. Notably, compounds **163** were then converted into the corresponding 2-(hetero)arylpyridines **165** via a two-step process involving the removal of the *N*-iminobenzoyl moiety by reductive cleavage of the N–N bond of the pyridinium salts **164**, which were obtained by methylation of compounds **163** in quantitative yield. As shown in Scheme 80, three methods could be used to convert compounds **164** to the corresponding 2-(hetero)arylpyridines **165**. In the first method (*Method A*) compounds **164** were reacted with 17.6 equiv of Zn dust in AcOH at room temperature for 1 h. In the second method (*Method B*) compounds **164** were treated with 11.0 equiv of ammonium formate and a catalytic amount of Pt on carbon, and in the third method (*Method C*) the cleavage of the N–N bond of compounds **164** was carried out with tris(trimethylsilyl)silane and AIBN.[97]



165	(Het)Ar	Method	Yield (%)
a	Ph	A	80
a	Ph	B	83
a	Ph	C	85
c	1,3-benzodioxol-5-yl	A	86

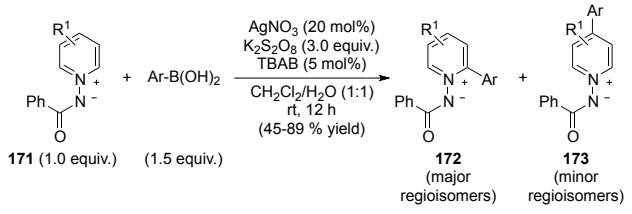
Scheme 80. Removal of the *N*-iminobenzoyl moiety of compounds **163**

Charette and coworkers also reported that *N*-benzoyliminoquinolinium ylide (**166**) and *N*-benzoyliminoisoquinolinium ylide (**168**) undergo $Pd(OAc)_2/P(t\text{-}Bu)_3$-catalyzed *ortho*-arylation with bromobenzene to give compounds **167** (Scheme 81, eq. a) and **169** (Scheme 81, eq. b) in 50 and 78% yield, respectively. The subsequent removal of the *N*-iminobenzoyl moiety from **169** by methylation followed by N–N cleavage according to *Method A* allowed to obtain 1-phenylisoquinoline (**170**) in 80% yield (Scheme 81, eq. b).[97]



Scheme 81. $Pd(OAc)_2/P(t\text{-}Bu)_3$-catalyzed *ortho*-phenylation of compounds **166** and **168** and regioselective synthesis of 2-phenylisoquinoline (**170**)

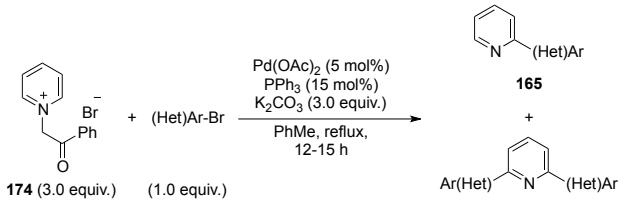
In 2014, a novel Ag-catalyzed C-H arylation of *N*-benzoyliminopyridinium ylides of general formula **171** with arylboronic acids was described by Yu, Wand and coworkers.[99] The reactions (Scheme 82) were carried out by treating 1.0 equiv of compounds **171** with 1.5 equiv of arylboronic acids, 20 mol% $AgNO_3$, 5 mol% TBAB and 3.0 equiv of $K_2S_2O_8$ in a 1 : 1 mixture of CH_2Cl_2 and water under air at room temperature.



Scheme 82. Ag-catalyzed direct C-H arylation of *N*-benzoyliminopyridinium ylides **171** with arylboronic acids

Unfortunately, the reactions, unlike those involving the Pd-catalyzed (hetero)arylation of iminium ylide **162**,[97] proved to be non-regioselective and in general provided mixture of 2-arylated and 4-arylated products, **172** and **173** respectively, in which compounds **172** were often the major products. Compounds **172** and **173** could be separated by chromatography,[99] but their conversion into the corresponding arylpyridines was not investigated.

Five years earlier, Wang Hu and coworkers described that the *N*-phenacyl group acts as a traceless *ortho*-directing group in the highly regioselective Pd-catalyzed direct arylation of *N*-phenacylpyridinium bromide (**174**) with (hetero)aryl bromides.[100] In fact, the reactions between 3.0 equiv of **174** and 1.0 equiv of (hetero)aryl bromides in the presence of 5 mol% $Pd(OAc)_2$, 15 mol% PPh_3 and 3.0 equiv of K_2CO_3 in toluene under reflux gave rise to 2-(hetero)arylpyridines **165** that in many cases were obtained together with significant amounts of the corresponding 2,6-di(hetero)arylpyridines **175** (Scheme 83).



165	175	(Het)Ar	Yield % of 165	Yield % of 175
a	**a**	Ph	46	40
b	**b**	4-$MeOC_6H_4$	50	38
d	**d**	4-FC_6H_4	35	32
e	**e**	3-FC_6H_4	40	33
f	**f**	2-MeC_6H_4	49	38
g	**g**	2-$MeOC_6H_4$	45	36
h	**h**	4-$(NO_2)C_6H_4$	76	-
i	**i**	4-$MeOOCC_6H_4$	72	-
j	**j**	2-pyridyl	62	-
k	**k**	1-naphthyl	80	-

Scheme 83. $Pd(OAc)_2/PPh_3$-catalyzed *ortho*-arylation of *N*-phenacylpyridinium bromide (**174**) with (hetero)aryl bromides

However, compounds **165** were obtained as single product in high yields when (hetero)aryl bromides bearing electron-withdrawing or large sterically sized substituents were used as arylating reagents.[100]

It should be noted that a kinetic isotope effect study proved that the *ortho*-arylation reactions proceeded through a C-H bond activation pathway and that compounds **175** were produced stepwise from 2-(hetero)arylpyridines **165**. Moreover, experimental results and DFT calculations indicated that the amazing *N*-phenacyl group activates the pyridine ring by forming the *N*-iminopyridinium ylid **176** (Figure 13) and controls the regioselectivity of the (hetero)arylation reactions by coordination with Pd at the *ortho*-position of pyridine.[100]

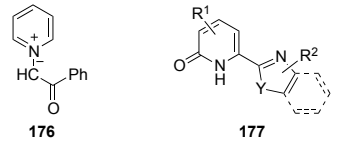
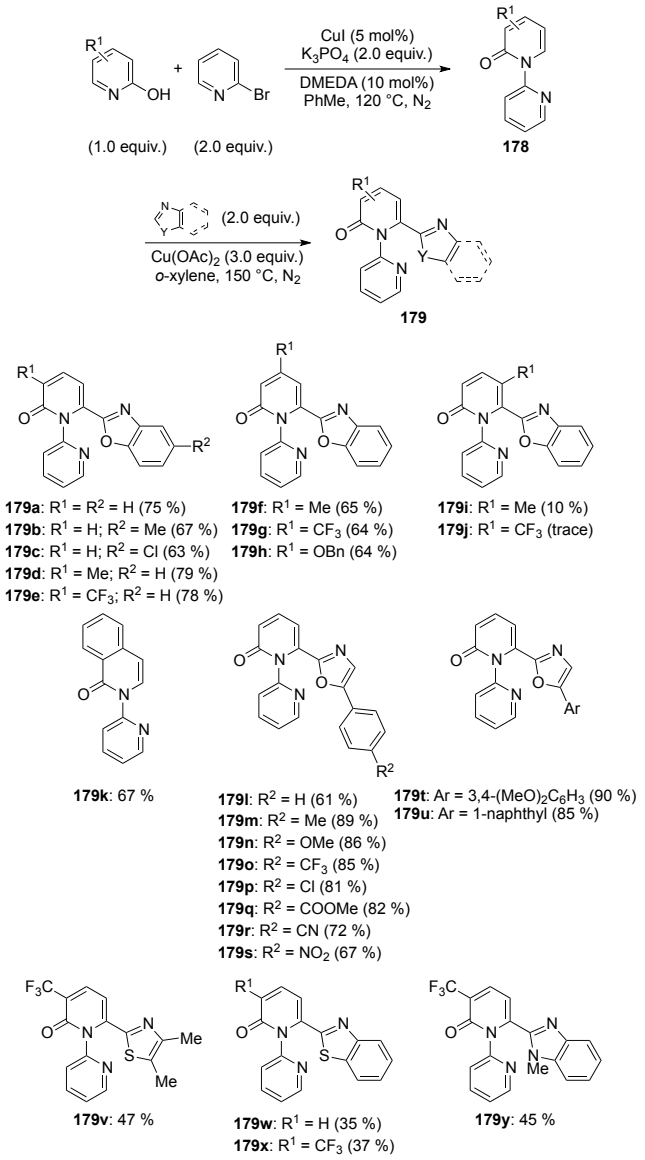


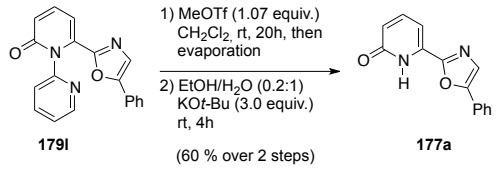
Figure 13. Chemical structures of ylid **176** and 6-[5-(aryl)azol-2-yl]pyridine-2(1*H*)-ones **177**

In 2014, Hirano, Miura and coworkers developed a new interesting method for the high regioselective synthesis of 6-[5-(aryl)azol-2-yl]pyridine-2(1*H*)-ones **177** (Figure 13) in which the first step involved the Cu-mediated C-6 selective dehydrogenative heteroarylation of 1-(2-pyridyl)-2-pyridones **178** with 1,3-azoles.[101]



Scheme 84. Cu-mediated dehydrogenative heteroarylation reactions of 1-(2-pyridyl)-2-pyridones **178** with 1,3-azoles

The synthesis of compounds **178** was carried out by treatment of 1.0 equiv of the corresponding 2-hydroxypyridines with 2.0 equiv of 2-bromopyridine, 5 mol% CuI, 2.0 equiv of K_3PO_4 and 10 mol% DMEDA in toluene at 120 °C for 20 h under a nitrogen atmosphere. Notably, these dehydrogenative heteroarylation reactions allowed the first successful highly selective direct arylation of a pyridine ring at the C-6 position and their regioselectivity was directed by the *N*-2-pyridyl group of compounds **178** which could be readily removed from the coupling products. As shown in Scheme 84, the heteroarylation reactions, which were carried out by the reaction of 1.0 equiv of compounds **178** with 2.0 equiv of azoles, 1.0 equiv of pivalic acid and 3.0 equiv of $Cu(OAc)_2$ at 150 °C under a nitrogen atmosphere, provided 6-(1,3-azol-2-yl)-2*H*-[1,2'-bipyridin]2-ones **179** generally in moderate to good yields. However, the presence of a substituent at position C-5 of the 2-pyridone ring turned out to be detrimental. In fact, compounds **179i** and **179j** were obtained in 10% yield and in trace amounts, respectively (Scheme 84).[101] Hirano, Miura and coworkers also investigated the removal of the 2-pyridyl directing group from compounds **179** and found that this result could be achieved at room temperature via quaternization-driven[102] alcoholysis. The reaction conditions used for the synthesis of 6-(5-phenyloxazol-2-yl)pyridin-2(1*H*)-one (**177a**) from compound **179l** are illustrated in Scheme 85.[101]

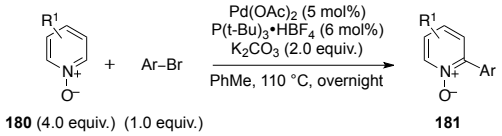


Scheme 85. *N*-Deprotection of compound **179l**

Finally, in order to have information on the C-H bond cleavage step of the Cu-mediated dehydrogenative heteroarylation reactions, Hirano, Miura and coworkers carried out deuterium labeling experiments and found that the obtained results suggested no-rate-limiting C-H bond cleavage. These authors also observed that in certain cases it was possible to carry out the dehydrogenative heteroarylation reactions of 2-pyridones **178** with benzoxazole in air using 20 mol% $Cu(OAc)_2$ and 1.0 equiv of AcOH instead under the conditions of Scheme 84. Interestingly, the catalytic conditions allowed the synthesis of compounds **179e**, **179l**, **179n** and **179t** in yields comparable to those obtained with the standard procedure involving the use of 3.0 equiv of $Cu(OAc)_2$. However, the catalytic reactions leading to compounds **179a** and **179d**, unexpectedly, were found to be less efficient.[101]

Since 2005, another removable directing functionality, the

N-oxide group, has been widely used in several highly regioselective direct arylation reactions, *i.e.* the Pd-catalyzed direct *ortho*-arylations of azine *N*-oxides. In 2005, in a pioneering study, Fagnou and coworkers developed a protocol for the regioselective *ortho*-arylation of pyridine *N*-oxides **180** that involved the reaction between 4.0 equiv of compounds **180** with 1.0 equiv of aryl bromides in toluene at 110 °C overnight in the presence of 5 mol% $Pd(OAc)_2$, 15 mol% $P(t\text{-}Bu)_3{\cdot}HBF_4$ (an air stable non-pyrophoric ligand precursor) and 2.0 equiv of K_2CO_3 (Scheme 86).[105] The arylation reactions produced 2-arylpyridine-1-oxides **181** in good to excellent yields using both electron-rich and electron-poor aryl bromides as well as pyridine *N*-oxides bearing an electron-donating or an electron-withdrawing substituent at C-4 position.[105]

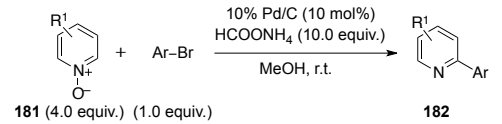


180 (4.0 equiv.) (1.0 equiv.) **181**

181	R^1	Ar	Yield %
a	H	4-MeC_6H_4	91
b	H	3,5-$Me_2C_6H_3$	95
c	H	3-$MeOC_6H_4$	97
d	H	1-naphthyl	88
e	H	2-MeC_6H_4	87
f	H	4-$MeOC_6H_4$	80
g	H	4-$MeOOCC_6H_4$	74
h	H	4-$CF_3C_6H_4$	76
i	4-MeO	4-MeC_6H_4	80
j	4-NO_2	4-MeC_6H_4	78

Scheme 86. Pd-catalyzed *ortho*-arylation of pyridine *N*-oxides **180** with aryl bromides

For this study, the pyridine *N*-oxides were purchased from commercial sources but could also be synthesized by the reaction of 1.0 equiv of pyridines with 1.4 equiv of *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature or by treatment of a solution of 1.0 equiv of pyridines in acetone and phosphate buffer with 2.4 equiv of oxone and 2N NaOH at room temperature keeping the pH between 7 and 8.[105]



181 (4.0 equiv.) (1.0 equiv.) **182**

182	R^1	Ar	Yield %
a	H	4-MeC_6H_4	95
b	H	3-$MeOC_6H_4$	87
c	4-MeO	4-MeC_6H_4	84
d	H	4-$MeOOCC_6H_4$	87

Scheme 87. Pd/C-catalyzed deoxygenation of pyridine *N*-oxides **181**

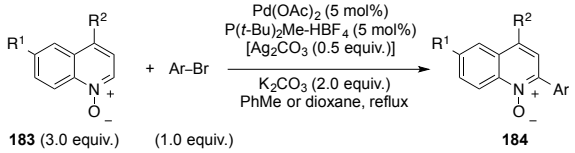
Compounds **181** were then converted to the corresponding 2-arylpyridines **182** under mild conditions and in high yields via Pd/C-catalyzed reduction with ammonium formate (Scheme 87).[105]

More recently, the C-2 regioselectivity of the Pd-catalyzed direct arylation reactions of pyridine *N*-oxides was explained on the basis of the increased strength of the C2-H bond[106] and the increased acidity of this bond caused by the adjacent electron-withdrawing N-O group.[107]

In 2010, detailed mechanistic studies by Campeau and coworkers supported the inner-sphere concerted metalation-deprotonation pathway that does not involve the coordination of the *N*-oxide oxygen atom to Pd.[108] In 2012, Hartwig and coworkers reinvestigated the direct arylation of pyridine *N*-oxides catalyzed by $Pd(OAc)_2$ and $P(t\text{-}Bu)_3$ and proposed that the reaction occurs by the generation of the cyclometalated complex $\{Pd(OAc)[t\text{-}Bu)_2PCMe_2CH_2]\}$ and that this complex serves as a catalysts for the *ortho*-arylation of pyridine *N*-oxide.[109]

In 2009, attention was devoted to the synthesis of 2-arylquinolines **185** through Pd-catalyzed direct *ortho*-arylation of quinoline *N*-oxides **183**. In fact, 2-arylquinolines include compounds with fluorescence properties,[110] naturally-occurring compounds[111a] and substances that display antimicrobial properties.[111b] Fagnou and coworkers investigated the direct arylation of quinoline *N*-oxide (**183**, $R^1 = R^2 = H$) under the conditions originally developed for the arylation of pyridine *N*-oxides **180**, but they found that the reactions occurred in a low yield.[112] Thus, they modified the original conditions and observed that $P(t\text{-}Bu)_2Me{\cdot}HBF_4$ was the best preligand among those examined and that reducing the ligand/Pd molar ratio from 3 : 1 to 1 : 1 resulted in an increased yield of the arylation reaction. These modified conditions were used for the regioselective *ortho*-arylation of numerous quinoline *N*-oxides **183** with aryl bromides, which provided the required 2-arylquinoline *N*-oxide in good to excellent yields (Scheme 88).[112] Compounds **183** were in turn prepared by addition of a 50% aqueous solution of H_2O_2 to a solution of 1.0 equiv of the parent quinolines and 1-4 mol% methylrhenium dioxide[103k] in CH_2Cl_2 in an ice bath and allowing the resulting mixtures to warm to room temperature for 12–24 h. After consumption of the starting material a small amount of MnO_2 (5-10 mg) was added to destroy unreacted peroxide. Interestingly, the procedure was easily scalable with limited by-products. It was found that both electron-donating and electron-withdrawing substituents were tolerated in the arylation reactions and the coupling involving 1-bromo-2-chlorotoluene resulted to take place selectively at the C-Br bond to provide compound **183g** in 70% yield. Notably, the arylation reactions involving the

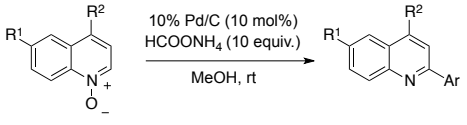
use of *ortho*-substituted aryl bromides and 1-bromonaphthalene were carried out in the presence of Ag_2CO_3, but the authors did not explain the use of this additional base.



184	Addition of Ag_2CO_3	Solvent	R^1	R^2	Ar	Yield %
a	-	PhMe	H	H	4-MeC_6H_4	96
b	-	PhMe	H	H	Ph	89
c	-	PhMe	H	H	*t*-BuC_6H_4	94
d	-	PhMe	H	H	4-$MeOC_6H_4$	87
e	-	PhMe	H	H	4-$EtOOCC_6H_4$	61
f	0.5 equiv.	PhMe	H	H	2-MeC_6H_4	70
g	0.5 equiv.	PhMe	H	H	2-ClC_6H_4	70
h	-	PhMe	H	H	3-$MeOC_6H_4$	87
i	-	PhMe	H	H	3,5-$Me_2C_6H_3$	92
j	-	PhMe	H	H	2-naphthyl	73
k	0.5 equiv.	PhMe	H	H	1-naphthyl	83
l	-	dioxane	MeO	H	Ph	72
m	-	PhMe	MeO	H	4-$MeOC_6H_4$	77
n	-	PhMe	MeO	H	4-MeC_6H_4	85
o	-	PhMe	MeO	H	4-ClC_6H_4	55
p	-	PhMe	H	COOMe	4-MeC_6H_4	91

Scheme 88. Pd-catalyzed direct *ortho*-arylation of quinoline *N*-oxides **183** with aryl bromides

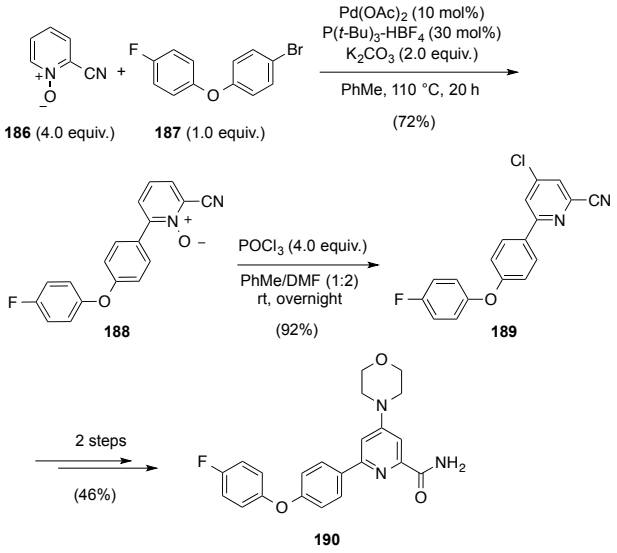
Compounds **184** were then converted to the corresponding 2-arylquinolines **185** in excellent yields by deoxygenation with ammonium formate in the presence of 10 mol% Pd/C (Scheme 89).[112,113]



185	R^1	R^2	Ar	Yield %
a	H	H	4-MeC_6H_4	94
b	H	H	4-$MeOC_6H_4$	93
c	H	H	4-$EtOOCC_6H_4$	80
d	OMe	H	Ph	93
e	OMe	H	4-$MeOC_6H_4$	79

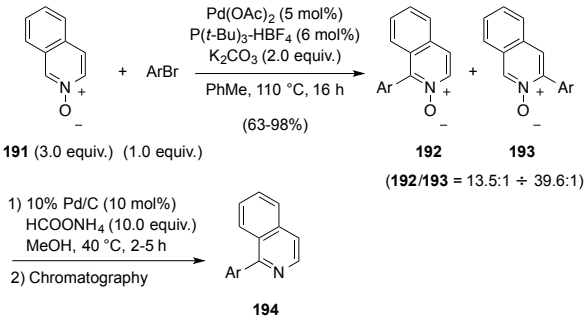
Scheme 89. Deoxygenation of quinoline *N*-oxides **184**

The protocol developed for the synthesis of 2-arylpyridine *N*-oxides **181** was also used to prepare the 2-aryl-6-cyanopyridine *N*-oxide **188** in 72% yield from 2-cyanopyridine *N*-oxide (**186**) and 1- (4-fluorophenoxy)-4-bromobenzene (**187**). Compound **188** was then subjected to deoxygenation by treatment with $POCl_3$ in a mixture of DMF and toluene to give 6-[4-(4-fluorophenoxy)phenyl]-4-chloropyridine-2-carbonitrile (**189**) in an excellent yield, which was used as an advanced intermediate in the synthesis of the sodium channel inhibitor **190**[114] (Scheme 90).[112]



Scheme 90. Synthesis of the sodium channel inhibitor **190**

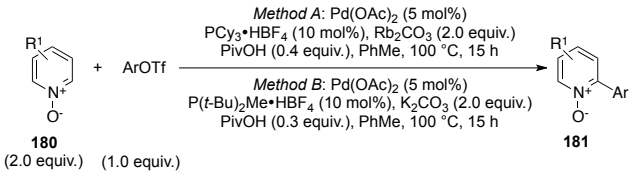
Finally, a protocol similar to that developed for the synthesis of 2-arylquinolines **185** from quinoline *N*-oxides **183** was employed to prepare 1-arylisoquinolines **194** from isoquinoline *N*-oxide (**191**) and aryl bromides (Scheme 91). Thus, the $Pd(OAc)_2/P(t\text{-}Bu)_2Me{\cdot}HBF_4$-catalyzed reaction of 3.0 equiv of **191** with 1.0 equiv of aryl bromides in toluene at 110 °C in the presence of K_2CO_3 as the base gave mixtures of 1-arylisoquinoline *N*-oxides **192** and 3-arylisoquinoline *N*-oxides **193** in which compounds **192** were always the major regioisomers. Unfortunately, compounds **192** and **193** often were inseparable by chromatography and thus they were subjected as a mixture to deoxygenation. The resulting regioisomeric arylisoquinolines could then be separated by chromatography allowing to obtain 1-arylisoquinolines **194** in good yields (Scheme 91).[113]



194	Ar	Yield %
a	4-MeC_6H_4	80
b	3,5-$Me_2C_6H_3$	73
c	4-$EtOOCC_6H_4$	83
d	4-$MeOC_6H_4$	83
e	4-ClC_6H_4	85

Scheme 91. Synthesis of 2-arylisoquinolines **194**

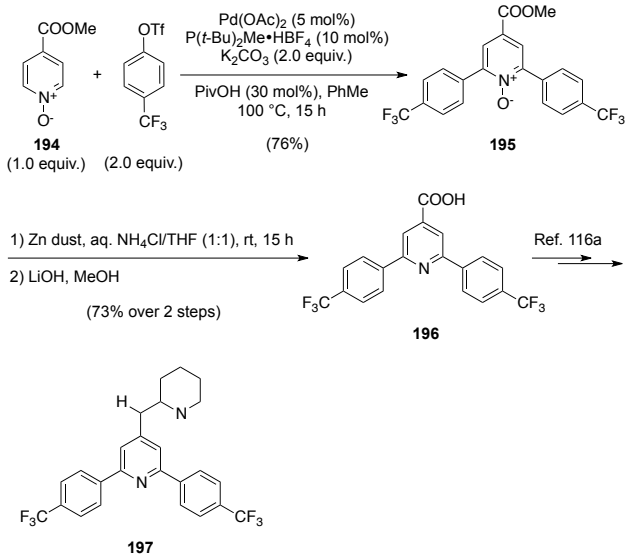
Again in 2009, Fagnou and coworkers described the Pd-catalyzed direct *ortho*-arylation of pyridine *N*-oxides **180** with aryl triflates according to two optimized reaction conditions.[115] The first set of conditions (*Method A*) involved treatment of 2.0 equiv of compounds **180** with 1.0 equiv of aryl triflates, 5 mol% $Pd(OAc)_2$, 10 mol% $PCy_3{\cdot}HBF_4$, 2.0 equiv of Rb_2CO_3, and 0.4 equiv of pivalic acid in toluene at 100 °C for 15 h. This method allowed to minimize the formation of 2,6-diarylation products thus maximizing the yield of the monoarylation products **181** (Scheme 92).



Method	**181**	R^1	Ar	Yield
A	**a**	H	4-MeC_6H_4	89
A	**d**	H	1-naphthyl	75
A	**f**	H	4-$MeOC_6H_4$	75
A	**k**	H	4-NCC_6H_4	49
A	**l**	4-Me	4-MeC_6H_4	71
A	**m**	4-CN	4-MeC_6H_4	38
A	**n**	4-MeOOC	1-naphthyl	59
B	**o**	2-Me_2, 5-CN	4-MeC_6H_4	74
A	**p**	3-F	4-$MeOC_6H_4$	90

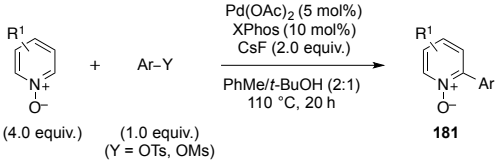
Scheme 92. Pd-catalyzed *ortho*-arylation of pyridine *N*-oxides with aryl triflates

The second set of conditions (*Method B*) involved the reaction of 2.0 equiv of compounds **180** with 1.0 equiv of aryl triflates, 5 mol% $Pd(OAc)_2$, 10 mol% P(*t*-Bu)$_2$Me·HBF_4, 2.0 equiv of K_2CO_3, and 30 mol% pivalic acid in toluene at 110 °C for 15 h. This method was used to maximize the yields of the reactions with substrates for which the diarylation reaction was not problematic. *Method B* was then used for the synthesis of 4-methoxycarbonyl-2,6-bis[4-(trifluoromethyl)phenyl]pyridine1-oxide (**195**) in 76% yield from methyl isonicotinate *N*-oxide (**194**) and 4-(trifluoromethyl)phenyl triflate (Scheme 93). Deoxygenation of **195** with Zn dust in a mixture of aqueous NH_4Cl and THF at room temperature followed by saponification gave 2,6-bis[4-(trifluoromethyl)phenyl]isonicotinic acid (**196**),[115] a key intermediate in the synthesis of diarylpyridine **197**,[116a] which exhibits antimalarial[116b] and antimicrobial activitites[116c] (Scheme 93).



Scheme 93. Formal synthesis of 2,6-diarylpyridine **197**

In 2011, Ackermann and Fenner reported that 2-arylpyridine *N*-oxides of general formula **181** could also be synthesized in good yields by $Pd(OAc)_2$/XPhos-catalyzed reaction of pyridine *N*-oxides **180** with both electron-deficient and electron-rich aryl tosylates or mesylates (Scheme 94).[117] However, the yields of some of the compounds **181** were lower than those obtained using the protocol outlined in Scheme 92.



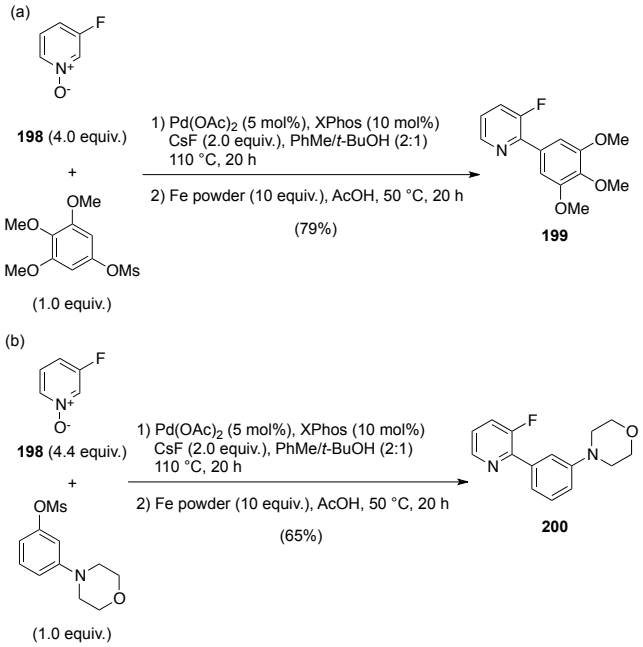
181	Y	R^1	Ar	Yield %
a	OTs	H	4-MeC_6H_4	58
b	OTs	H	3,5-$Me_2C_6H_3$	64
d	OTs	H	1-naphthyl	60
f	OTs	H	4-$MeOC_6H_4$	52
r	OTs	H	3-$CF_3C_6H_4$	51
s	OTs	H	3-$Me_2NC_6H_4$	50
t	OTs	H	3,4,5-$(MeO)_3C_6H_2$	67
u	OTs	3-F	2-pyridyl	64
v	OMs	3-F	4-*n*-pentC_6H_4	66
w	OMs	3-F	4-*t*-BuC_6H_4	64
x	OMs	3-F	4-$MeOC_6H_4$	62
y	OMs	3-F	3-$Me_2NC_6H_4$	82
z	OMs	3-F	3-$MeOC_6H_4$	70
aa	OMs	3-F	3-MeC_6H_4	69
ab	OMs	3-F	3,5-$Me_2C_6H_3$	72
ac	OMs	3-F	3,5-$(MeO)_2C_6H_3$	78
ad	OMs	3-F	H_2C-4,3-(O,O)-C_6H_4	64
ae	OMs	3-F	2-naphthyl	74

Scheme 94. $Pd(OAc)_2$/XPhos-catalyzed *ortho*-arylation of pyridine *N*-oxides **180** with aryl tosylates or mesylates

Importantly, the optimized conditions of Scheme 94 were found also applicable to the regioselective arylation of

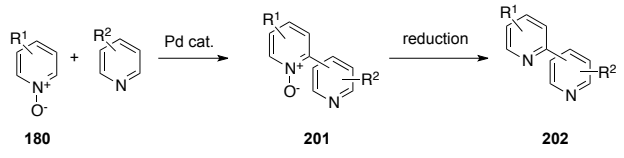
diazine *N*-oxides, such as pyridazine, pyrazine and quinoxaline *N*-oxides, as well as of quinoline *N*-oxide with aryl tosylates.[117]

Ackermann and Fenner also described the high yielding syntheses of 2-aryl-3-fluoropyridines **199** and **200** via $Pd(OAc)_2$/XPhos-catalyzed *ortho*-arylation of 3-fluoropyridine *N*-oxide (**198**) with the required aryl mesylates, followed by deoxygenation of the resulting arylated derivatives by treatment with Fe powder and AcOH at 50 °C (Scheme 95, eqs. a and b, respectively).[117]



Scheme 95. Synthesis of 2-aryl-3-fluoropyridines **199** and **200**

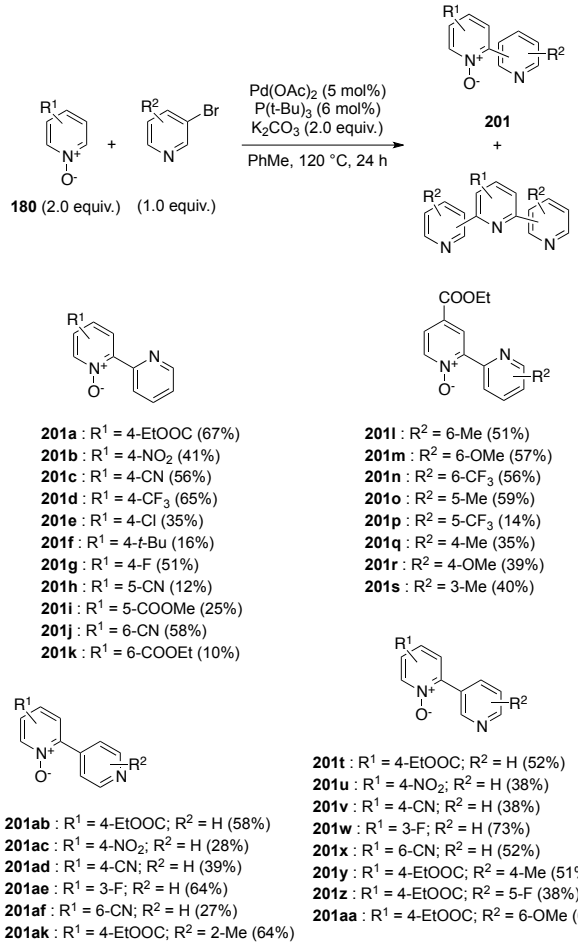
Duric and Tzschucke investigated the synthesis of bipyridines of general formula **202** via a two-step process involving the Pd-catalyzed direct *ortho*-arylation of pyridine *N*-oxides **180** with bromopyridines, and the subsequent deoxygenation reaction of the resulting arylated derivatives **201** (Scheme 96).[118]



Scheme 96. Strategy used for the synthesis of bipyridines **202**

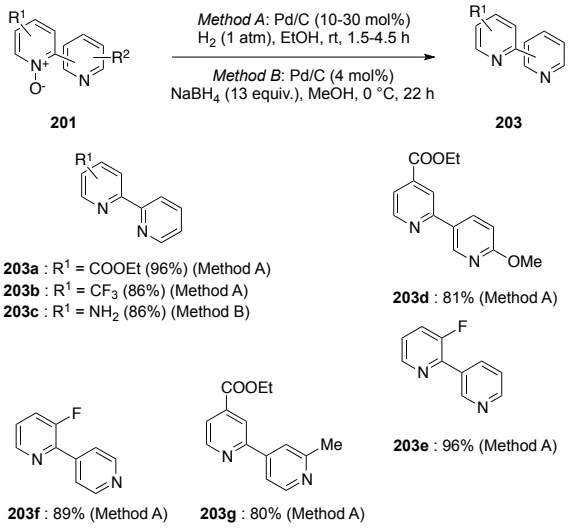
Attention was turned to compounds **202** because they represent an important class of heterocyclic deivatives.[119] In particular, 2,2'-bipyridines include naturally-occurring compounds,[120] effective ligands for transition metal-catalyzed reactions,[121] liquid crystalline materials,[122] and derivatives that play an important role in polymer science.[123] In addition, 4,4'-bipyridine is a compound which is mainly used as a precursor to paraquat (the trade name of *N,N'*-dimethyl-4,4'-bipyridinium dichloride), one of the most used herbicides.[124]

The first step of the synthesis of unsymmetrically substituted bipyridines **202** involved the $Pd(OAc)_2$/P(*t*-Bu)$_3$-catalyzed direct arylation of pyridine *N*-oxides **180** with bromopyridines in toluene at 120 °C for 24 h in the presence of K_2CO_3 as the base.[118] Unfortunately, in many cases the arylation reactions (Scheme 97), which were carried out using a 1 : 2 molar ratio between bromopyridines and compounds **180**, provided the required 2-arylated derivatives **201** together with significant amounts of terpyridine *N*-oxides **202**. Illustrative examples of syntheses of bipyridine *N*-oxides are shown in Scheme 97.



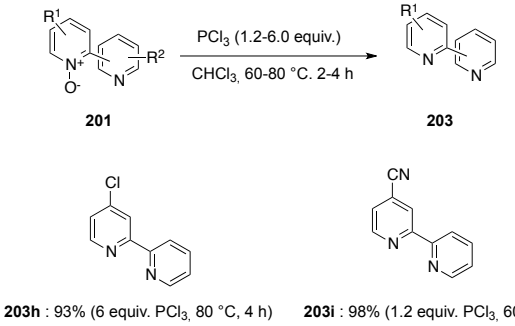
Scheme 97. $Pd(OAc)_2$/P(*t*-Bu)$_3$-catalyzed direct *ortho*-arylation of pyridine *N*-oxides with bromopyridines

Compounds **201** were then deoxygenated, and in most cases their reduction to the corresponding bipyridines **203** was carried out with hydrogen (*Method A*) or $NaBH_4$ (*Method B*) using Pd/C as the catalyst (Scheme 98).



Scheme 98. Deoxygenation of compounds **201** according to *Methods A* and *B*

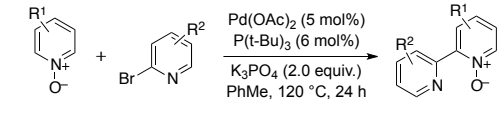
However, in the case of compounds **201** bearing a CN or Cl substituent on the pyridine *N*-oxide moiety the deoxygenation reaction was carried out using PCl_3 as a reducing agent (Scheme 99).



Scheme 99. Deoxygenation of compounds **201** with PCl_3 in $CHCl_3$

In fact, the reduction reaction according to *Method A* or *B* could cause the reduction of the CN group to amino functionality and the possible dehalogenation of the compound bearing the Cl substituent. As shown in Scheme 99, the deoxygenation reaction with PCl_3 in $CHCl_3$ allowed the preparation of bipyridines **203h** and **203i** in 93 and 98% yield, respectively.[118]

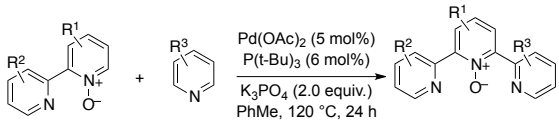
In 2013, Tzschucke and coworkers turned their attention to the synthesis of unsymmetrically substituted 2,2':6',2"-terpyridines via Pd-catalyzed direct C-H arylation of pyridine *N*-oxides.[125] Terpyridines have in fact attracted substantial interest in recent years[126] because the use of their metal complexes as catalysts in organic reactions[127] and their uses as photosensitizers in solar cells,[128] antitumor chemo-therapeutics,[129] and colorimetric and fluorescent sensors for fluoride ions.[130] The synthesis of 2,2':6',2"- terpyridines was carried out in three-steps.[125] In the first of these, 2,2'-bipyridine *N*-oxides **204** were regioselectively synthesized by $Pd(OAc)_2/P(t\text{-}Bu)_3$-catalyzed arylation of pyridine *N*-oxides **180** with 2-bromopyridines under conditions changed compared to those originally developed by the same research group to prepare bipyridine *N*-oxides **201**.[118] In particular, the molar ratio between compounds **180** and 2-bromopyridines was 2.0 instead of 4.0 and the base was K_3PO_4, which gave better yields than K_2CO_3 (Scheme 100). The resulting compounds **204** were obtained in yields ranging from 31 to 68%.



204	R^1	R^2	Yield %
a	4-EtOOC	H	61
b	4-EtOOC	6-OMe	66
c	4-EtOOC	6-CF_3	46
d	4-EtOOC	4-*t*-Bu	57
e	4-EtOOC	4-OMe	54
f	4-EtOOC	4-CN	31
g	4-CN	H	51
h	4-CF_3	5-Me	68
i	4-NO_2	6-OMe	57

Scheme 100. Synthesis of bipyridine *N*-oxides **204**

In the second step, compounds **204** were reacted with 1.2 equiv of 2-bromopyridines in the presence of 5 mol% $Pd(OAc)_2$, 6 mol% $P(t\text{-}Bu)_3$ and 2.0 equiv of K_3PO_4 in toluene at 120 °C for 24 h to give 2,2':6',2"-terpyridine *N*-oxides **205**, including symmetrically and unsymmetrically substituted derivatives, generally in low to satisfactory yields (Scheme 101).

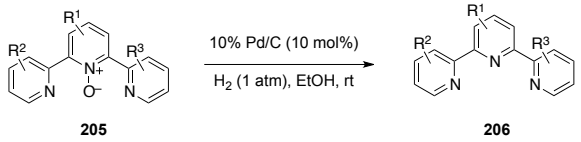


205	R^2	R^1	R^3	Yield %
a	H	4-EtOOC	H	64
b	H	4-EtOOC	6-Me	41
c	6-Me	4-EtOOC	H	64
d	H	4-EtOOC	5-Me	55
e	H	4-EtOOC	4-Me	48
f	H	4-EtOOC	4-*t*-Bu	71
g	4-*t*-Bu	4-EtOOC	H	55
h	6-OMe	4-EtOOC	H	62
i	H	4-EtOOC	6-OMe	47
j	H	4-EtOOC	5-OMe	41
k	5-OMe	4-EtOOC	H	77
l	6-CF_3	4-EtOOC	H	69
m	H	4-EtOOC	6-CF_3	11
n	4-CN	4-EtOOC	H	18
o	6-Me	4-EtOOC	6-Me	42

205	R^2	R^1	R^3	Yield %
p	6-Me	4-EtOOC	6-OMe	46
q	6-OMe	4-EtOOC	6-Me	44
r	6-OMe	4-EtOOC	4-*t*-Bu	64
s	6-OMe	4-EtOOC	6-OMe	53
t	4-OMe	4-EtOOC	4-*t*-Bu	67
u	4-*t*-Bu	4-EtOOC	4-*t*-Bu	59
v	4-*t*-Bu	4-EtOOC	5-OMe	33
w	4-OMe	4-EtOOC	6-CF_3	10
x	5-Me	4-CF_3	6-Me	70
y	5-Me	4-CF_3	6-OMe	40
z	6-OMe	4-NO_2	5-Me	24
aa	6-OMe	4-NO_2	4-Me	17
ab	6-OMe	4-NO_2	6-CF_3	18
ac	H	H	H	24

Scheme 101. Synthesis of 2,2':6',2"-terpyridine *N*-oxides **205**

However, the $Pd(OAc)_2/P(t\text{-}Bu)_3$ catalyzed reactions of bipyridine *N*-oxide **204a** with 2-bromo-4-, 5- and 6-cyanopyridines did not provide the expected terpyridine *N'*-oxides, and also 4-cyanobipyridine *N*-oxide (**204g**) was completely unreactive with 4-methoxy- and 4-*t*-butyl-2-bromopyridine. Finally, in the third step, compounds **205** were deoxygenated with hydrogen and Pd/C as the catalyst providing 2,2':6',2"-terpyridines **206** in high yields (Scheme 102).[125]



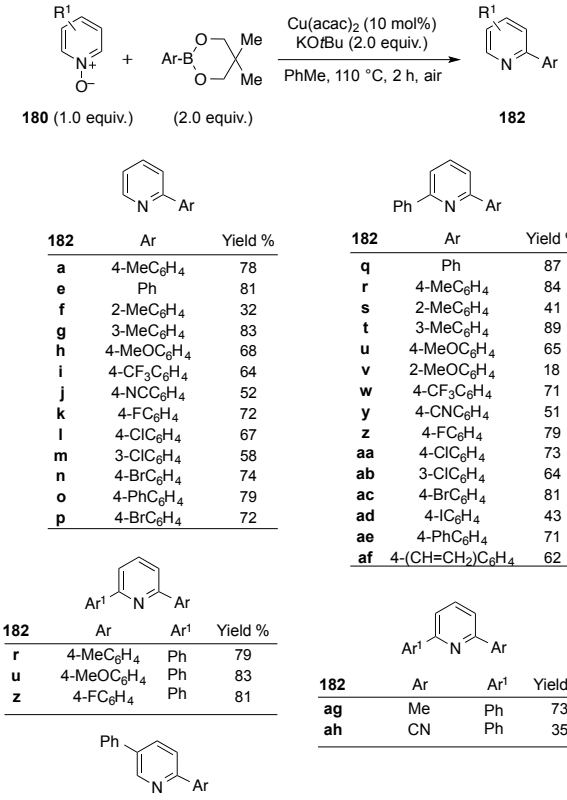
205 **206**

206	R^2	R^1	R^3	Yield %
a	H	4-EtOOC	H	96
b	H	4-EtOOC	6-Me	94
c	H	4-EtOOC	5-Me	96
d	H	4-EtOOC	4-Me	99
e	H	4-EtOOC	4-*t*-Bu	97
f	H	4-EtOOC	6-OMe	96
g	H	4-EtOOC	4-OMe	98
h	H	4-EtOOC	6-CF_3	99
i	6-Me	4-EtOOC	6-OMe	83
j	6-OMe	4-EtOOC	4-*t*-Bu	99
k	6-OMe	4-EtOOC	H	86
l	4-*t*-Bu	4-EtOOC	4-*t*-Bu	95
m	4-OMe	4-EtOOC	4-*t*-Bu	92
n	6-CF_3	4-EtOOC	4-OMe	93
o	5-Me	4-CF_3	4-Me	97
p	4-EtOOC	4-EtOOC	H	99

Scheme 102. Deoxygenation of 2,2':6',2"-terpyridine *N*-oxides **205**

Tzschucke and coworkers also carried out competition experiments and simple kinetic studies to derive information about the mechanism of the Pd-catalyzed direct arylations of pyridine *N*-oxides.[125] They obtained results in agreement with the cooperative mechanism proposed by Hartwig and coworkers.[131]

In 2014, a particularly economical method for the synthesis of 2-arylpyridines **182** was developed by Chen, Wu and coworkers.[132] It involved a Cu-catalyzed direct *ortho*-arylation of pyridine *N*-oxides **180** accompanied by deoxygenation without the use of an additional reducing agent.[132] Thus, the *N*-oxide functionality acted as a traceless *ortho*-directing group. The synthesis of compounds **182** was carried out by the reaction of 1.0 equiv of pyridine *N*-oxides **180** with 2.0 equiv of arylboronic acid 2,2-dimethyl-1,3-propanediol esters,[133] 10 mol% $Cu(acac)_2$, and 3.0 equiv of KO*t*-Bu in toluene at 110 °C for 2 h under air atmosphere (Scheme 103).



180 (1.0 equiv.) (2.0 equiv.) **182**

182	Ar	Yield %
a	4-MeC_6H_4	78
e	Ph	81
f	2-MeC_6H_4	32
g	3-MeC_6H_4	83
h	4-$MeOC_6H_4$	68
i	4-$CF_3C_6H_4$	64
j	4-NCC_6H_4	52
k	4-FC_6H_4	72
l	4-ClC_6H_4	67
m	3-ClC_6H_4	58
n	4-BrC_6H_4	74
o	4-PhC_6H_4	79
p	4-BrC_6H_4	72

182	Ar	Yield %
q	Ph	87
r	4-MeC_6H_4	84
s	2-MeC_6H_4	41
t	3-MeC_6H_4	89
u	4-$MeOC_6H_4$	65
v	2-$MeOC_6H_4$	18
w	4-$CF_3C_6H_4$	71
y	4-CNC_6H_4	51
z	4-FC_6H_4	79
aa	4-ClC_6H_4	73
ab	3-ClC_6H_4	64
ac	4-BrC_6H_4	81
ad	4-IC_6H_4	43
ae	4-PhC_6H_4	71
af	4-$(CH{=}CH_2)C_6H_4$	62

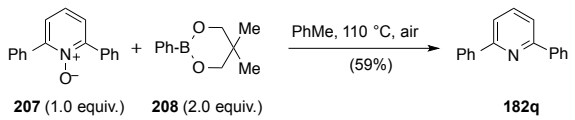
182	Ar	Ar^1	Yield %
r	4-MeC_6H_4	Ph	79
u	4-$MeOC_6H_4$	Ph	83
z	4-FC_6H_4	Ph	81

182	Ar	Ar^1	Yield %
ag	Me	Ph	73
ah	CN	Ph	35

Scheme 103. Cu-catalyzed one-pot synthesis of 2-arylpyridines **182** from pyridine *N*-oxides **180** and arylboronic acid 2,2-dimethyl-1,3-propanediol esters

Under these optimized conditions 2-arylpyridines and symmetrical and unsymmetrical 2,6-diarylpyridines **182** were generally obtained in moderate to good yields. It was also noted that the electronic properties of the substituents on the phenyl group of the boronic esters had little effect on the reaction and that halogen substituents in the boronic esters and groups such as F, OMe and CN in the pyridine *N*-oxides were tolerated.[132]

Experiments were also carried out to elucidate the mechanism of formation of 2-arylpyridines **182**, and in this context it was found that the reaction of 2,6-diphenylpyridine *N*-oxide (**207**) with 2.0 equiv of boronic ester **208** in toluene at 110 °C under air atmosphere gave 2,6-diphenylpyridine (**182q**) in 59% yield (Scheme 104).



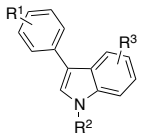
207 (1.0 equiv.) **208** (2.0 equiv.) **182q**

Scheme 104. Deoxygenation of pyridine *N*-oxide **207** with boronic ester **208**

On the basis of the result of this reaction, which was the first example of reduction of a pyridine *N*-oxide by an arylboron reagent, Chen, Wu and coworkers proposed a

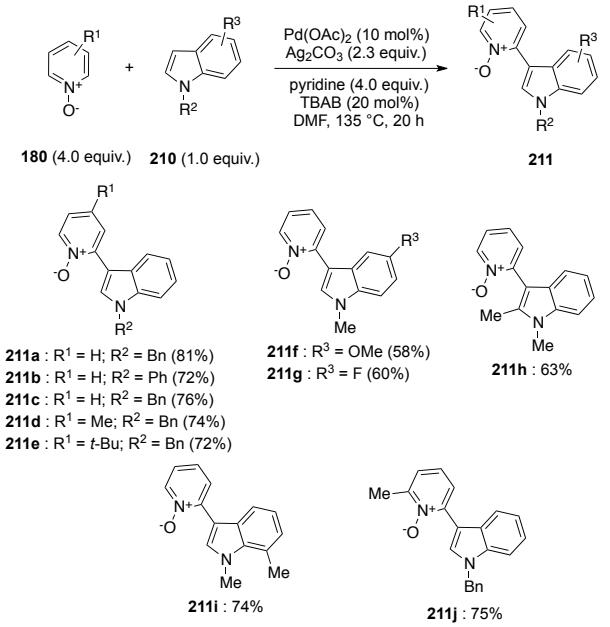
possible reaction pathway for the formation of compounds **182** in which the Cu-catalyzed direct *ortho*-arylation of pyridine *N*-oxides is followed by the deoxygenation reaction of the resulting 2-arylpyridine *N*-oxides by the arylboron reagents.[132]

In recent years significant attention has also been directed to the synthesis of 2-heteroaryl-substituted pyridines through protocols involving transition metal-catalyzed cross-dehydrogenative couplings of pyridine *N*-oxides with heteroarenes. In 2011, Zhang, Li and coworkers turned their attention to the synthesis of 3-(2-pyridyl)indoles **209** (Figure 14) via Pd(II)-catalyzed oxidative coupling of pyridine *N*-oxides **180** with indoles **210** (Scheme 105).[134]



209

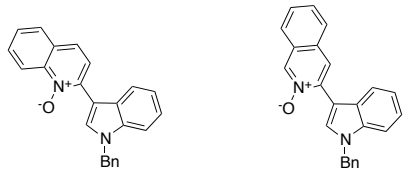
Figure 14. Chemical structure of 3-(2-pyridyl)indoles **209**



Scheme 105. Pd-catalyzed cross-dehydrogenative coupling of pyridine *N*-oxides **180** with indoles **210** using pyridine as an additive

After a careful screening it was found that treatment of 4.0 equiv of compounds **180** with 1.0 equiv of indoles **210**, 10 mol% $Pd(OAc)_2$, 2.3 equiv of Ag_2CO_3, 4.0 equiv of pyridine, and 20 mol% TBAB in DMF at 135 °C for 20 h gave the C-3 substituted indolylpyridine *N*-oxide **211** in moderate to good yields. It should be noted that compounds **211** are known to be useful precursors to indole alkaloids.[135]

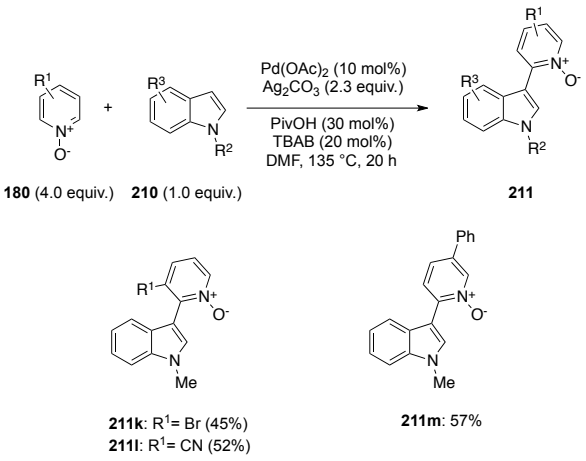
The reaction conditions illustrated in Scheme **105**, in which pyridine was used as an additive[136] that likely serves to stabilize the Pd(II) catalyst, resulted also suitable for the regioselective synthesis of the C-3-substituted indolylquinoline and indolylisoquinoline *N*-oxides **212** and **213** respectively, in 68 and 70% yield (Figure 15).[134] Also in these cases, the reactions proceeded selectively at the C-3 position of the indole ring and at the C-2 position of the azine *N*-oxides.



212 **213**

Figure 15. Chemical structures of compounds **212** and **213**

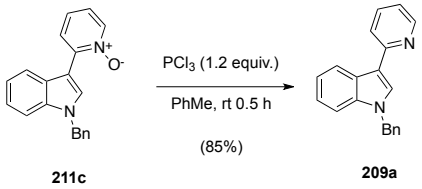
Unfortunately, these conditions were found not applicable to cross-dehydrogenative couplings involving pyridine *N*-oxides bearing electron-withdrawing substituents. Nevertheless, under the free-pyridine conditions illustrated in Scheme 106, the oxidative couplings of 3-bromo- and 3-cyanopyridine *N*-oxides as well as of 3-phenylpyridine *N*-oxide with 1-methyl-1*H*-indole provided compounds **211k**, **211l** and **211m** in 45, 52 and 57% yield, respectively. In the latter reaction the coupling occurred at the less sterically hindered *ortho*-position of the pyridine *N*-oxide.



Scheme 106. Pd-catalyzed cross-dehydrogenative coupling of pyridine *N*-oxides **180** with indoles **210** under pyridine-free conditions

Finally, Zhang, Li and coworkers demonstrated that the coupled pyridine *N*-oxide products **211** could be easily deoxygenated by treatment with PCl_3 in toluene at room

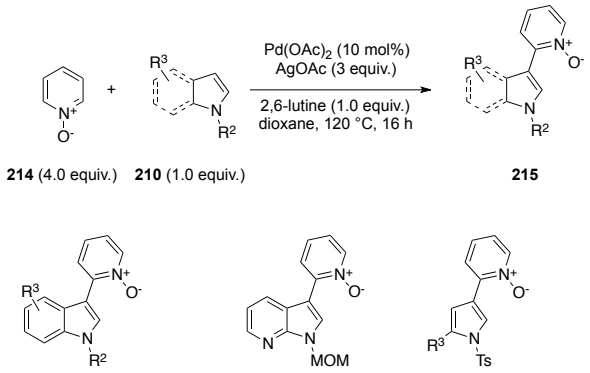
temperature to give the corresponding 2-heteroarylpyridines **209**. For example, the reaction of compound **211c** with 1.2 equiv of PCl_3 at room temperature for 0.5 h gave cleanly 2-heteroarylpyridine **209a** in 85% yield (Scheme 107).[134]



211c **209a**

Scheme 107. Deoxygenation of compound **211c**

Again in 2011, Yamaguchi and coworkers developed a Pd-catalyzed oxidative C-H/C-H coupling of indoles/pyrroles with azine *N*-oxides and found that treatment of 1.0 equiv of indole/pyrroles **210** with 4.0 equiv of azine *N*-oxides, 10 mol% $Pd(OAc)_2$, 3.0 equiv of AgOAc and 1.0 equiv of 2,6-lutidine in dioxane at 120 °C for 16 h selectively produced in moderate to good yields compounds **215** resulting from oxidative coupling at the C-2 position of the azine *N*-oxides (Scheme 108).[137] Interestingly, the reactions tolerated functional groups such as NO_2, OMe, CN and COOMe in the indole ring. Similar reaction conditions were then used to synthesize 1-[1-(methoxymethyl)-1*H*-indol-3-yl]isoquinoline-2-oxide (**216**) in 57% yield from isoquinoline *N*-oxide (**191**) and 1-(methoxymethyl)-1*H*-indole (**210a**) (Scheme 109).[137]



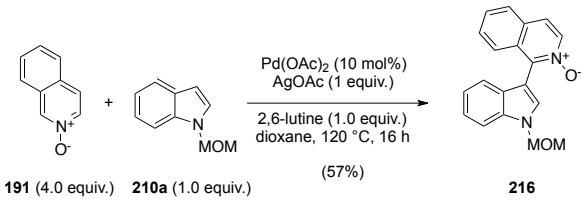
214 (4.0 equiv.) **210** (1.0 equiv.) **215**

215a: R^2= MOM; R^3 = H (73%)
215b: R^2= Ts; R^3 = H (67%)
215c: R^2= Ts; R^3 = 5-CN (52%)
215d: R^2= Ts; R^3 = 6-OMe (38%)
215e: R^2= MOM; R^3 = 5-NO_2 (56%)
215f: R^2= MOM; R^3 = 6-NO_2 (49%)
215g: R^2= MOM; R^3 = 6-COOME (55%)

215h: 46%

215i: R^3 = H (73%)
215j: R^3 = Ac (73%)

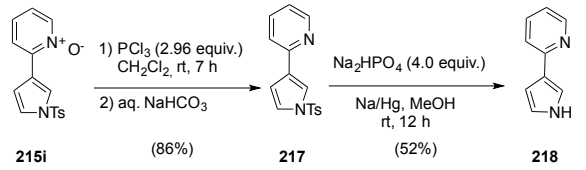
Scheme 108. Pd-catalyzed oxidative C-H/C-H coupling of pyridine *N*-oxide (**214**) with indoles/pyrroles **210**



191 (4.0 equiv.) **210a** (1.0 equiv.) **216**

Scheme 109. Regioselective synthesis of compound **216**

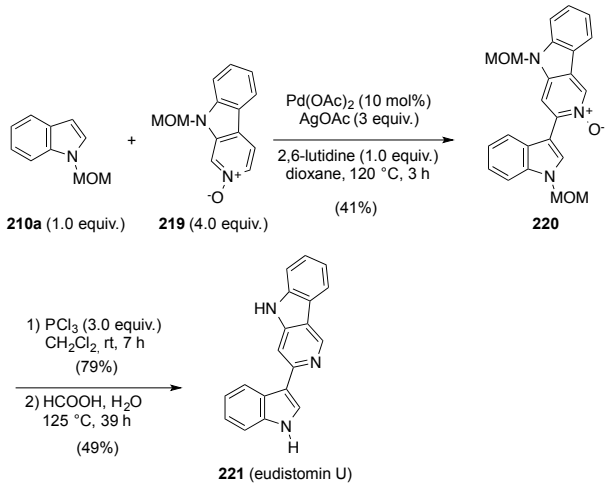
It was also found that compounds **215** were readily deoxygenated by treatment with PCl_3. For instance, the reaction of compound **215i** with 2.96 equiv of PCl_3 in CH_2Cl_2 for 7 h followed by quenching with aqueous $NaHCO_3$ gave 2-(1-tosyl-1*H*-pyrrol-3-yl)pyridine **217** in 86% yield (Scheme 110).[137] The latter compound could then be *N*-deprotected by treatment with Na_2HPO_4 and a small amount of Na/Hg in methanol at room temperature for 12 h to give 2-(1*H*-pyrrol-3-yl)pyridine (**218**) in 52% yield (Scheme 110).[137]



215i **217** **218**

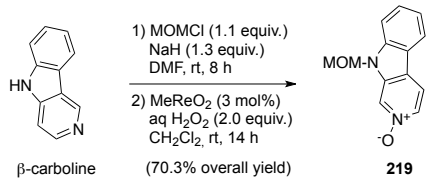
Scheme 110. Deoxygenation of compound **215i** and *N*-deprotection of the resulting compound **217**

Yamaguchi, Itami and coworkers then applied their protocol for the oxidative C-H/C-H coupling of indoles/pyrroles with azine *N*-oxides to the regioselective synthesis of eudistomin U (**221**), an alkaloid isolated from the Caribbean ascidian *Lissoclinum fragile,*[138] which possesses DNA binding activity[139a] and potent antibacterial activity against Gram-positive bacteria.[139b] As shown in Scheme 211, the Pd-catalyzed oxidative coupling of compound **210a** with 9-(methoxymethyl)-9*H*-pyrido[3,4-*b*]indole-2-oxide (**219**) provided compound **220** in 41% yield. Reduction of this *N*-oxide with PCl_3[140] followed by deprotection of MOM groups of the resulting compound with formic acid in water then completed the synthesis of the natural product.[137]



Scheme 111. Regioselective synthesis of eudistomin U (**221**)

Compound **219**, which was used as a starting material, was synthesized in 70.3 % yield by treatment of β-carboline with 1.1 equiv of MOM-Cl and 1.3 equiv of NaH in DMF at room temperature for 8 h followed by the reaction of the resulting *N*-MOM protected compound with 3 mol% $MeReO_2$ and 2.0 equiv of aq. H_2O_2 in CH_2Cl_2 at room temperature for 14 h (Scheme 112).[137]



Scheme 112. Synthesis of compound **219** from β-carboline

In 2013, Kuang and coworkers directed their attention to the synthesis of 2-pyridinyl-1,2,3-triazoles of general formula **222** (Figure 16),[141a] a class of substances that includes inhibitors of the transforming factor β1 type receptor.[142]

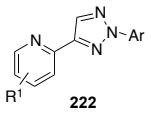
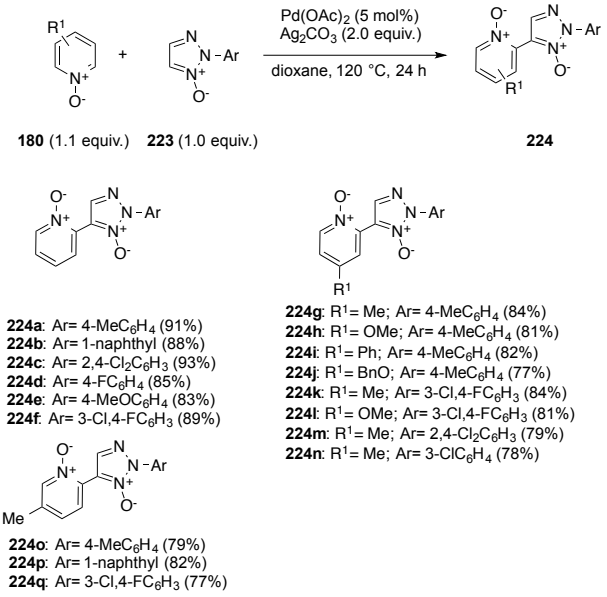


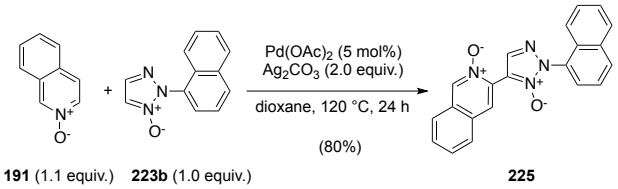
Figure 16. Chemical structure of compounds **222**

The approach followed for the synthesis of these compounds involved the first example of a highly efficient Pd-catalyzed oxidative C-H/C-H coupling of pyridine *N*-oxides **180** with 2-aryl-1,2,3-triazole *N*-oxides **223** and the subsequent reduction of the resulting 2-(1-oxido-2-aryl-2*H*-1,2,3-triazol-5-yl)pyridine 1-oxides **224**.[141a] Compounds **223** were available using a reported three-step procedure in which arylhydrazines were the starting materials.[141b] The oxidative cross-couplings (Scheme 113) were carried out by the reaction of 1.0 equiv of compounds **223** with 1.1 equiv of pyridine *N*-oxides **180**, 5 mol% $Pd(OAc)_2$ and 2.0 equiv of Ag_2CO_3 in dioxane at 120 °C for 24 h which provided compounds **224** in yields ranging from 77 to 93%.



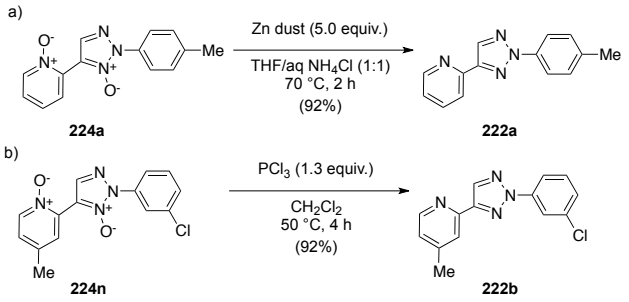
Scheme 113. Oxidative coupling of pyridine *N*-oxides **180** with 2-aryl-1,2,3-triazole *N*-oxides **223**

It was also established that the reaction conditions used for the synthesis of compounds **224** were suitable for the oxidative coupling of isoquinoline *N*-oxide (**191**) with 2-(1-naphthyl)-1,2,3-triazole *N*-oxide (**223b**), which only occurred at the C-3 position of **191** providing compound **225** in 80% yield (Scheme 114).[141a]



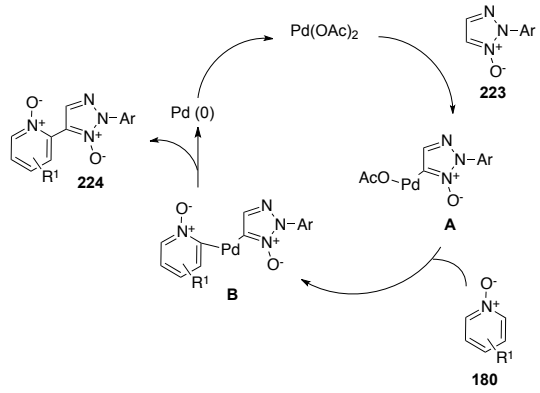
Scheme 114. Regioselective synthesis of compound **225**

Kuang and coworkers then demonstrated that compounds **224** could be easily and efficiently converted to the corresponding 2-(2-aryl-2*H*-1,2,3-triazol-4-yl)pyridines **222**. In fact, they prepared 2-(2-*p*-tolyl-2*H*-1,2,3-triazol-4-yl)pyridine (**222a**) in 92% yield by the reaction of 1.0 equiv of **224a** with 5.0 equiv of Zn dust in a 1 : 1 mixture of THF and aqueous NH_4Cl at 70 °C for 2 h (Scheme 115, eq. a). Moreover, they obtained 2-[2-(3-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]-4-methylpyridine (**222b**) in 94% yield by treatment of 1.0 equiv of compound **224n** with 1.2 equiv of PCl_3 in CH_2Cl_2 at 50 °C for 4 h (Scheme 115, eq. b).[141a]



Scheme 115. Deoxygenation reactions of compounds **224a** and **224n**

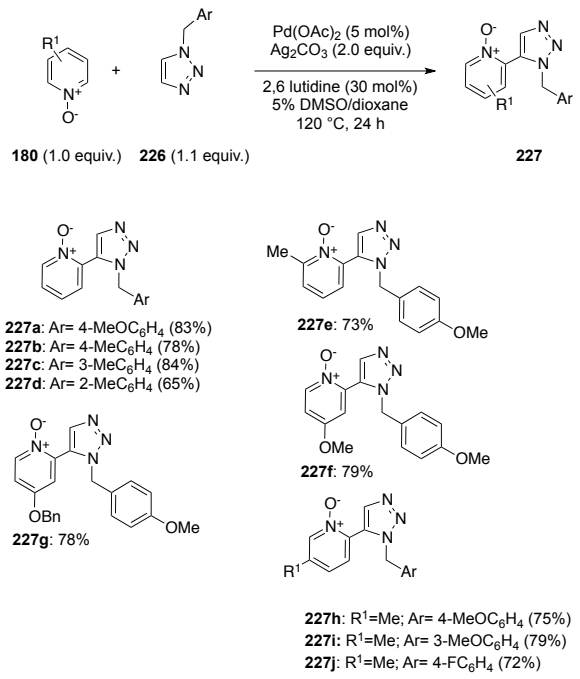
A plausible catalytic cycle for the Pd-catalyzed oxidative coupling between compounds **180** and **223** was also proposed (Scheme 116).[141a]



Scheme 116. Plausible catalytic cycle for the oxidative cross-coupling between compounds **223** and **180**

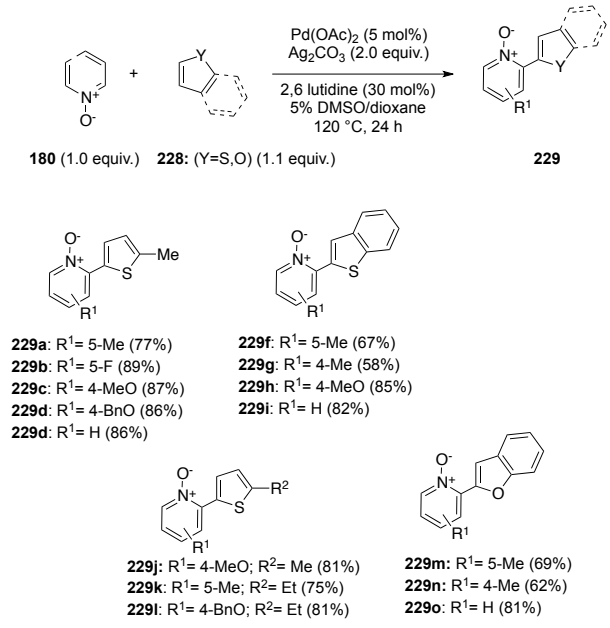
In the first step of the cycle, compounds **223** would undergo regioselective electrophilic C-H substitution of $Pd(OAc)_2$ to give intermediates **A**. In the second step, bisheteroarylpalladium species **B** would be formed by C-H substitution of intermediates **A** with **180**. Intermediates **B** would then undergo reductive elimination to give the required cross-coupling products **224** together with Pd(0). Finally, oxidation of Pd(0) with Ag_2CO_3 would complete the catalytic cycle.[141a]

In 2014, an efficient protocol for the Pd-catalyzed oxidative C-H/C-H cross-coupling of pyridine *N*-oxides **180** with five membered heteroarenes such as 1-benzyl-1,2,3-triazoles **226**, thiophenes and furans of general formula **228** was designed and developed by Kuang and coworkers.[143] The general procedure for the regioselective coupling of pyridine *N*-oxides **180** with 1-benzyl-1,2,3-triazoles **226** involved treatment of 1.0 equiv of **180** with 1.1 equiv of **226**, 5 mol% $Pd(OAc)_2$, 2.0 equiv of Ag_2CO_3 and 30 mol% 2,6-lutidine in a mixture of DMSO and dioxane at 120 °C for 16 h providing 2-(1-benzyl-1*H*-1,2,3-triazol-5-yl)pyridine 1-oxides **227** in yields ranging from 65 to 84% (Scheme 117).



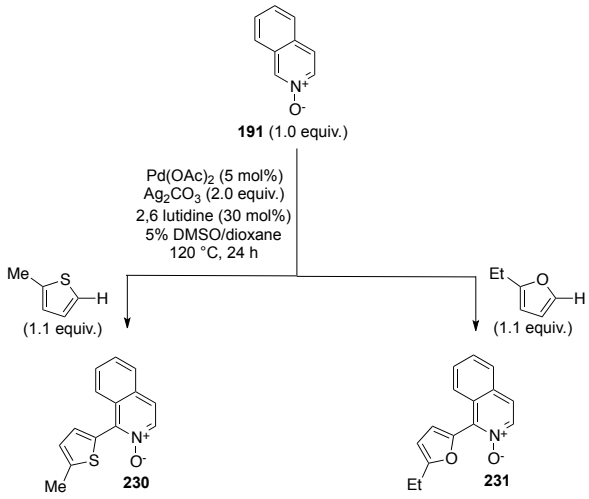
Scheme 117. Pd-catalyzed oxidative coupling of pyridine *N*-oxides **180** with triazoles **226**

Similar reaction conditions were then employed for the high yielding, regioselective synthesis of 2-heteroarylpyridine *N*-oxides **229** from pyridine *N*-oxides **180** and five-membered heteroarenes **228** (Scheme 118).[143]



Scheme 118. Pd-catalyzed regioselective oxidative coupling of pyridine *N*-oxides **180** with five-membered heteroarenes **228**

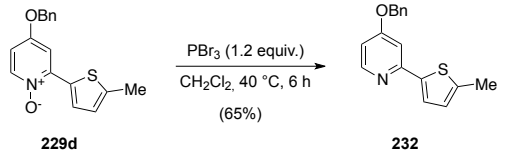
Interestingly, the procedure developed for the synthesis of compounds **227** and **229** also allowed to prepare 1-(5-methylthiophen-2-yl)isoquinoline-2-oxide (**230**) and 1-(5-ethylfuran-2-yl)isoquinoline-2-oxide (**231**) in high yields by oxidative coupling of isoquinoline *N*-oxide (**191**) with 2-methylthiophene and 2-ethylfuran, respectively (Scheme 119).



Scheme 119. Synthesis of 1-heteroarylisoquinoline-2-oxides **230** and **231**

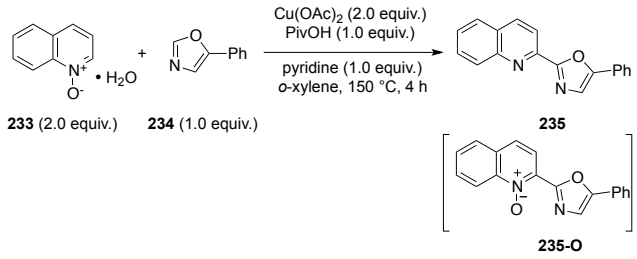
In contrast to what observed in the Pd-catalyzed oxidative coupling of **191** with 2-(1-naphthyl)-1,2,3-triazole *N*-oxide (**223b**) which occurred at the C-3 position of **191**,[141] in this case the cross-coupling reactions were found to occur selectively at the C-1 position of **191**.[143]

Kuang and coworkers also investigated the removal of the N-O group from the oxidative cross-coupling products and found that the reaction of compound **229d** with 1.2 equiv of PBr_3 in CH_2Cl_2 at 40 °C for 6 h gave 5-(5-methylthiophen-2-yl)-2-*p*-tolyl-2*H*-1,2,3-triazole (**232**) in 65% yield (Scheme 120).[143]



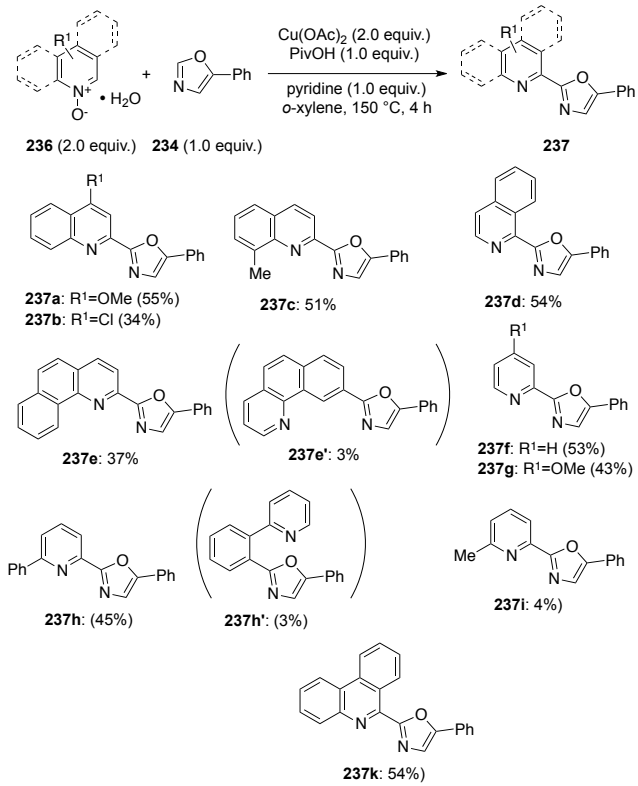
Scheme 120. Deoxygenation of compound **229d**

More recently, Hirano, Miura and coworkers developed a Cu-mediated formally dehydrative coupling of azine *N*-oxides with oxazoles and observed that the C–C bond process was accompanied by the removal of the oxygen atom from the azine core.[144] Interestingly, the developed protocol did not require the use of Pd, which is the noble transition metal of catalyst systems used in several related dehydrogenative couplings with azine *N*-oxides.[145] At the outset of the study Hirano, Miura and coworkers investigated the reaction of 2.0 equiv of quinoline *N*-oxide monohydrate (**233**) with 1.0 equiv of commercially available 5-phenyloxazole (**234**) in *o*-xylene at 150 °C in the presence of 2.0 equiv of $Cu(OAc)_2$, 1.0 equiv of pivalic acid and 1.0 equiv of pyridine and found that, surprisingly, the reaction product was 5-phenyl-2-(quinolin-2-yl)oxazole (**235**) instead of the *N*-oxide **235–O** (Scheme 121).[144]



Scheme 121. Cu-mediated formally dehydrative coupling of quinoline *N*-oxide monohydrate (**233**) with 5-phenyloxazole (**234**)

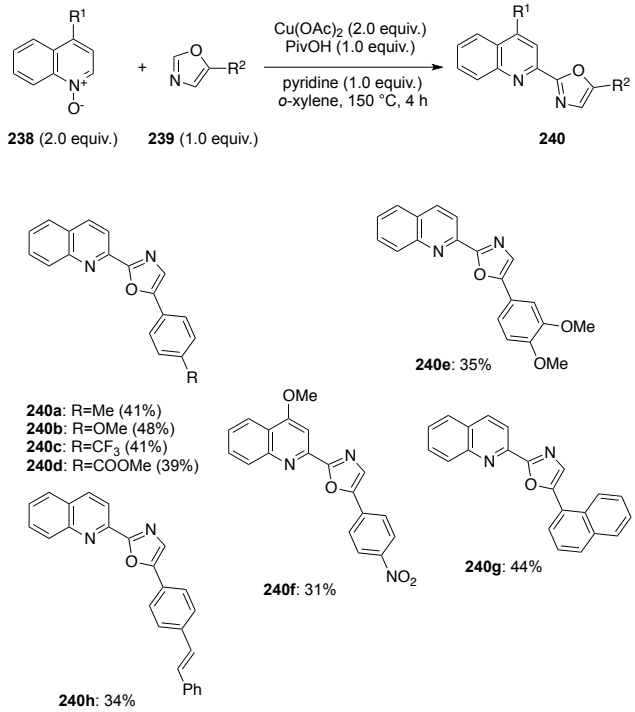
In an optimization study it was then found that $Cu(OAc)_2$ was preferable to other Cu(I) and Cu(II) salts and that the use of pivalic acid and pyridine was necessary.



Scheme 122. Cu-mediated formally dehydrative coupling of azine *N*-oxides **236** with 5-phenyloxazole (**234**)

The optimized reaction conditions illustrated in Scheme 122 were employed for the formally dehydrative coupling of 5-phenyloxazole (**234**) with various azine *N*-oxides **236**, which included pyridine *N*-oxides and benzo[*h*]quinoline *N*-oxide. The cross-coupling products **237** were generally obtained in moderate yields also when fused azine *N*-oxides were used as coupling partners. For example, phenanthridine *N*-oxide coupled with **234** to give compound **237k** in 54% yield. Moreover, benzo[*h*]quinoline *N*-oxide coupled with **234** to furnish **237e** in 37% yield, but in this case the C-10 arylated product **237e'** was also obtained in 3% GLC yield.

It was also established that the Cu-based conditions were suitable for the formally dehydrative coupling of quinoline *N*-oxides **238** with oxazoles **239** bearing diverse substituents at C-5 position.[144] The reaction provided regioselectively the cross-coupling products **240** in yields ranging from 31 to 48% (Scheme 123).[144]



Scheme 123. Cu-mediated formally dehydrative coupling of quinoline *N*-oxides **238** with 5-susbstituted oxazoles **239**

Other 1,3-azoles were tested in these Cu-mediated couplings, but thiazole, benzothiazole and oxadiazoles produced the desired products in less than 5% yield, However, the Cu-mediated reaction of 1-methyl-1*H*-benzimidazole with 4-methoxyquinoline *N*-oxide gave 4-methoxy-2-(1-methyl-1*H*-benzo[*d*]imidazole-2-yl)quinoline (**241**) (Figure 17) in 28% yield.

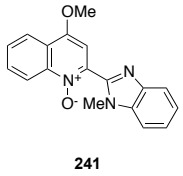
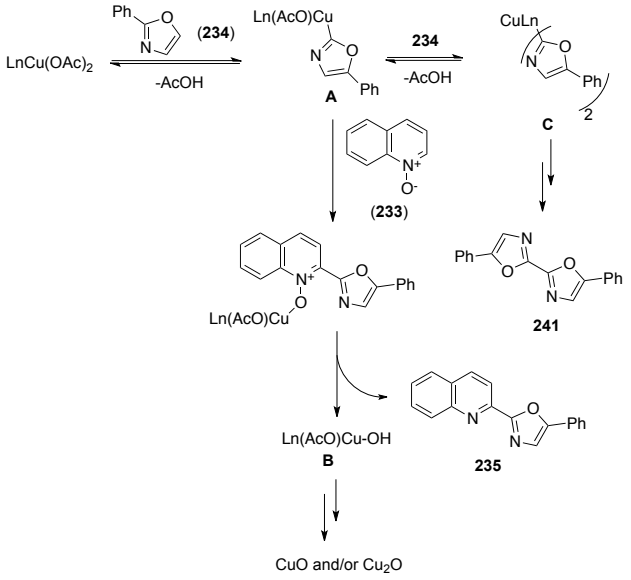


Figure 17. Chemical strcture of compound **241**

It was also established that the competitive homocoupling of 5-substituted oxazoles was the major reason for the modest yields of the cross-coupling products **237** and **240**.[146]

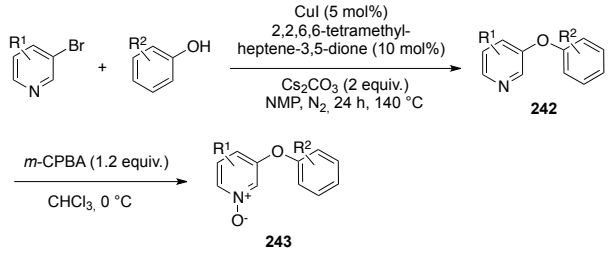
Hirano, Miura and coworkers did not elucidate the detailed mechanism of the Cu-mediated reaction of quinoline *N*-oxide hydrate (**233**) with 5-phenyloxazole (**234**). Nevertheless, they proposed the mechanism shown in Scheme 124 in which the first step would be the acetate ligand assisted C-H cupration of **234** that generated the oxazolylcopper intermediate **A**.



Scheme 124. Plausible mechanism for the Cu-mediated formally dehydrative coupling of quinoline *N*-oxide hydrate (**233**) with 5-phenyloxazole (**234**)

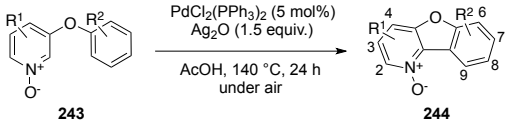
Subsequent nucleophilic addition to quinoline *N*-oxide (**233**) followed by deoxygenative elimination with concomitant rearomatization of the quinoline ring would furnish the required cross-coupling product **235** and the hydroxylcopper species **B**. The latter could be finally converted to insoluble copper oxide CuO or Cu_2O. In this way, the necessary use of a stoichiometric amount of $Cu(OAc)_2$ would be justified. On the other hand, the reaction of intermediate **A** with **234** would provide the bis(oxazolyl)copper species **C**, which would be the precursor to the homocoupling byproduct **241**.[144]

Again in 2015, Min Wang, Lei Wang and coworkers developed a novel, efficient and regioselective synthesis of benzofuro[2,3-*b*]pyridine *N*-oxides **244** involving the Pd-catalyzed oxidative cyclization of 3-aryloxypyridine-1-oxides **243**.[147] Compounds **243** were in turn synthesized according to the literature[148] by oxidation of the corresponding 3-aryloxypyridines **242**, which were prepared by an Ullmann C-O coupling reaction[149] (Scheme 125).



Scheme 125. Synthesis of 3-aryloxypyridine-1-oxides **243**

The optimized reaction conditions for the dehydrogenative cyclization of compounds **243** involved treatment of these substrates with 5 mol% $PdCl_2(PPh_3)_2$ and 1.5 equiv of Ag_2O in acetic acid at 140 °C for 24 h under air to give compounds **244** in good to excellent yields with excellent functional group tolerance (Scheme 126).[147]



244	R^1	R^2	Yield %
a	H	H	65
b	H	8-Me	74
c	H	8-Et	77
d	H	8-*i*-Pr	69
e	H	8-*t*-Bu	70
f	H	8-Ph	59
g	H	8-OMe	53
h	H	6-Me	66
i	H	6-Ph	63
j	H	7-Me	57
k	H	7-OMe	55
l	H	6,7-Me_2	52
m	H	7,8-Me_2	59
n	H	7,9-Me_2	59
o	H	6-*t*-Bu	73

244	R^1	R^2	Yield %
p	H	8-Ac	53
q	H	8-PhCO	59
r	H	8-COOEt	56
s	H	8-NO_2	44
t	H	8-NHCOPh	55
u	H	8-Cl	53
v	H	8-F	59
w	H	6-Cl	54
x	H	7-Me,8-Cl	49
y	4-Me	8-Me	57
z	3-Me	8-Me	58
aa	3-Ph	8-Ph	63
ab	3-Cl	8-NO_2	52

Scheme 126. Pd-catalyzed oxidative cyclization of compounds **243**

Compounds **244** are known to include non-selective endothelin ET_A/ET_B as well as selective ET_B receptor anatagonists,[150] inhibitors of topoisomerase II,[151] and derivatives that inhibit the tumor growth and metastasis.[152] Remarkably, 3-(2-chlorophenoxy)pyridine-pyridine-1-oxide and 3-(4-chloro-3-methylphenoxy)-1-oxide underwent C-H/C-H cyclization reaction rather than C-H/C-Cl coupling reaction providing compounds **244w** and **244x** (Figure 18) in 54 and 49% yield, respectively.

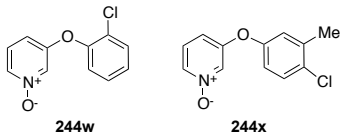
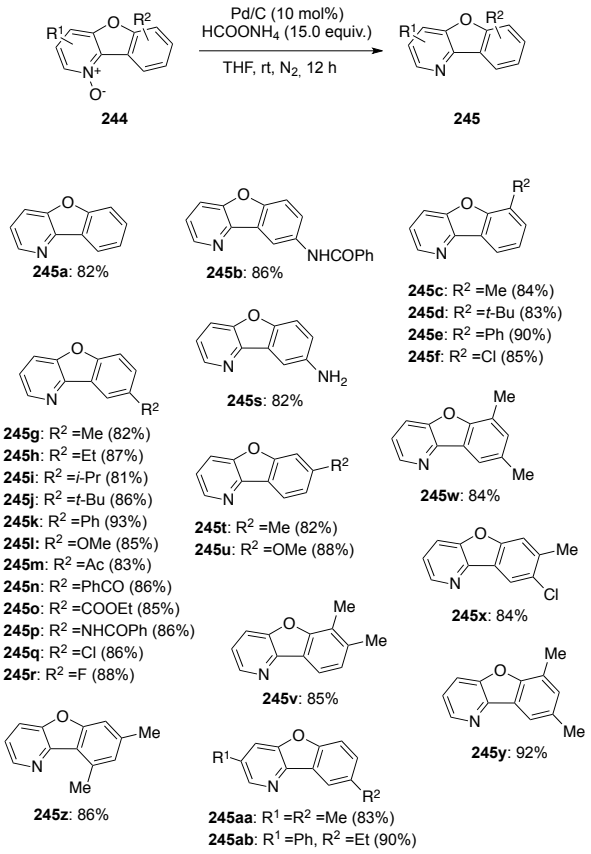


Figure 18. Chemical structures of compounds **244w** and **244x**

Compounds **244** were then deoxygenated by reduction with ammonium formate in the presence of Pd/C, generating benzo[4.5]furo[3,2-*b*]pyridines **245** in good to excellent yields (Scheme 127).[147]



Scheme 127. Deoxygenation of compounds **244**

However, the Pd-catalyzed deoxygenation of 8-nitro-[4,5]furo[3,2-*b*]pyridine-1-oxide (**244s**) also caused reduction of the nitro group of this compound providing benzo[4,5]furo[3.2-*b*]pyridine-8-amine (**245s**) in 89% yield.

Finally, to gain insight into the mechanism of the Pd-catalyzed oxidative cyclization of benzofuro[3,2-*b*]pyridine-1-oxides, an H/D exchange experiment involving 3-phenoxypyridine-1-oxide (**243a**) and its

deuterated analogue [D5]-**243a** (Figure 19) was carried out.

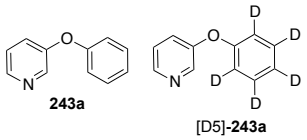
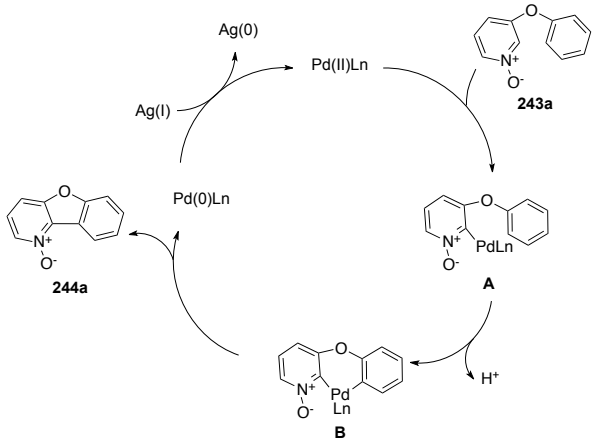


Figure 19. Chemical structures of compounds **243a** and [D5]-**243a**

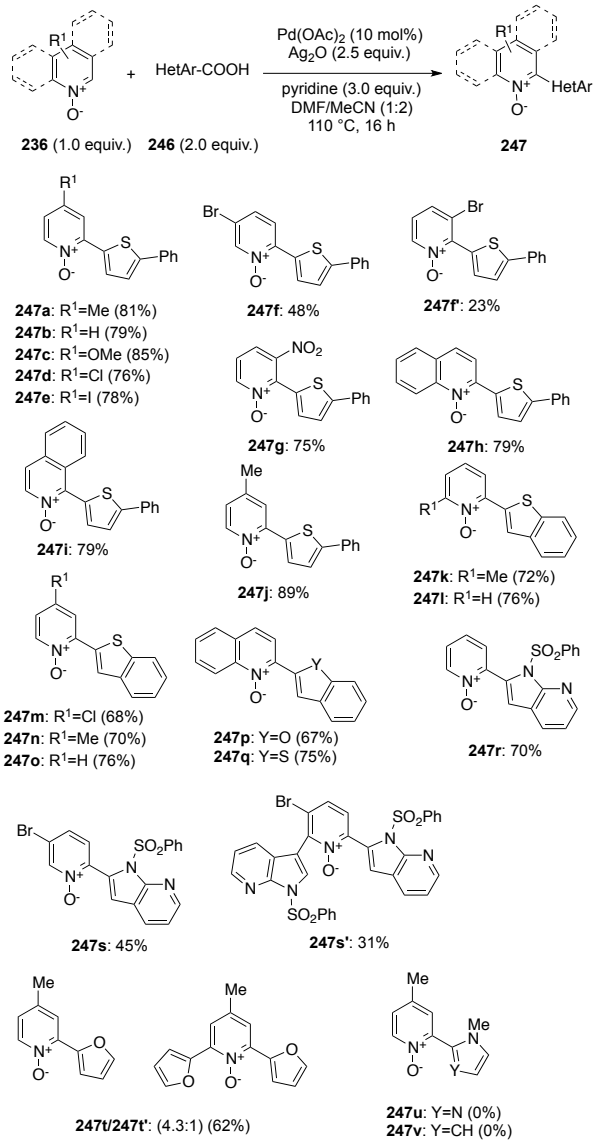
On the basis of the result of this experiment, which indicated that the C-H bond cleavage of the arene moiety is not the rate-determining step of the cyclization reaction as well as of literature data,[141,153] Ming Wang, Lei Wang and coworkers proposed the reaction mechanism depicted in Scheme 128.



Scheme 128. Plausible mechanism for the Pd-catalyzed oxidative cyclization of benzofuro[3,2-*b*]pyridine-1-oxide (**243a**)

The catalytic cycle in this mechanism would begin with the reaction of **243a** with the Pd(II) catalyst to afford the *ortho*-palladated species **A**. This intermediate would undergo intramolecular cyclization to form the bis-arylpalladium species **B** via another C-H bond activation. Finally, reductive elimination would give the cross-coupling product **244a** and Pd(0), which would be oxidized by Ag(I) regenerating the Pd(II) species.[147]

Recently, important advances in the synthesis of 2-(hetero)aryl-substituted pyridine-1-oxides, -quinoline-1-oxides and -isoquinoline-1-oxides have also been achieved by the research group of Muthusubramanian.[154–156] Their studies showed that these compounds could be efficiently and regioselectively synthesized through processes involving Pd-catalyzed decarboxylative couplings with heteroaryl carboxylic acids.[154–156] Thus, in May 2014, this group reported that the reaction of 1.0 equiv of azine *N*-oxides **236** with 2.0 equiv of heteroaryl carboxylic acids **246**, 10 mol% $Pd(OAc)_2$, 3.0 equiv of pyridine and 2.5 equiv of Ag_2O in a 1 : 2 mixture of DMF and MeCN at 110 °C for 16 h produced heterobiaryl *N*-oxides **247** in good yields with excellent regioselectivity with respect to both carboxylic acids and azine *N*-oxides (Scheme 129).[154] In particular, compounds **247** were found to derive from *ortho*-heteroarylation of azine *N*-oxides **236** and *ipso*-substitution of carboxylic acids **246**.

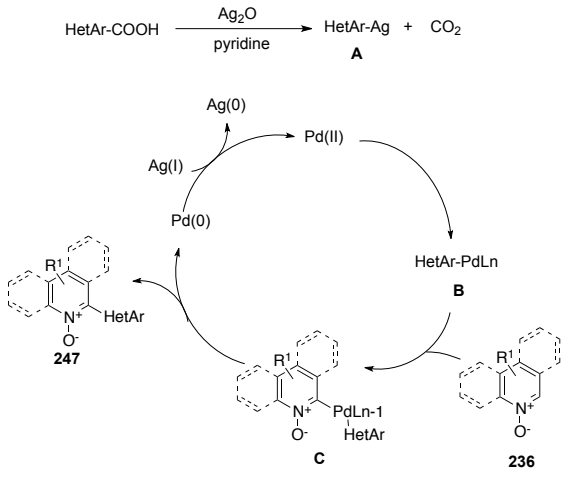


Scheme 129. Pd-catalyzed coupling of azine *N*-oxides **236** with heteroaryl carboxylic acids **246**

It was found that a wide range of functional groups including Cl and Br groups was compatible with the reaction conditions and that also benzofused pyridine *N*-oxides gave the corresponding coupling products. However, the *ortho*-arylation of compounds **236** with heteroarylcarboxylic acids **246** showed some limitations. In fact, the Pd-catalyzed reaction of 3-bromopyridine *N*-

oxide with 5-phenylthiophene-2-carboxylic acid furnished two regioisomers, **247f** and **247f'**, in a 2 : 1 ratio respectively, and the decarboxylative arylation of 3-bromopyridine *N*-oxide with 1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid led to compound **247s** along with the bis-coupled product **247s'** in a 3 : 2 ratio, respectively (Scheme 129). However, the decarboxylative arylation of 4-methylpyridine *N*-oxide with furan-2-carboxylic acid yielded an inseparable mixture of compounds **247t** and **247t'**. In addition, 4-methylpyridine *N*-oxide failed to undergo decarboxylative *ortho*-arylation with 1-methylimidazole 2-carboxylic acid and 1-methylpyrrole-2-carboxylic acid.

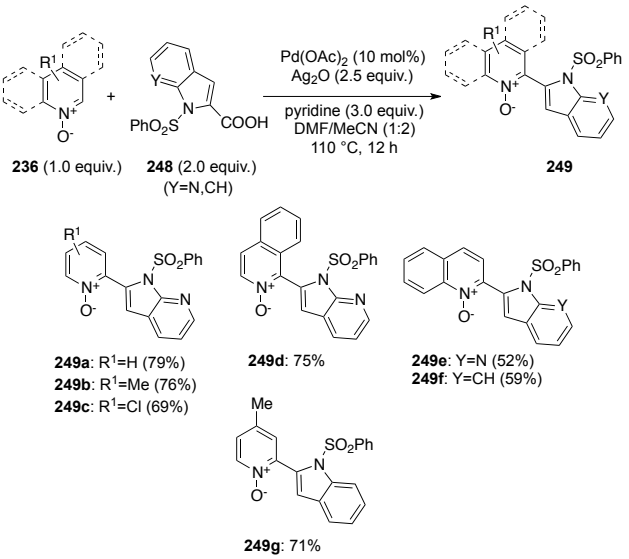
Muthusubramanian and coworkers also formulated a plausible mechanism for the decarboxylative couplings reported in Scheme 129. In this mechanism (Scheme 130), heteroaryl carboxylic acids **246** would undergo Ag-promoted decarboxylation to give intermediates **A**, which by transmetalation with Pd(II) would lead to intermediates **B**. The subsequent reaction of **B** with azine *N*-oxides **236** would produce intermediates **C**, which by reductive elimination would give the *ipso*-heteroarene *N*-oxides **247** with regeneration of the Pd catalyst.[154,157]



Scheme 130. Plausible mechanism for the Pd-catalyzed decarboxylative heteroarylation of *N*-oxides **236** with heteroaryl carboxylic acids **246**

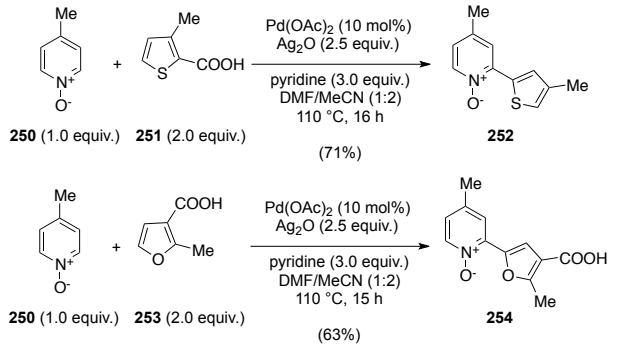
Unfortunately, Muthusubramanian did not examine the deoxygenation of 2-heteroaryl-substituted azine *N*-oxides. Nevertheless, it should be noted that this reaction might be carried out using one of the methods reported in the literature for the deoxygenation of pyridine *N*-oxides,[158] quinoline *N*-oxides,[113] and isoquinoline *N*-oxides.[159]

On September 2014, Muthusubramanian and coworkers carried out the synthesis of 2-heteroaryl-substituted azine *N*-oxides **249** via regioselective cross-dehydrogenative coupling of (aza)indole-2-carboxylic acids **248** with azine *N*-oxides **236** followed by protodecarboxylation.[155] These regioselective couplings, which were found to occur at the *ortho*-position rather than at the *ipso*-position of carboxylic acids **248**, were carried out by treatment of 1.0 equiv of **236** with 2.0 equiv of **248**, 10 mol% $Pd(OAc)_2$, 2.5 equiv of Ag_2O and 3.0 equiv of pyridine in a 1 : 2 mixture of DMF and MeCN at 110 °C for 12 h providing compounds **249** in good yields (Scheme 131).[155]



Scheme 131. Pd-catalyzed cross-dehydrogenative coupling of azine *N*-oxides **236** with (aza)indole-2-carboxylic acids **248**

Interestingly, *ortho*-arylation reactions also occurred by the reaction of azine *N*-oxides with 2-thienyl and 2-furyl carboxylic acids.

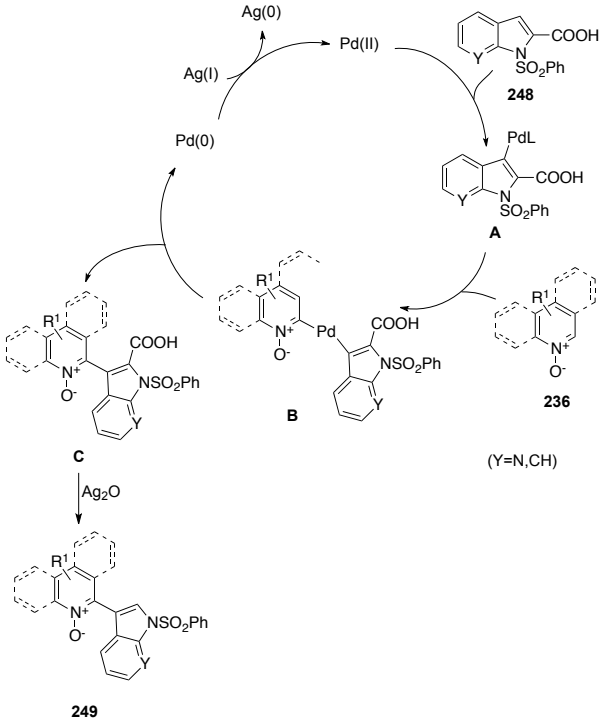


Scheme 132. Regioselective synthesis of compounds **252** and **254**

In fact, the dehydrogenative cross-couplings of 4-methylpyridine *N*-oxide (**250**) with 3-methylthiophene-2-carboxylic acid (**251**) and 2-methylfuran-3-carboxylic acid (**253**) under the optimized conditions developed to prepare compounds **249** led to compounds **252** and **254**, respectively, in 71 and 63% yield (Scheme 132).[155] Interestingly, the reaction of **250** with **251** involved a

cross-dehydrogenative protodecarboxylation process leading to compound **252**. However, the reaction of **250** with **253** after a reduced time (5 h) led to carboxylic acid **254**, indicating that decarboxylation takes place at the late stage.

Muthusubramanian and coworkers also proposed a mechanism for the formation of compounds **249** from Pd(II) and carboxylic acids **248**.[152] It involved the reaction of Pd(II) with carboxylic acids **248** leading to intermediates **A** (Scheme 133).



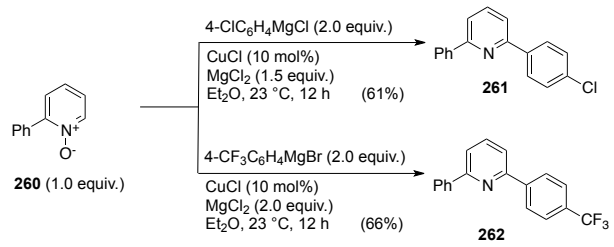
Scheme 133. Proposed mechanism for the formation of compounds **249**

A subsequent transmetalation reaction involving **A** and azine *N*-oxides **236** would give intermediates **B**, which would undergo reductive elimination providing compounds **C**. Finally, Ag-mediated decarboxylation of **C** would give the required compounds **249**.[155]

Unfortunately, also in this case, Muthusubramanian and coworkers did not perform the deoxygenation reaction of compounds **249**.

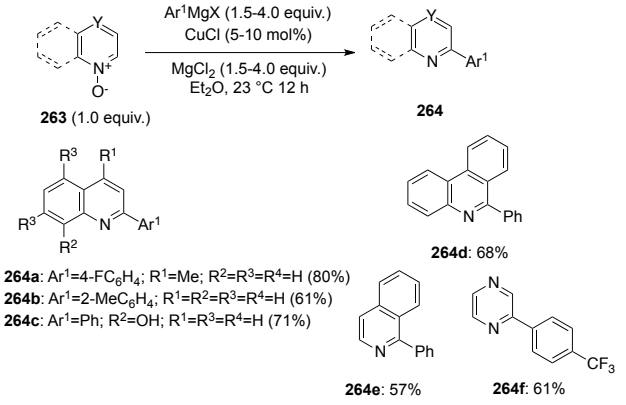
In the last years, attention has also been paid to the regioselective synthesis of 2-(hetero)aryl-substituted azines via transition metal-catalyzed direct arylation reactions of azine *N*-oxides with (hetero)aryl Grignard reagents. In fact, 2-arylpyridines are important structural motifs of fluorescent probes,[160] metal-complexing ligands[161] and pharmaceuticals,[162] and 2-heteroarylquinolines include compounds possessing activity against endemic parasites such as *Leishmania chagasi* and *Trypanosoma cruzi*.[163]

In 2014, Larionov and coworkers described a direct one-step method for the regioselective conversion of six-membered *N*-heteroarene *N*-oxides including pyridine-, quinoline-, phenanthridine-, isoquinoline- and pyrazine *N*-oxides to the corresponding 2-aryl-substituted *N*-heteroarenes, which consisted of the CuCl-catalyzed reaction of the heteroarene *N*-oxides with aryl Grignard reagents in the presence of $MgCl_2$ as an additive that was found to improve the chemoselectivity of the reaction.[164] The new method made possible the synthesis of 2-(4-chlorophenyl)-6-phenylpyridine (**261**) and 2-phenyl-6-[4-(trifluoromethyl)phenyl]pyridine (**262**) in good yields by treating 2-phenylpyridine-1-oxide (**260**) with the required aryl Grignard reagents (Scheme 134).



Scheme 134. Synthesis of 2-arylpyridines **261** and **262**

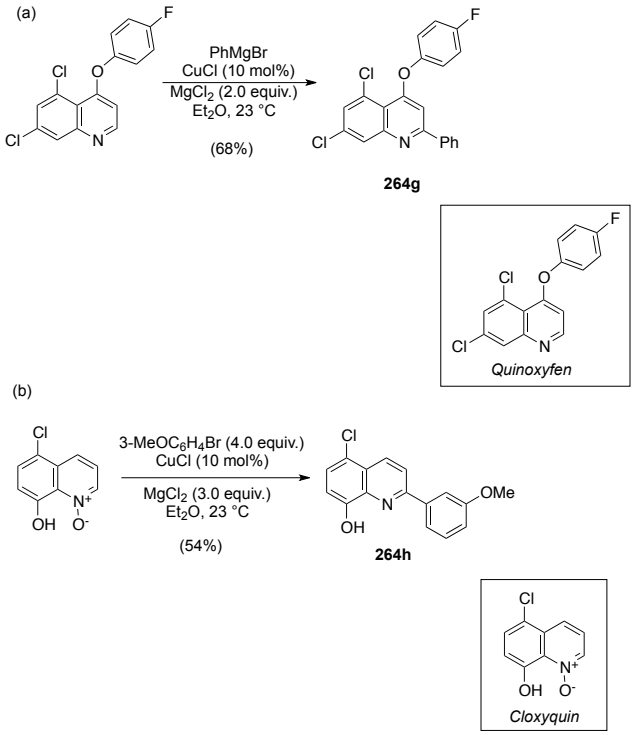
Good yields were also obtained in the chemo- and regioselective conversion of a variety of six-membered heteroarene *N*-oxides of general formula **263** to the corresponding 2-aryl-substituted *N*-heteroarenes **264** (Scheme 135).[164]



Scheme 135. Synthesis of the CuCl-catalyzed reaction between six-membered heteroarene *N*-oxides and aryl Grignard reagents

Larionov and coworkers also demonstrated the utility of these Cu-catalyzed reactions by the synthesis of 5,7-dichloro-4-(fluorophenyl)-2-phenylquinoline (**264g**) (Scheme 136, eq. a),[164] a new structural analogue of the

selective agrochemical fungicide quinoxyfen,[165] and of 5-chloro-2-(3-methoxyphenyl)quinolin-8-ol (**264h**) (Scheme 136, eq. b),[164] a structural analogue of cloxyquin, a compound with good antituberculosis activity[166] which is also an activator of the two-pore domain potassium channel TRESK.[167]



Scheme 136. Synthesis of compounds **264g** and **264h**

4. Conclusion and outlook

The growing demand for environmentally benign processes for the highly regioselective synthesis of (hetero)aryl-substituted heteroarenes, including structural motifs of biologically and pharmacologically active compounds, natural substances and their precursors, has stimulated scientists to develop a variety of protocols for the transition metal-catalyzed direct C-H (hetero)arylation of heteroarenes in which the regioselectivity is acquired by suitable strategies involving the use of removable protecting/blocking substituents or traceless directing groups that are installable or already present in the heteroarene substrates.

In the two previous sections of this review we have illustrated the state of the art in the field of these types of (hetero)arylation reactions of heteroarenes with one heteroatom. In fact, limitations of space led us to not review in this article the use of direct (hetero)arylation reactions of heteroarenes with two or more heteroatoms, although in the last decade these have been the subject of an impressive number of publications.[168]

The (hetero)arylation protocols reviewed here lack at various degrees of atom economy, but in many cases provide access with high or complete regioselectivity to regioisomers of (hetero)aryl-substituted heteroarenes that cannot be synthesized via direct (hetero)arylation reactions of heteroarenes devoid of protecting/blocking groups or traceless substituents. Thus, these protocols occupy a prominent position in organic synthesis.

However, the area of research reviewed in this article needs further intensive studies. In fact, the existing strategies still do not allow access to some classes of regioisomerically pure (hetero)aryl-substituted heteroarenes of significance for their biological/pharmacological properties such as 4-arylpyrimidines, which include potent and selective corticotropin-releasing factor$_1$ receptor antagonists,[169] 5-(hetero)arylpyrimidines, which include derivatives active *in vitro* against *Mycobacterium tuberculosis,*[170] antiviral[172] and anticancer properties,[173] 3-aryl- and 3,4-diarylisoquinolines, which include potent and selective anticancer agents with topoisomerase inhibitory activity,[174] 3-substituted 6-arylpyridazines, which include non-peptide irreversible inhibitors of interleukin-1β converting enzyme[175] and derivatives that are acyl-CoA:cholesterol acyltransferase inhibitors,[176] and 3-arylquinolines, which include derivatives with antiproliferative activity.[177]

We believe, however, that the current ongoing efforts may soon allow significant progress in the development of efficient strategies to access classes of regioisomerically pure biologically active (hetero)aryl-substituted heteroarenes that currently can be synthesized only through multi-step protocols involving stoichiometric amounts of organometallic reagents,[178] which often have a relatively high price and/or sensitivity to air and moisture.

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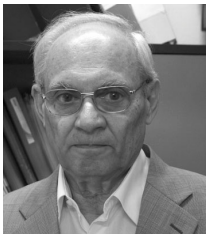

Renzo Rossi was born in Pisa (Italy) and graduated in Organic Chemistry with first-class honours at the University of Pisa defending a thesis performed under the guidance of Professor Piero Pino. In 1969 he became Assistant Professor and in 1971 he earned the *libera docenza* in Organic Chemistry. After holding other intermediate positions at the University of Pisa and the Scuola Normale Superiore of Pisa, in 1980 he became Full

Professor of Organic Chemistry at the University of Calabria. In 1982, he again joined the University of Pisa where he has held the Chair of Chemistry of Naturally Occurring Compounds. In 1999, the University of Pisa awarded him the *Ordine del Cherubino*. His current research interests include: i) new catalytic methods for the synthesis of oxygen-containing heterocycles; *ii)* the synthesis of compounds exhibiting significant cytotoxicity against human tumor cell lines and antivascular properties; *iii)* the study of new methodologies for palladium-catalyzed chemo- and regioselective carbon–carbon bond formation reactions that involve the use of organometallic reagents; *iv)* transition metal-catalyzed direct arylation reactions of substrates with activated sp^3-hybridized C–H bonds with aryl halides and pseudohalides; *v)* the design, development and applications of new, highly chemo- and regioselective methods for the transition metal-catalyzed direct *C*- and *N*-arylation reactions of electron-rich heteroaromatic systems, including free (NH)-azoles, with aryl halides and pseudohalides. In recent years, several successful studies have also been performed by his research group in the field of the synthesis and evaluation of the biological properties of pheromone components of insects which damage agricoltural crops, wood and paper, insecticidal carboxyamides, natural phototoxins, and naturally-occurring compounds of marine origin and their structural analogues which are characterized by the 2(5*H)*-furanone ring. Professor Rossi, who has coauthored over 230 research publications and a number of highly cited review articles and patents, is a fellow of the Royal Society of Chemistry and the American Chemical Society. He is a reviewer for several international journals dealing with synthetic organic chemistry and organometallics.

Marco Lessi was born in Livorno (Italy) in 1979. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in June 2004 defending a thesis performed under the guidance of Professor Dario Pini. In January 2005, he began his PhD fellowship in the laboratory of Professor Pini and received his PhD degree in 2008, submitting a thesis on the preparation and applications of new insoluble polymer-bound (IPB) enantioselective catalytic systems. The studies were focused on the synthesis of transition metal complexes obtained from bisoxazoline and BINOL ligands. In the period January 2008–March 2009, Dr. Lessi worked for Solvay Solexis S.p.A. on the development of new routes for the preparation of high-fluorinated low-molecular-weight molecules and oligomers. In March 2009, he re-joined the University of Pisa where he currently cooperates with Professor Bellina. The current research interests of Dr. Lessi involve the development of novel and efficient protocols for highly selective transition metal-catalyzed direct $C(sp^3)$-H and $C(sp^2)$-H arylation reactions, and the discovery of new synthetic routes and applications of functionalized ionic liquids obtained from naturally-occurring building blocks.

Chiara Manzini was born in Lucca (Italy) in 1986 and graduated in Chemistry with first-class honours at the University of Pisa in 2011. Currently she holds a position as PhD student at the Department of Chemistry and Industrial Chemistry of the University of Pisa under the guidance of Professor Fabio Bellina. She is currently working on the development and application of new protocols for the selective arylation of N-containing heteroaromatics.

Giulia Marianetti was born in Lucca (Italy) in 1988 and graduated in Organic Chemistry with first-class honours at the University of Pisa in 2013. She currently holds a PhD scholarship at the Scuola Normale Superiore of Pisa under the supervision of Prof. Fabio Bellina and Prof. Vincenzo Barone. She is currently working on the synthesis and the computational studies of new organic fluorophores.

Fabio Bellina was born in Catania (Italy) in 1964. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in 1990. In 1992, he joined the University of Pisa as an Organic Chemistry Researcher in the Department of Chemistry and Industrial Chemistry. In October 2003, he was appointed by the Faculty of Science of the University of Pisa as an Associate Professor of Organic Chemistry. In January 2016 he became Full Professor of Organic Chemistry at the same University. His research interests were initially mainly devoted to the total synthesis of naturally occurring compounds of biological and/or pharmacological interest and to the synthesis of structural analogues of naturally occurring fungicidal derivatives of agrochemical interest. More recently, Prof. Bellina focused his attention on new and efficient protocols for regioselective transition metal-mediated carbon-carbon and carbon-heteroatom bond forming reactions, with a particular interest in the selective functionalization of oxygen-containing unsaturated heterocycles such as 2(5*H*)-furanones and 2(2*H*)-pyranones. Currently, he is working on the development of novel and efficient protocols for the transition metal-catalyzed direct C–H and N–H bond arylation of heteroarenes, the direct functionalization of active C(sp^3)-H bonds, the alkynylation of (hetero)aromatic scaffolds, and on the application of these new procedures to the selective preparation of bioactive natural and synthetic compounds and to new organic chromophores.

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Tetrahedron