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Transition-Metal-Catalyzed Regiodivergent C-H Arylations of Aryl-Substituted Azoles

Linhao Liu,^[a] Manisha Durai,^[a] and Henri Doucet^{*,[a]}

[a] Mr L. Liu, Mrs M. Durai, Dr. H. Doucet
CNRS, ISCR-UMR 6226
Univ Rennes
F-35000 Rennes, France
E-mail: henri.doucet@univ-rennes1.fr

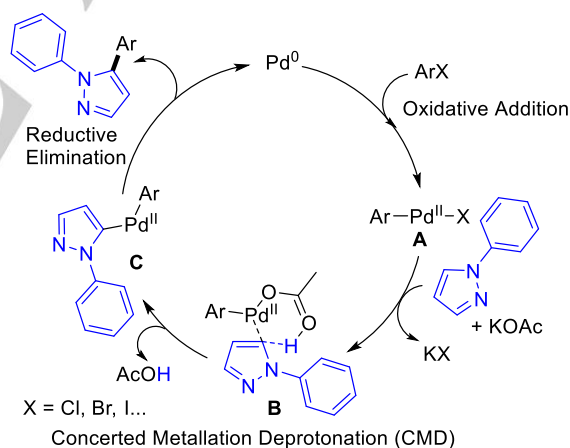
Abstract: The metal-catalyzed direct functionalization of two different C-H bonds of the same organic molecule - also called regiodivergent C-H bond functionalization - is an important research topic in organic chemistry. Over the last decades, the number of tools to control such regiodivergent C-H bond functionalizations has increased significantly. One of the most effective tools consists to employ different metal sources as the catalysts. Palladium and copper catalysts are very effective to promote the direct arylation of 5-membered ring heteroarenes; whereas the direct arylation using ruthenium and rhodium catalysts generally relies on the coordination of heteroelements to the metal. As a consequence, in the presence of several aryl-substituted azoles, the arylation of both the aryl unit using Ru- or Rh-catalysis and of the azole unit using Pd or Cu catalysts is possible. In this review, we will describe the scope and current limits of the use of this tool for the regiodivergent direct arylation of aryl-substituted azoles.

1. Introduction

One of the most straightforward method for the synthesis of arylated (hetero)aromatics is the metal-catalyzed functionalization of C-H bonds.^[1] Since the seminal reports by Nakamura, Tajima and Sakai in 1982 and by Ohta et al. in 1985 on the Pd-catalyzed arylation of heteroarenes, and by Oi, Inoue et al. in 2001 on the Ru-catalyzed directed arylation of 2-arylazoles, the metal-catalyzed so called "direct arylation" via the C-H bond functionalization of arenes and 5-membered heteroaromatics revealed to be one of the most powerful methods for the access to poly(hetero)aromatics.^[2,3]

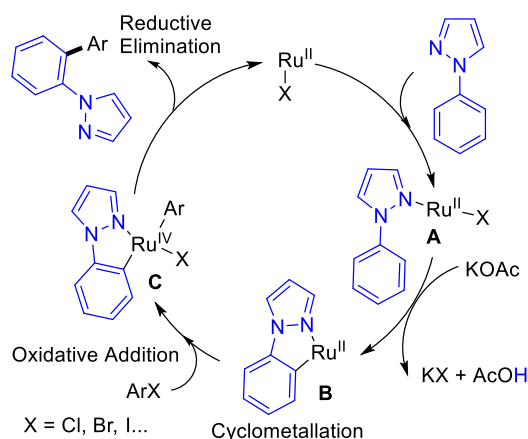
The major drawback of this methodology is that for many substrates, only one C-H bond can be functionalized reducing the synthetic efficiency of such reactions.^[1] However, since two decades, several sets of different reaction conditions have been discovered allowing to functionalize more than one C-H bond of some (hetero)arenes giving rise to different poly(hetero)aryls. Such so-called regiodivergent functionalizations, currently represent one of the most important research topic of the metal-catalyzed C-H bond functionalization. One of the most effective tools to control such regiodivergent functionalizations of aryl-substituted (hetero)arenes consists to employ different metal sources as the catalysts.

With palladium or copper catalysts, in general regioselective arylations on the 5-membered heteroaryl rings are observed. This is due to the inherent electronic bias of the heterocycle itself which often allows to control the regioselectivity. For the Pd-catalyzed reactions, the first step of the catalytic cycle is the oxidative addition of the aryl (pseudo)halides to palladium (Scheme 1, intermediate **A**). Then, the reaction might proceed via several pathways such as electrophilic aromatic substitution.^[4] For many heteroarenes such as pyrazoles, concerted metallation-deprotonation (CMD) pathway has also been suggested (Scheme 1, intermediate **B**).^[5] The final step is a reductive elimination with the formation of a C-C bond on the heteroaryl ring.



Scheme 1. Pd-catalyzed direct C5-arylation of the pyrazole unit of 1-phenylpyrazole.

By contrast, the Ru-catalyzed C-H arylation relies, in most cases, on the coordination of functional groups or heteroelements on the ruthenium center that act as directing groups. With 1-phenylpyrazole the directing group is a nitrogen atom of the pyrazole ring (Scheme 2, intermediate **A**).^[6] Then, a cyclometallation which directs the C-H bond cleavage, followed by an oxidative addition and reductive elimination provides the arylated product with the formation of one or two C-C bonds at *ortho*-position(s) of the phenyl ring.



Scheme 2. Ru-catalyzed direct monoarylation of the phenyl unit of 1-phenylpyrazole using pyrazole as directing group.

Therefore, by changing the nature of the metal catalyst, it is possible to control the arylation of 1-phenylpyrazole at two different sites of the molecule. These regiodivergent arylations are not limited to 1-arylpyrazoles, and several other aryl-substituted azoles can be arylated at two or even three positions. In this review, we will describe the current state of the art for the arylation of either the heteroaryl unit (mostly *via* Pd-catalysis and in a few cases *via* Cu-catalysis) or the aryl unit using the heteroarene as a directing group (mostly *via* Ru-catalysis and in a few cases *via* Rh-catalysis) of aryl-substituted azoles^[7] containing reactive C-H bonds on both rings. The use of these different metals allowed in many cases to obtain regiodivergent arylations. First, the reactivity of 1-arylazoles such as 1-arylpyrazoles and 1-aryltriazoles for regiodivergent arylations will be described (Figure 1, a). The next three parts summarize the reactivity of 2-aryl- (Figure 1, b), 3-aryl- (Figure 1, c) and 4-arylazoles (Figure 1, d). The reactions proceeding *via* the substrate deprotonation with a strong base are generally not included in this review.

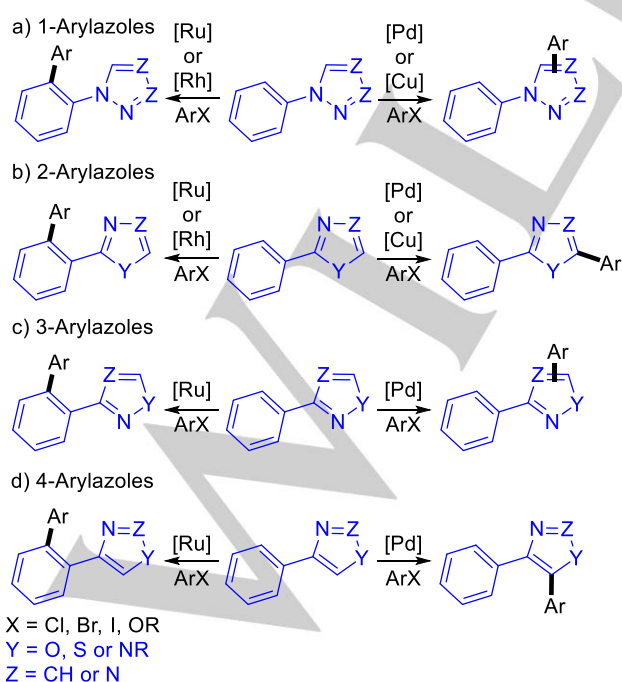


Figure 1. Regiodivergent metal-catalyzed direct arylations of aryl-substituted azoles.

2. 1-Arylazoles

The catalyzed direct arylations of both aryl and heteroaryl rings of 1-arylpyrazoles and 1-aryltriazoles have been reported; whereas for 1-aryltetrazole only the arylation of the heteroaryl ring has been described (Figure 2). For these couplings, in most cases, Pd or Ru catalysts were employed, but in a few cases, Rh or Cu catalysts were used.

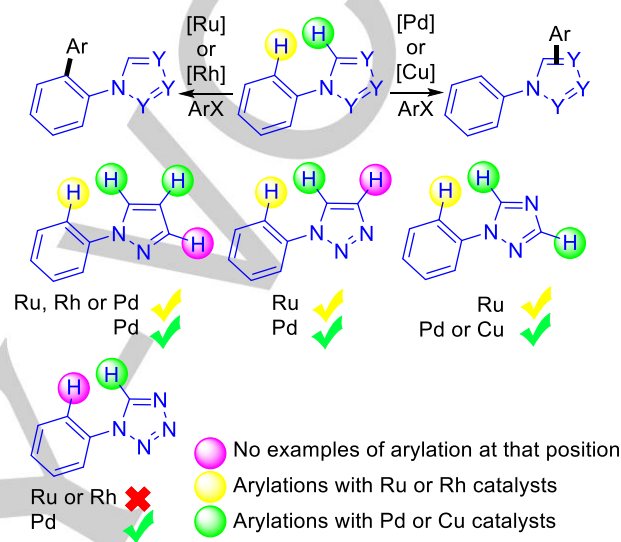
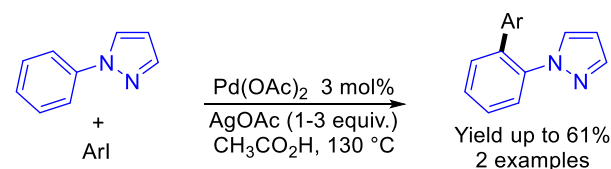


Figure 2. Regiodivergent metal-catalyzed direct arylations of 1-arylazoles.

2.1. 1-Arylpyrazoles

The direct arylation of 1-arylpyrazoles has been reported by several groups. Using Ru- or Rh-catalysts and unexpectedly in one case with a Pd catalyst, the aryl ring can be functionalized; whereas the use of Pd- or Cu-catalysts allows to arylate C4-and/or C5-positions of the pyrazole unit.

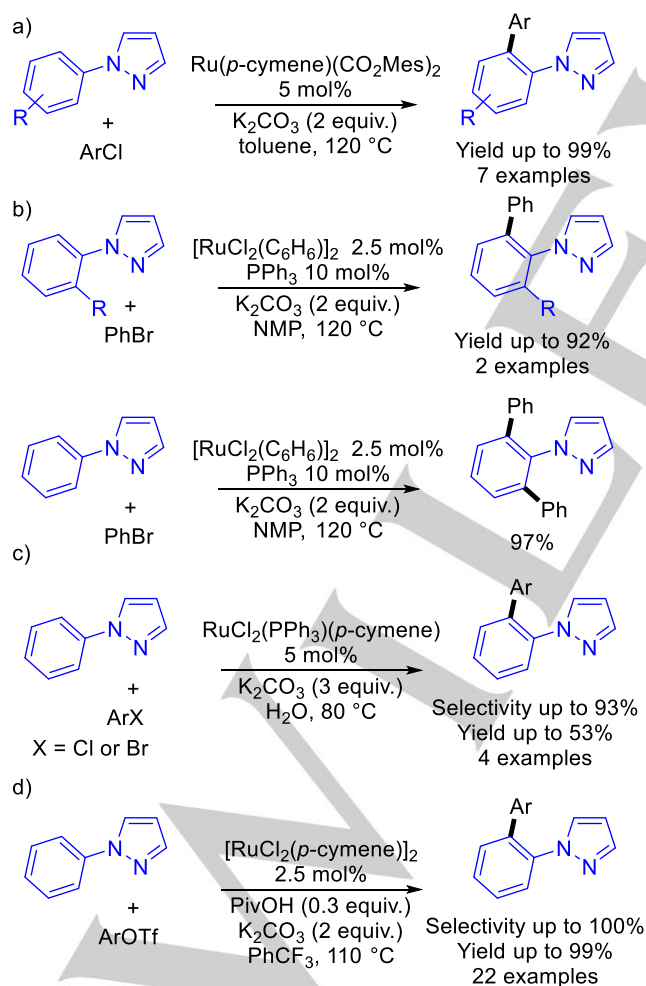
The first example of direct arylation of the aryl unit of 1-arylpyrazoles was reported by Shabashov and Daugulis in 2005.^[8] Using a Pd-catalyst and AgOAc base in acetic acid, the phenyl substituent of 1-phenylpyrazole was selectively arylated (Scheme 3). However, in general, with Pd-catalysts the arylation occurred regioselectively on the pyrazole ring (see scheme 6).



Scheme 3. Pd-catalyzed direct arylations of the phenyl ring of 1-phenylpyrazole.

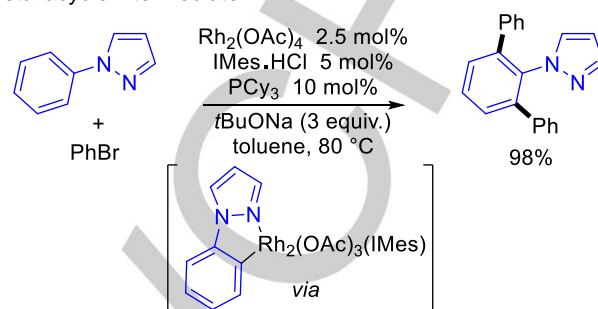
From 2006, Ackermann et al. extended this reaction to several other aryl sources using Ru-catalysis. For example his group

described some couplings using aryl tosylates as the reaction partners and with the green solvent PEG-20000.^[9] They also employed aryl chlorides as the aryl source with 1-arylpyrazoles bearing *ortho*-, *meta*-substituents or without substituent (Scheme 4, a).^[10] In all cases, the mono-arylated compounds were selectively obtained. The mechanism proposed for these couplings involves a cyclometalation through a carboxylate-assisted deprotonation such as in scheme 2. Three years after their seminal work on the Ru-catalyzed C-H arylation of 2-aryloxazolines described in 2005,^[11] Oi, Inoue et al. employed a similar procedure – [Ru(C₆H₆)Cl₂]/PPh₃ catalyst, K₂CO₃ base in NMP – for the arylation of the aryl group of 1-arylpyrazoles by bromobenzene (Scheme 4, b).^[12] From *ortho*-substituted 1-arylpyrazoles, the monoarylated pyrazoles were selectively obtained; whereas, with 1-phenylpyrazole the two *ortho*-positions of the aryl unit were arylated. In 2013, Bruneau, Dixneuf et al. described conditions for the mono-arylation of 1-phenylpyrazole with aryl bromides or chlorides using water as green solvent (Scheme 4, c).^[13a] In 2017, Kwang, Kantchev et al. extended the use of aryl chlorides as the aryl source using a (heterobiaryl)diarylphosphane as ligand.^[13b] Quite recently, the mono-arylation reaction was extended by Roger and Hierso to the coupling with aryl triflates.^[14] The reaction could be performed in (trifluoromethyl)benzene or solvent-free (Scheme 4, d).



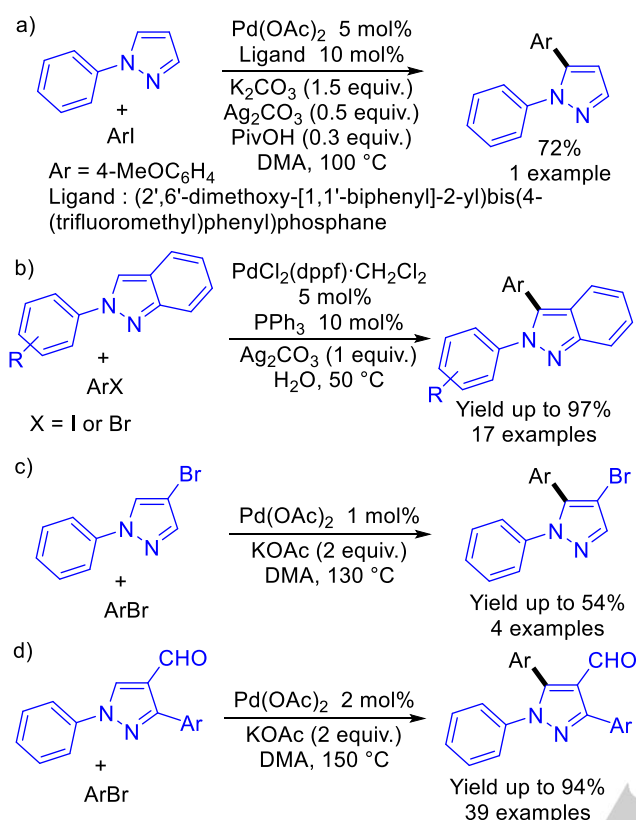
Scheme 4. Ru-catalyzed direct arylations of the aryl ring of 1-arylpyrazoles.

Some examples of Rh-catalyzed C-H arylations of the aryl group of 1-arylpyrazoles have also been described. For example, Chang et al. arylated 1-phenylpyrazole using Rh₂(OAc)₄/IMes·HCl/PCy₃ as catalyst precursor (Scheme 5).^[15] The diarylated product was obtained in 98% yield. The reaction was proposed to proceed *via* a proton abstraction by the action of sodium *tert*-butoxide base to afford a five-membered metallacycle intermediate.



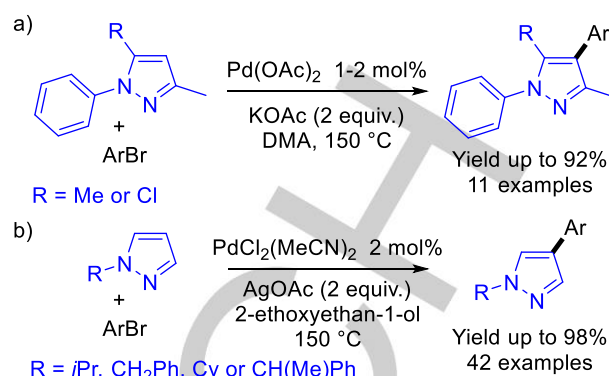
Scheme 5. Rh-catalyzed direct arylation of the phenyl ring of 1-phenylpyrazole.

Concerning the arylation of the pyrazole ring of 1-arylpyrazoles, both the C4- and C5-positions can be arylated using Cu- or Pd-catalysis. The first example of C5-arylation was described by Daugulis group in 2008 using Cu-catalysis and Et₃COLi as the base.^[16] This reaction likely proceed *via* a base deprotonation. Then in 2010, Rene and Fagnou reported an example of C5-arylation of 1-phenylpyrazole by 4-iodoanisole (Scheme 6, a).^[17] For this reaction a complex mixture of base/additive was used – e.g. K₂CO₃ (1.5 equiv.), Ag₂CO₃ (0.5 equiv.) and PivOH (0.3 equiv.) – and a sophisticated ligand derived from S-Phos ligand was employed. The experimental results were in agreement with a CMD mechanism (Scheme 1) where metalation of the pyrazole and C-H bond cleavage occur simultaneously. The same year, Greaney et al. reported the “on water” Pd-catalyzed direct C5-arylation of 2-phenylindazoles (Scheme 6, b). For these reactions, a low reaction temperature of 50 °C was used.^[18] In 2014 and 2015, our group described conditions for the C5-arylation of pyrazoles bearing formyl- or bromo-substituents at the C4-position (Scheme 6, c and d).^[19] These reactions employed phosphine-free Pd(OAc)₂ catalyst and KOAc as inexpensive base at 130 °C. Under these conditions, no debromination or deformylation of the pyrazole ring was observed.



Scheme 6. Pd-catalyzed direct C5-arylations of the pyrazole ring of 1-arylpyrazoles.

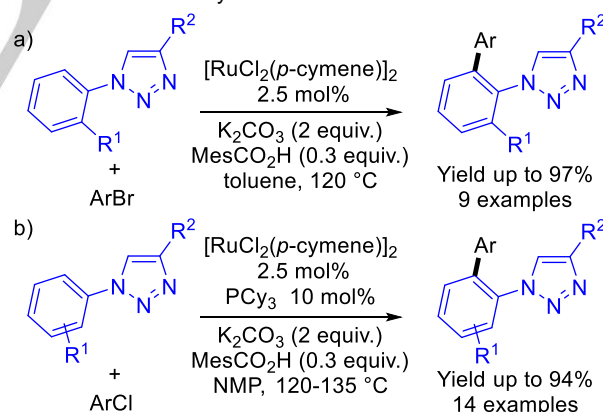
A few examples of regioselective C4-arylations of 1-arylpyrazoles also have been reported by our group (Scheme 7). We first studied the reactivity of 3,5-dimethyl-1-phenylpyrazole (Scheme 7, a).^[20] This reactant gave the expected C4-arylated 1-phenylpyrazoles in 58–80% yields. However, the reaction was limited to electron-deficient aryl bromides such as bromobenzonitriles or 4-bromobenzaldehyde. Using 4-bromoanisole, no formation of C4-arylated product was detected. 5-Chloro-3-methyl-1-phenylpyrazole exhibits a similar reactivity affording the 4-arylated products without cleavage of the C-Cl bond.^[21] The direct arylations of pyrazole rings which have a free C5 position generally occurred preferentially at the C5-position using palladium-catalysis (See scheme 6). However, very recently our group reported general conditions for regioselective direct arylation at the C4-position of pyrazoles, while C-H 5-position was free (Scheme 7, b).^[22] This regioselectivity was highly dependent on the nature of the solvent and the base. With Pd(OAc)₂ catalyst and AgOAc as base in 2-ethoxyethan-1-ol, the C4-arylated pyrazoles were obtained in 70–98% regioselectivity with pyrazoles bearing isopropyl, cyclohexyl, benzyl, or 1-phenylethyl substituents on the nitrogen atom. Conversely, with 1-phenyl-3-methylpyrazole, a mixture of C4- and C5-arylated pyrazoles was obtained in 76:24 ratio. DFT calculations revealed that the protic solvent 2-ethoxyethan-1-ol enhances the acidity of the proton at C4-position of the pyrazole ring and thus favors this direct C4-arylation.



Scheme 7. Pd-catalyzed direct C4-arylations of the pyrazole ring of pyrazoles.

2.2. 1-Aryl-1,2,3-triazoles

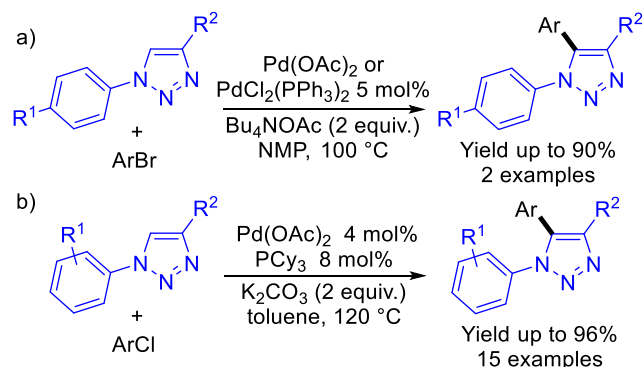
Both aryl and triazole units of 1-aryl-1,2,3-triazoles have been arylated via metal-catalyzed C-H bond functionalization. Concerning the aryl unit, the first examples were described in 2008 by Ackermann et al. using [RuCl₂(*p*-cymene)]₂ catalyst and aryl bromides as the aryl source (Scheme 8, a).^[23] A variety of functionalized electron-poor as well as electron-rich aryl bromides and also a heteroaryl bromide were successfully employed. One year later, they extended the reaction to aryl chlorides and also to an aryl tosylate (Scheme 8, b).^[24] This group also described a procedure for the arylation of the aryl-substituent of 1-aryl-1,2,3-triazoles with the benign reaction media polyethylene glycol PEG-20000 under air.^[9] These reactions likely proceed via a CMD mechanism with the formation of a ruthenacycle such as in scheme 2.



Scheme 8. Ru-catalyzed direct arylations of the aryl ring of 1-aryl-1,2,3-triazoles.

So far, the metal catalyzed direct C4-arylation of 1-aryl-1,2,3-triazoles has not been described; whereas, its Pd-catalyzed C5-arylation has been reported by several groups. The first examples were described in 2007 by Gevorgyan et al. using Pd(OAc)₂ or PdCl₂(PPh₃)₂ catalysts, Bu₄NOAc base and aryl bromide as coupling partners (Scheme 9, a).^[25] One year later, Ackermann et al. extended the reaction to aryl chlorides with

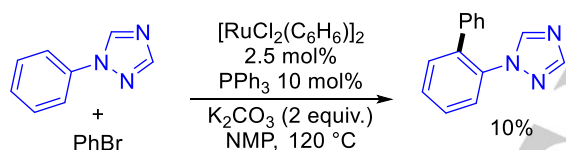
K_2CO_3 as the base (Scheme 9, b).^[26a] This reaction can also be performed under microwave irradiation.^[26b]



Scheme 9. Pd-catalyzed direct C5-arylations of the triazole ring of 1-aryl-1,2,3-triazoles.

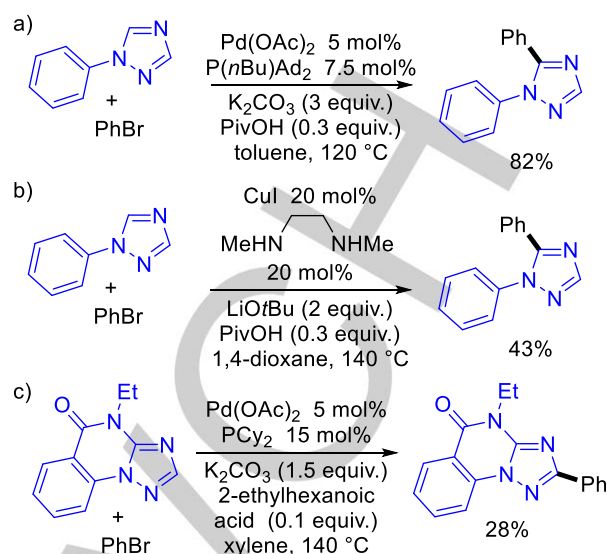
2.3. 1-Aryl-1,2,4-triazoles

The direct arylation of 1-aryl-1,2,4-triazoles has attracted less attention than that of the 1-aryl-1,2,3-triazoles. Only one example of arylation of its aryl unit was described. In the presence of a Ru-catalyst, Oi et al. obtained only 10% of the desired biphenyl derivative (Scheme 10).^[12]



Scheme 10. Ru-catalyzed direct arylation of the phenyl unit of 1-phenyl-1,2,4-triazole.

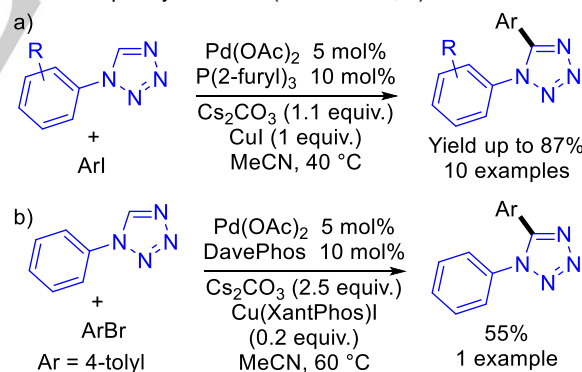
A few examples of C5-arylations of 1-aryl-1,2,4-triazoles have been reported. In 2013, Sames et al. described a single example of C5-arylation of the triazole ring using a Pd-catalyst and bromobenzene as the aryl source (Scheme 11, a).^[27] In 2016, Jamal and Teo prepared 1,5-diphenyl-1,2,4-triazole in 43% yield using $CuI/N^1,N^2$ -dimethylethane-1,2-diamine as catalyst and lithium *tert*-butoxide as base (Scheme 11, b).^[28] This reaction probably proceeds *via* a base deprotonation of the triazole ring. The C3-position of a 1-aryl-1,2,4-triazole has also been functionalized when the C5-position was blocked using Pd-catalysis (Scheme 11, c).^[29] However, the expected product was obtained in a quite low yield (28%).



Scheme 11. Pd- or Cu-catalyzed direct C5-arylations of 1-aryl-1,2,4-triazoles.

2.4. 1-Aryl-1,2,3,4-tetrazoles

The arylation or vinylation of the aryl group of 1-aryl-1,2,3,4-tetrazoles has not been described. On the other hand, Pour et al. reported conditions for the C5-arylation of the tetrazole unit using Pd-catalysis (Scheme 12, a).^[30a] This coupling reaction was achieved in the presence of a stoichiometric amount of CuI and 1.2 equiv. of Cs_2CO_3 using aryl iodides as the aryl source. Zhang et al. employed a very similar procedure for the C5-arylation of 1-phenyltetrazole (Scheme 12, b).^[30b]



Scheme 12. Pd-catalyzed direct C5-arylations of the tetrazole ring of 1-aryltetrazoles.

3. 2-Arylazoles

The 2-aryl-oxazoles, -thiazoles or -imidazoles can be arylated either at the aryl ring using Ru or Rh catalysts or at the C5-position of the azole ring with Pd- or Cu-catalysts (Figure 3). In all cases, the reactions were regioselective. Conversely, only the Pd- or Cu-catalyzed C5-arylations of 2-aryldiazoles have been described.

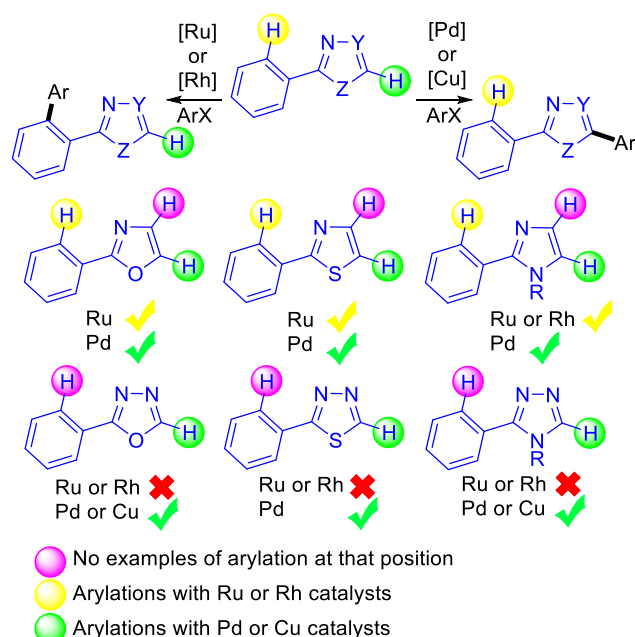
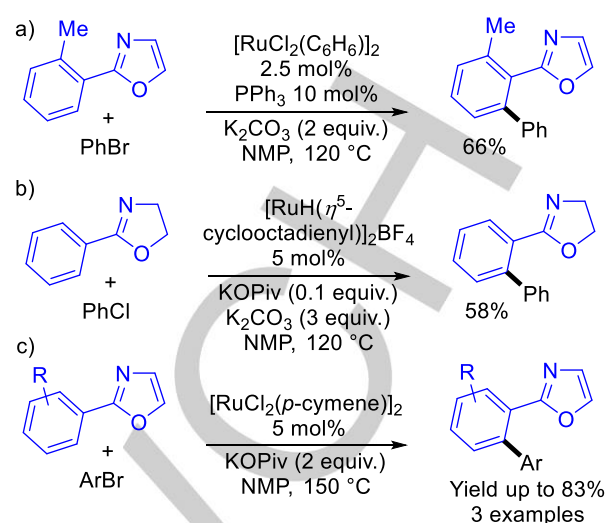


Figure 3. Regiodivergent metal-catalyzed direct arylations of 2-aryloxazoles.

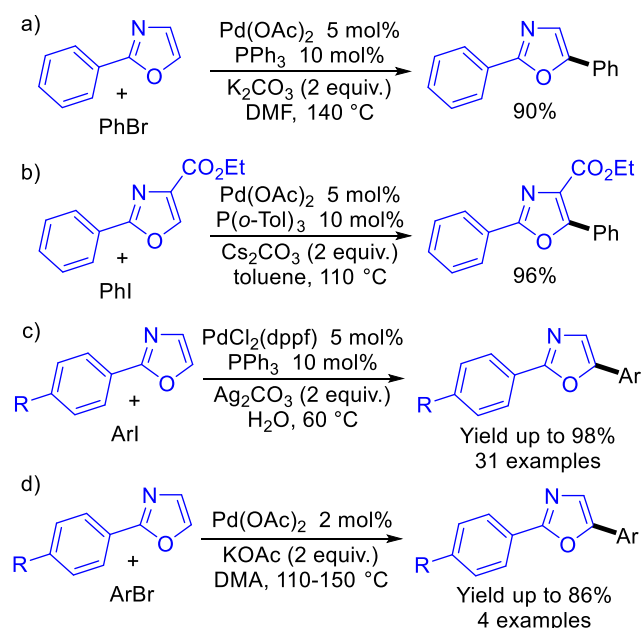
3.1. 2-Aryloxazoles

Again, the first example of Ru-catalyzed direct arylation of the aryl ring of a 2-aryloxazole was described by Oi et al. in 2008 (Scheme 13, a).^[12] From a 2-tolyl substituted oxazole and bromobenzene the tolyl unit was arylated in 66% yield. In 2005, Oi et al. described conditions for the di-arylation of the phenyl substituents of the related substrate 2-phenyloxazolines.^[11] Six years later, Fischmeister, Dixneuf et al. reported conditions for the selective mono-arylation of the phenyl unit of 2-phenyloxazoline (Scheme 13, b).^[31] The use of KOⁱPiv associated to K₂CO₃ as base system gave the monocoupling product in 99% selectivity and in 58% yield. Our group also studied the reactivity of 2-aryloxazoles using Ru catalysts.^[32] From 2-aryloxazoles and a set of aryl bromides, in the presence of [Ru(*p*-cymene)Cl₂]₂ as the catalyst and KOⁱPiv as the only base, the regioselective direct mono-arylation of the aryl unit of 2-aryloxazoles was also observed (Scheme 13, c).



Scheme 13. Ru-catalyzed direct arylations of the aryl ring of 2-aryloxazoles.

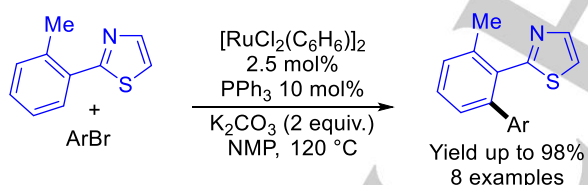
Several procedures for the direct C5-arylation of 2-aryloxazoles have been reported (Scheme 14). The first one was described by Miura et al in 1998 (Scheme 14, a).^[33] The reaction of 2-phenyloxazole with bromobenzene regioselectively gave 2,5-diphenyloxazole in high yield, whereas no arylation on the phenyl ring was observed. In 2005, Hoarau et al. investigated the reactivity of ethyl 2-phenyl-4-oxazolecarboxylate (Scheme 14, b).^[34] The use of Pd(OAc)₂/P(*o*-Tol)₃ catalytic system using Cs₂CO₃ base selectively gave the 2,5-diphenyloxazole derivative in 96% yield. Then, in 2007 and 2008, Greaney et al. arylated the C5-position of 2-phenyloxazole using water as the solvent at 60 °C (Scheme 14, c).^[35] Their procedure employed Ag₂CO₃ base and PhI as the aryl source. In 2019, our group described a phosphine-free procedure for the arylation of a set of 2-aryloxazoles using aryl bromides as the aryl source (Scheme 14, d).^[32] This procedure required the use of a higher reaction temperature (110–150 °C), but KOAc was employed as inexpensive base.



Scheme 14. Pd-catalyzed direct C5-arylations of the oxazole ring of 2-aryloxazoles.

3.2. 2-Arylthiazoles

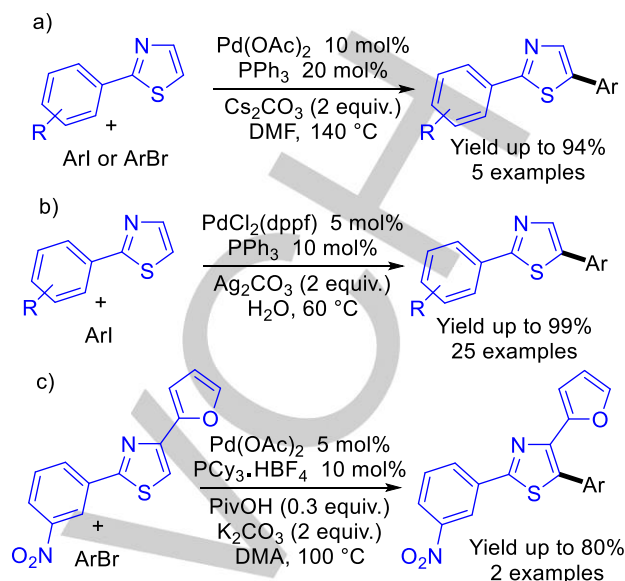
The only examples of Ru-catalyzed direct arylations of 2-arylthiazoles were described by Oi et al. in 2008. They reported the arylation of the tolyl group of 2-(*o*-tolyl)thiazole by aryl bromides using $[\text{Ru}(\text{C}_6\text{H}_6)_2\text{Cl}_2]/\text{PPh}_3$ catalyst (Scheme 15).^[12] The reaction tolerated a variety of substituents on the aryl bromide such as acetyl, methoxy or fluoro.



Scheme 15. Ru-catalyzed direct arylations of the aryl unit of 2-arylthiazoles.

By contrast, the Pd-catalyzed direct arylation of 2-arylthiazoles was described by several groups. For example, in 2003, Mori et al. arylated the C5-position of the thiazole unit of 2-(4-methoxyphenyl)thiazole with aryl halides (Scheme 16, a).^[36] However, the substrate scope was quite limited. Then, in 2007, Greaney et al. arylated the C5-position of a variety of 2-arylthiazoles using water as the solvent (Scheme 16, b).^[35a] Their procedure which employed Ag_2CO_3 base and $\text{PdCl}_2(\text{dppf})$ tolerated a very wide variety of substituents on the aryl iodide. Fagnou et al. also reported a procedure for the arylation of a 2-arylthiazole.^[37] Their substrate also contained a furan ring which is also known to be reactive for direct arylation in the presence of palladium catalysts. In the presence of $\text{Pd}(\text{OAc})_2/\text{PCy}_3$ catalyst and $\text{PivOH}/\text{K}_2\text{CO}_3$ as additive/base, they only observed the arylation of the thiazole ring (Scheme 16, c). This reactivity is in agreement with the order (thiazole vs furan rings) predicted

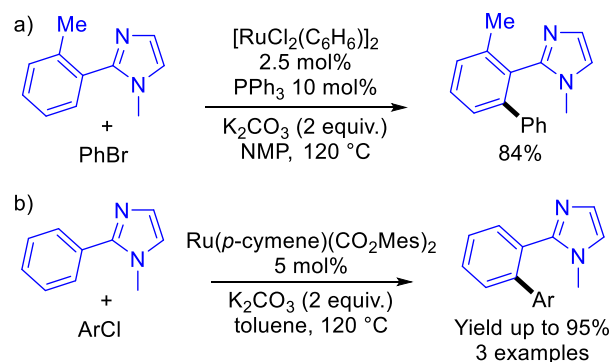
by the DFT calculated CMD pathway promoted by a palladium/carboxylate complexes such as in the scheme 1.



Scheme 16. Pd-catalyzed direct C5-arylations of 2-arylthiazoles.

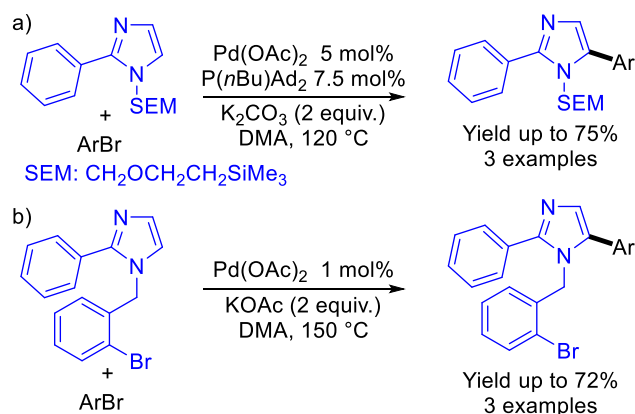
3.3. 2-Arylimidazoles

The first example of Ru-catalyzed direct arylation of the aryl group of a 2-arylimidazole was again described by Oi et al. in 2008 using $[\text{Ru}(\text{C}_6\text{H}_6)_2\text{Cl}_2]/\text{PPh}_3$ catalyst (Scheme 17, a).^[12] For this reaction, bromobenzene was used as the aryl source. Two years later, Ackermann et al. extended the reaction to a set of aryl chlorides (Scheme 17, b).^[10] Fluoro, ester or methyl *para*-substituted aryl chlorides were tolerated. This C-H bond functionalization likely proceed *via* the formation of a ruthenacycle through a carboxylate-assisted deprotonation (see Scheme 2). In 2017, Kwang, Kantchev et al. described a slightly different procedure for the arylation of 2-arylimidazoles which required a (heterobiaryl)diarylphosphane as ligand.^[13b] In 2008, the arylation of the aryl unit of 1-methyl-2-phenylimidazole using a rhodium catalyst and NaBPh_4 as aryl source has also been reported by Miura et al.^[38] However, this procedure is less attractive than those employing aryl halides due to the limited access to such aryl source.



Scheme 17. Ru-catalyzed direct arylations of the aryl ring of 2-arylimidazoles.

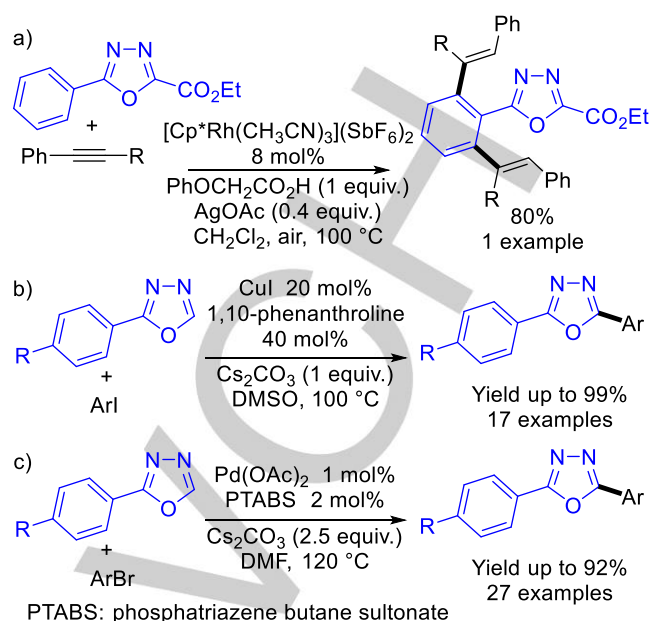
The Pd-catalyzed C5-arylation of 2-arylimidazoles has been reported by a few groups. For example, Sames et al. arylated the SEM-protected 2-phenylimidazoles with aryl bromides using $\text{Pd}(\text{OAc})_2/\text{P}(\text{nBu})\text{Ad}_2$ catalyst in 69–75% yields (Scheme 18, a).^[39] Our group also described a simple procedure – e.g. phosphine-free catalyst $\text{Pd}(\text{OAc})_2$ and KOAc base – for the arylation of an imidazole bearing an *ortho*-bromo substituted benzyl on the nitrogen atom (Scheme 18, b).^[40] In the presence of electron-deficient aryl bromides, the intermolecular coupling reaction proceeded in good yield and the C-Br bond of the benzyl unit remained untouched.



Scheme 18. Pd-catalyzed direct C5-arylations of the imidazole ring of 2-arylimidazoles.

3.4. 2-Aryl-1,3,4-oxadiazoles

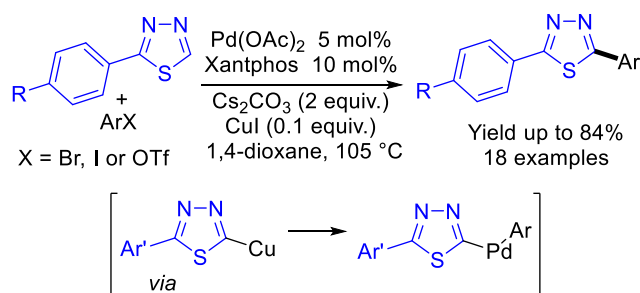
So far, the metal-catalyzed direct arylation of 2-aryloxadiazoles is limited to the oxadiazole unit. However, a single example of Rh-catalyzed vinylation of the aryl moiety of a C5-substituted 2-aryloxadiazole has been reported by Lin and Dong.^[41] They employed a phenylacetylene derivative as the coupling partner to prepare the di-*ortho*-vinyated aryl derivative (Scheme 19, a). Concerning the C5-arylation of 2-aryloxadiazoles, several procedures have been reported and both copper and palladium catalysts were successfully employed. In 2009, Miura et al. described a copper-based method for the direct arylation of the C5-position of 2-aryl-substituted 1,3,4-oxadiazoles using aryl iodides as aryl sources (Scheme 19, b).^[42a] For this reaction, both electron-rich and -poor aryl iodides were tolerated. In 2019, Kapdi et al. described a low-loading palladium-catalyzed procedure for the arylation of 2-aryl-1,3,4-oxadiazoles (Scheme 19, c).^[42b] They employed $\text{Pd}(\text{OAc})_2$ /phosphatriazene butane sulfonate as catalytic system and aryl bromides as aryl source. The reaction tolerated methoxy and trifluoromethyl substituents on the aryl bromide and also several heteroaryl bromides.



Scheme 19. Catalyzed direct vinylation or C5-arylations of 2-aryl-1,3,4-oxadiazoles.

3.5. 2-Aryl-1,3,4-thiadiazoles

The arylation of the aryl group of 2-aryl-1,3,4-thiadiazoles has not been reported yet; whereas, its C5-arylation has been described using a Pd-catalyst (Scheme 20).^[43] For this reaction, 10% CuI was added to the reaction mixture. This procedure was effective for the coupling of a wide range of aryl halides and aryl triflates bearing electron donating or withdrawing groups. According to the authors, a plausible mechanism might involve a base assisted cupration of the thiadiazole to give a thiadiazole-Cu species (Scheme 20). Subsequently, transmetalation with an Ar-Pd complex gives a Ar-Pd-thiadiazole intermediate which undergoes reductive elimination.



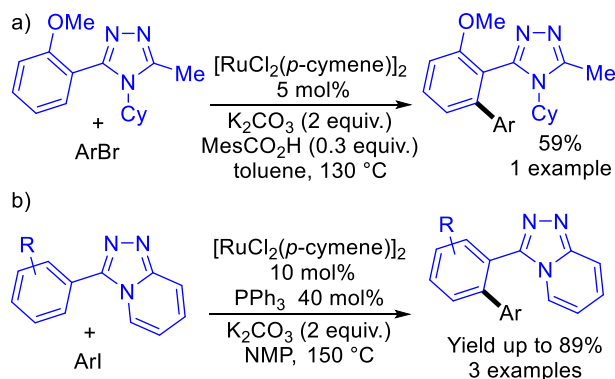
Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Scheme 20. Pd-catalyzed direct C5-arylations of the thiadiazole ring of 2-aryl-1,3,4-thiadiazoles.

3.6. 3-Aryl-1,2,4-triazoles

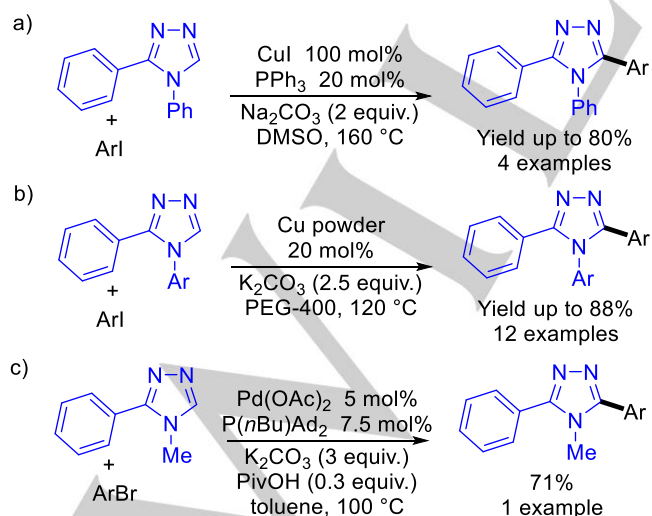
The Ru-catalyzed arylation of the aryl group of 3-aryl-1,2,4-triazoles which does not contain C5-substituent on the triazole ring has not been reported. Conversely, Charette et al.

described in 2015 the Ru-catalyzed arylation of the aryl moiety of a 3-aryl-5-methyl-1,2,4-triazole (Scheme 21, a).^[44a] For this reaction there was no regioselectivity issue. Three years later, Larrosa et al. reported a similar reaction, but a mixture of products was obtained.^[44b] The Ru-catalyzed C-H arylation of the aryl unit of 3-aryl-[1,2,4]triazolo[4,3-a]pyridines is also possible (Scheme 21, b).^[44c] Again, there was no regioselectivity issue for this coupling reaction.



Scheme 21. Ru-catalyzed direct arylations of the aryl unit of a 2-aryl-1,3,4-triazole or triazolopyridines.

The C5-arylation of the triazole ring of 3-aryl-1,2,4-triazoles has attracted more attention. Miura et al. described in 2009 a CuI/PPh_3 -promoted procedure to arylate 3,4-diphenyl-1,2,4-triazole by aryl iodides (Scheme 22, a).^[42a] Under their conditions, only the triazole ring was arylated. In 2015, Vidavalur et al. succeeded to perform this reaction using a catalytic amount of copper. Using Cu powder (20 mol%) and aryl iodides in PEG-400, the 3,4-diaryl-1,2,4-triazoles were arylated at C5-position in good yields (Scheme 22, b).^[45] In 2013, Sames et al. employed a Pd-catalyst for the C5-arylation of 3-phenyl-4-methyl-1,2,4-triazole by 4-bromoanisole (Scheme 22, c).^[27] Again, only the triazole ring was arylated.



Scheme 22. Pd-catalyzed direct C5-arylations of 2-aryl-1,3,4-triazoles.

4. 3-Arylazoles

3-Arylazoles have not been employed in the Ru-catalyzed C-H arylation and only a few examples of Rh-catalyzed vinylations of the aryl unit of 3-arylisoxazoles have been described. The Pd-catalyzed C-H arylation of the azole ring of 3-arylazoles has attracted more attention, but the reaction is still limited to isoxazoles, pyrazoles, 1,2,4-oxadiazole and 1,2,4-triazoles; whereas 3-arylisothiazoles and 3-arylthiadiazoles have not been employed so far (Figure 4). Therefore, except for 3-arylisoxazoles, currently 3-arylazoles does not appear to be appropriate structures for regiodivergent arylations.

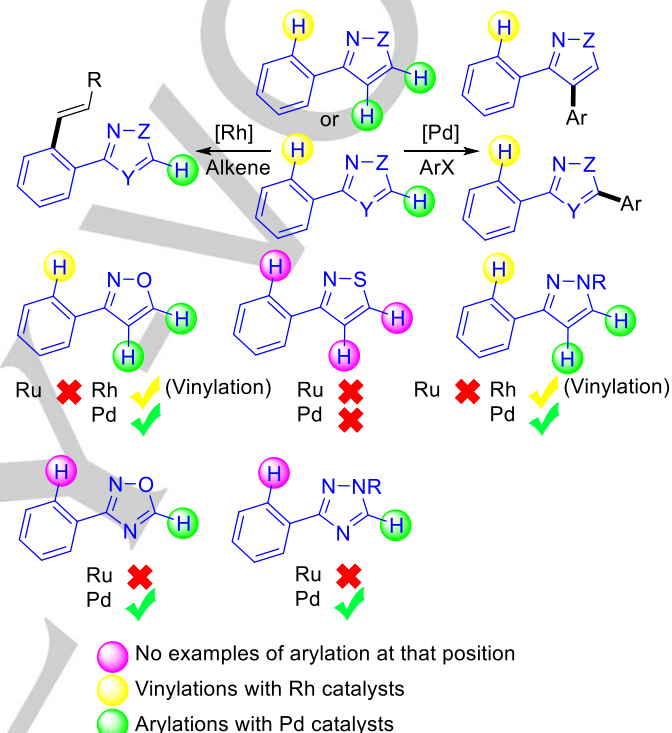
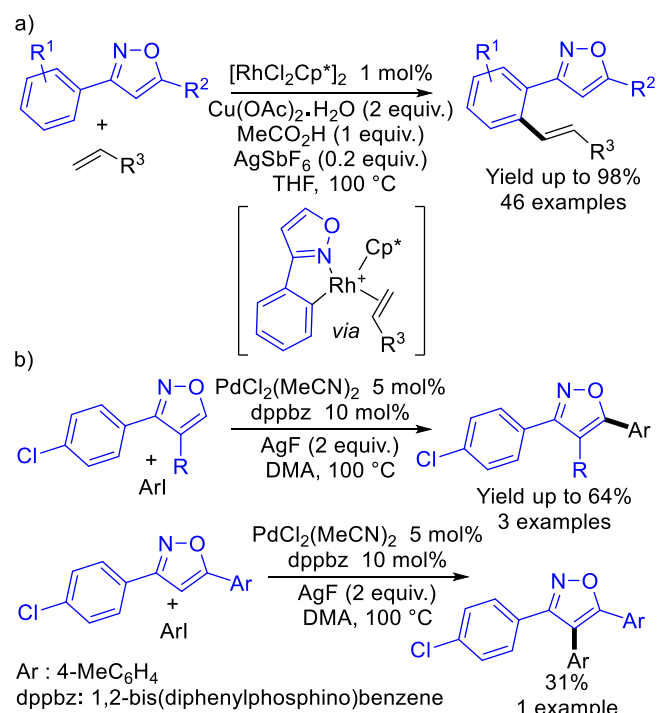


Figure 4. Regiodivergent metal-catalyzed direct arylations of 3-arylazoles.

4.1. 3-Arylisoxazoles

The arylation of the aryl substituent of 3-arylisoxazoles has not been described. However, in 2019, Kapur et al. reported conditions for the catalyst-controlled regioselective C-H vinylation of 3-arylisoxazoles (Scheme 23, a).^[46a] Using a Rh catalyst and due to the strong coordination to the nitrogen atom of the isoxazoles, the vinylation occurred on the 3-aryl substituent of the 3-arylisoxazoles. A variety of alkenes and substituents on the 3-arylisoxazole was tolerated. According to the authors, this reaction might proceed *via* the generation of a cationic catalyst followed by a directed C-H activation, probably *via* a base-assisted internal electrophilic substitution reaction. Then, coordination of the olefin to the cyclometalated Rh complex, followed by carboration and β -hydride elimination provides the coupling product. The arylation at the C5-position of a 3,4-diaryl isoxazole is possible using a Pd-catalyst (Scheme 23, b).^[46b] For this reaction, $\text{PdCl}_2(\text{MeCN})_2/(\text{dppbz})$ catalyst and AgF base were employed. Under the same conditions, a 3,5-

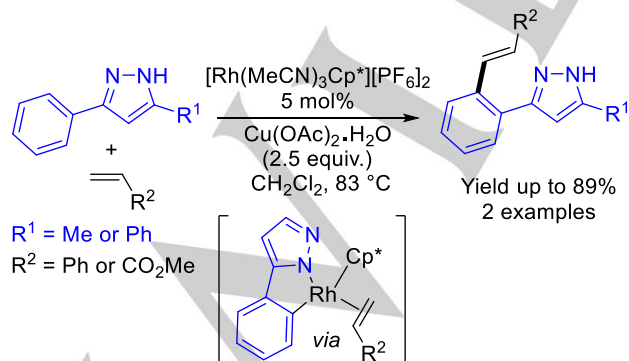
diarylisoxazole was regioselectively arylated at the C4-position of the isoxazole ring in a low 31% yield.



Scheme 23. Rh- or Pd-catalyzed direct vinylation or arylations of 3-arylisoxazoles.

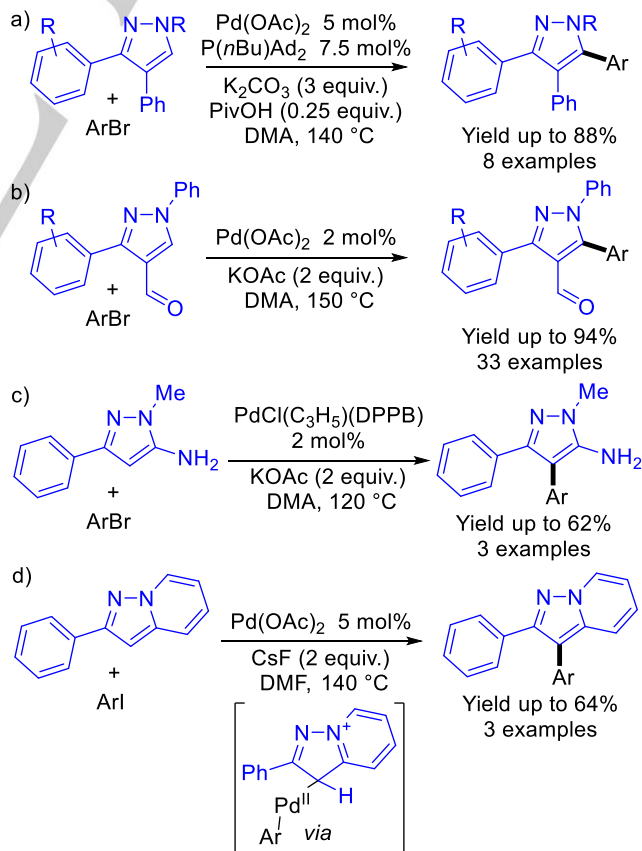
4.2. 3-Arylpyrazoles

The arylation of the aryl unit of 3-arylpyrazoles has not yet been described, but two examples of Rh-catalyzed vinylation have been reported by Davis, Macgregor et al. (Scheme 24).^[47] In all cases, the reaction gave mainly the mono-vinylation products. The authors used DFT calculations to probe the mechanism. First, sequential N-H and C-H activation produces a cyclometalated Rh complex. Substitution of acetic acid by an alkene gives the intermediate of scheme 24. Then, a migratory insertion into the Rh-aryl bond leads to seven-membered metallacycle.



Scheme 24. Rh-catalyzed direct vinylation of the aryl unit of 3-arylpyrazoles.

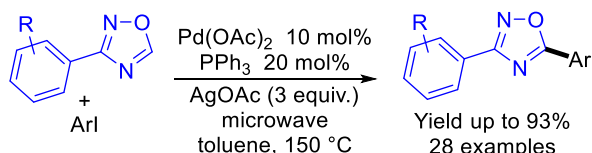
By contrast, several examples of C4- or C5-arylations of the pyrazole ring have been reported. The first examples of C5-arylations were described by Sames et al in 2009 (Scheme 25, a).^[48] They succeeded to arylate several 3,4-diarylpyrazoles in good yields using Pd(OAc)₂/P(*n*Bu)Ad₂ catalyst and aryl bromides as aryl source. Five years later, our group described conditions for the C5-arylation of 3-arylpyrazoles bearing a formyl group at C4-position (Scheme 25, b).^[19a] The reaction proceeded in moderate to high yields with a variety of aryl bromides in the presence of 2 mol% of Pd(OAc)₂ catalyst. The use of an aldehyde function at C4 position of the pyrazole ring presents several advantages as 4-formylpyrazoles are easily prepared from hydrazine derivatives, ketones, and *N,N*-dimethylformamide, as it allows the control of the regioselectivity of the arylation. Moreover, the aldehyde substituent can easily be transformed into a variety of other substituents or it can be removed via Pd-catalyzed decarbonylation. The palladium-catalyzed direct arylation at the C4-position of a non-protected 3-phenyl-5-aminopyrazole was also found to proceed in high yields using a variety of aryl bromides (Scheme 25, c).^[49] The choice of KOAc as the reaction base was found to be crucial to inhibit the amination reaction. In 2016, Chu, Wu et al. described conditions for the arylation of the 5-membered ring of 2-phenylpyrazolo[1,5-*a*]pyridine (Scheme 25, d).^[50] Again, under the Pd-catalyzed reaction conditions, the phenyl ring remained untouched. The authors suggested that the reaction proceeds via the reaction of Pd with a zwitterion form of phenylpyrazolo[1,5-*a*]pyridine to generate the intermediate of scheme 25d.



Scheme 25. Pd-catalyzed direct C4- or C5-arylations of the pyrazole unit of 3-arylpyrazoles.

4.3. 3-Aryl-1,2,4-oxadiazoles

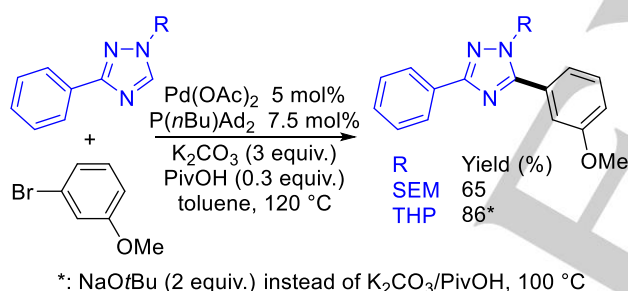
The arylation of the aryl unit of 3-aryl-1,2,4-oxadiazole has not been described, but several examples of Pd-catalyzed C5-arylations of this substrate have been reported by Sheng, Hu et al. (Scheme 26).^[51] In the presence of Pd(OAc)₂/PPh₃ catalyst and AgOAc base under microwave irradiation, a wide variety of 3,5-diaryl-substituted 1,2,4-oxadiazoles was obtained in moderate to very high yields.



Scheme 26. Pd-catalyzed direct C5-arylations of a 3-aryl-1,2,4-oxadiazole.

4.4. 3-Aryl-1,2,4-triazoles

Little is known concerning the C-H arylation of 3-aryl-1,2,4-triazoles. Their reactivity with ruthenium catalysts was not investigated. Conversely, in the presence of a Pd-catalyst, Sames group reported that good yields in the C5-arylated triazoles could be obtained with Pd(OAc)₂/P(*n*Bu)Ad₂ catalyst (Scheme 27).^[27] Both SEM (2-(trimethylsilyl)ethoxymethyl) and THP (tetrahydropyranyl) protecting groups on the triazole were tolerated.



Scheme 27. Pd-catalyzed direct C5-arylations of 3-aryl-1,2,4-triazoles.

5. 4-Arylazoles

The Pd-catalyzed C2- or C5-arylation of several 4-arylazoles has been described; whereas the Ru-catalyzed arylations of their aryl ring is limited to the use of 2-arylimidazo[1,2-*a*]pyridines and 4-aryltriazoles (Figure 5).

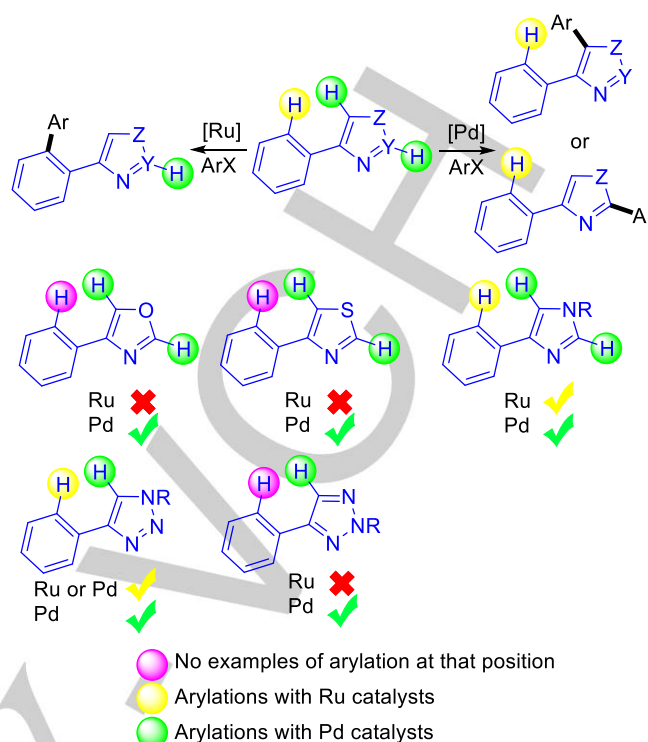
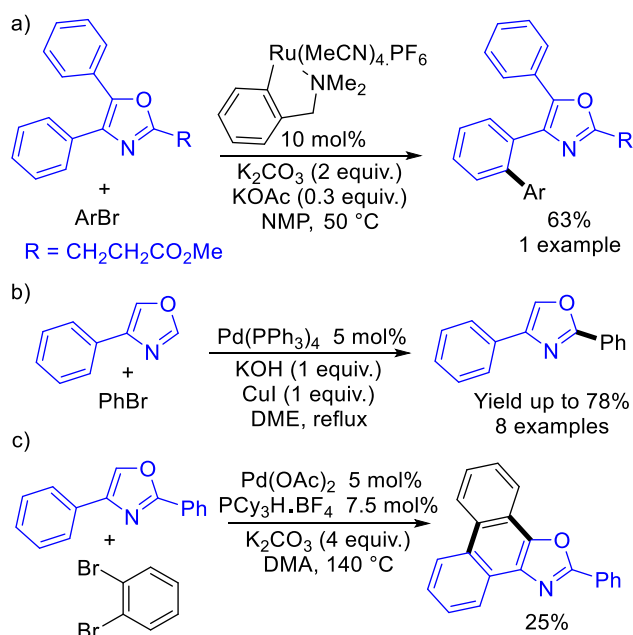


Figure 5. Regiodivergent metal-catalyzed direct arylations of 4-arylazoles.

5.1. 4-Aryloxazoles

Only a few examples of metal-catalyzed direct arylation of 4-aryloxazoles have been reported. Concerning the arylation of the aryl group of 4-aryloxazoles, only one reaction which employed a 2,4,5-trisubstituted oxazole and 1-bromo-3,5-xylene as the reaction partner has been described (Scheme 28, a). For this coupling reaction there was no regioselectivity issue.^[44b] However, it should be mentioned that the mono-arylated compound was obtained with a high selectivity (63%), whereas the di-arylated aryl was only obtained in 4% yield.

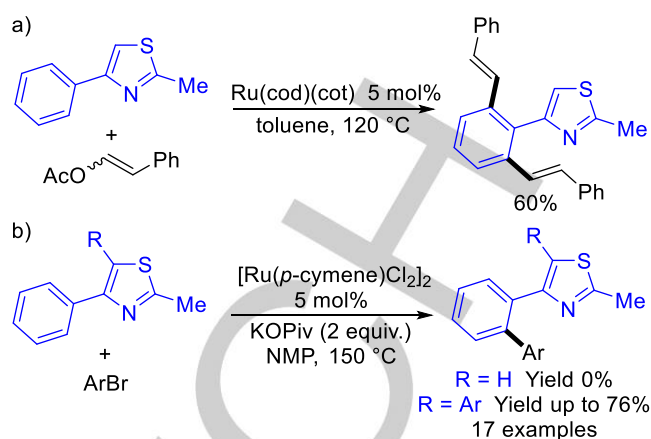
The regioselective Pd-catalyzed C2-arylation of 4-aryloxazoles in good yields has been described in 2018 using Pd(PPh₃)₄ catalyst with CuI as additive and KOH base (Scheme 28, b).^[52] Byon, Joo et al. prepared in 2020 a phenanthro[9,10-*d*]oxazole from a 2,4-diphenyloxazole and 1,2-dibromobenzene (Scheme 28, c).^[53] The reaction proceeded *via* a Pd-catalyzed C5-arylation of the oxazole derivative followed by an intramolecular arylation using K₂CO₃ as base. However, the phenanthro[9,10-*d*]oxazole was obtained in a low yield (25%).



Scheme 28. Pd- or Ru-catalyzed direct arylations of 4-aryloxazoles.

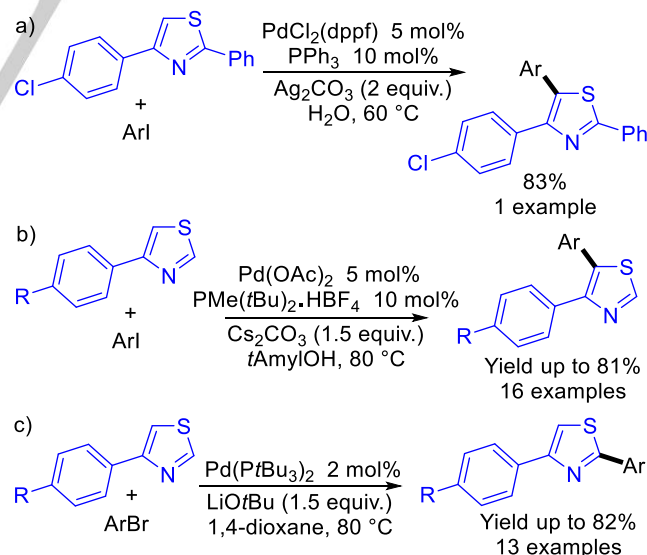
5.2. 4-Arylthiazoles

The Ru-catalyzed arylation of the aryl unit of 4-arylthiazoles which does not have a C5-substituent has not been reported yet, but the alkenylation of 2-methyl-4-phenylthiazole using an alkenyl acetate as vinyl source has been described by Kakiuchi et al. in 2007 (Scheme 29, a).^[54] The C-C bond formation took place at the two *ortho*-positions of the phenyl group. Our group also investigated the arylation of 4-arylthiazoles in 2019.^[55] 2-Methyl-4-phenylthiazole was found to be unreactive and was recovered; whereas, the introduction of an aryl unit at C5-position of 2-methyl-4-phenylthiazole enhances its reactivity. It allowed the selective mono-arylation of the C4-phenyl unit of 2-methyl-4-phenyl-5-arylthiazoles in moderate to high yields (Scheme 29, b). These couplings were performed with 5 mol% of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ catalyst associated to KO Piv as base. These results reveal that the conformation and electronic properties of 4-phenylthiazoles are crucial to allow the formation of suitable intermediates in the course of the catalytic cycle.



Scheme 29. Pd- or Ru-catalyzed direct vinylations or arylations of 4-arylthiazoles.

In 2007, Greaney et al. reported conditions for the C5-arylation of a 2,4-diarylthiazole (Scheme 30, a).^[35a] The reaction proceeded at a low temperature (60 °C) in water using Ag_2CO_3 base. Conditions for the regioselective arylation of either C2- or C5-positions of 4-arylthiazoles have been reported by Itami et al.^[56] The use of weak base Cs_2CO_3 using $\text{Pd}(\text{OAc})_2/\text{PMe}(\text{tBu})_2$ in $t\text{AmylOH}$ allowed to control the regioselectivity of the arylation in favor of the C5-position of the thiazole unit (Scheme 30, b). In the course of these reactions, the over-arylation products 2,4,5-triarylthiazoles were generally obtained in < 10% yield. For the C2-arylation of 4-arylthiazoles, they employed $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ catalyst and LiOtBu as stronger base in 1,4-dioxane (Scheme 30, c). Under these conditions, a complete C2-selectivity and good yields were obtained.

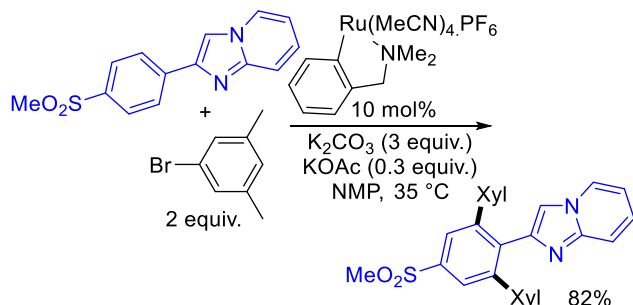


Scheme 30. Pd-catalyzed direct C2- or C5-arylations of 4-arylthiazoles.

5.3. 4-Arylimidazoles and 2-arylimidazo[1,2-a]pyridines

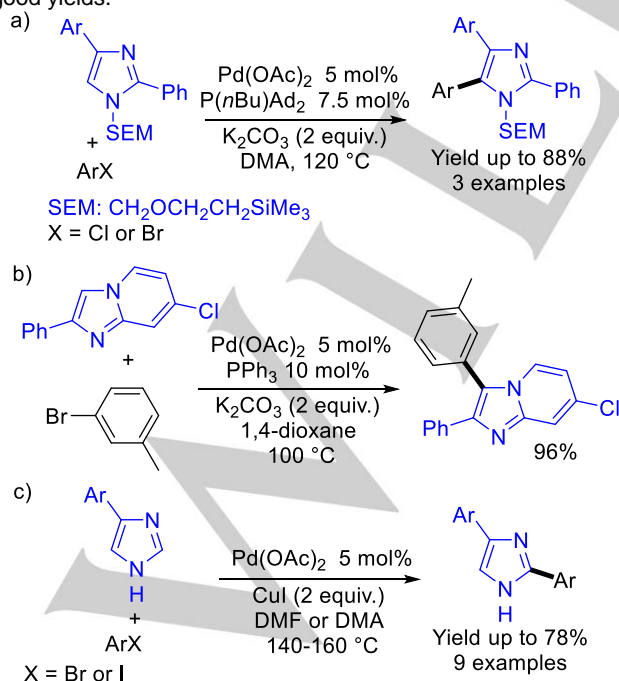
The Ru-catalyzed arylation of the aryl moiety of 4-arylimidazoles has not been reported so far, but an example of arylation of the

aryl group of a 2-arylimidazo[1,2-*a*]pyridine has been reported by Larrosa et al. in 2018 (Scheme 31).^[44b] They employed a cyclometalated ruthenium catalyst and 1-bromo-3,5-xylene as aryl source. The arylation occurred only on the benzene ring providing the diarylated 2-arylimidazo[1,2-*a*]pyridine in 83% yield.



Scheme 31. Ru-catalyzed direct arylations of the aryl unit of a 2-arylimidazo[1,2-*a*]pyridine.

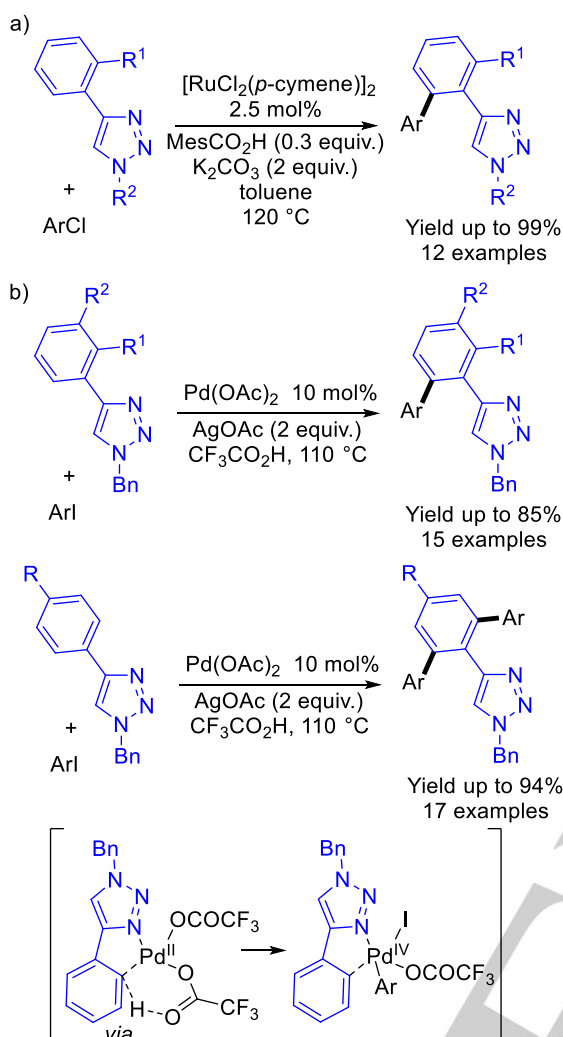
The Pd-catalyzed C5-arylation of C2,C5-unsubstituted 4-arylimidazoles has not been reported, but Sames et al. described three examples of C5-arylation of 2,4-diarylimidazoles (Scheme 32, a).^[39] The 2,4,5-triarylimidazoles were obtained in good yields using Pd(OAc)₂/P(*n*Bu)Ad₂ as the catalyst. The arylation of the heteroaryl unit of 2-arylimidazo[1,2-*a*]pyridine via Pd-catalysis has also been reported by several groups. For example, Berteina-Raboin et al. employed a 2-phenylimidazo[1,2-*a*]pyridine and Pd(OAc)₂/PPh₃ catalyst to prepare a 2,3-diarylimidazo[1,2-*a*]pyridine (Scheme 32, b).^[57] During the course of their studies on the arylation of imidazoles, Bellina et al. studied the reactivity of 4-arylimidazoles (Scheme 32, c).^[58] In the presence of Pd(OAc)₂ catalyst and CuI as additive they succeeded to arylate regioselectively the C2-position; whereas, the C5-position remained untouched. Moreover, the desired 2,4-diarylimidazoles were obtained in good yields.



Scheme 32. Ru- or Pd-catalyzed direct arylations of 4-arylimidazoles.

5.4. 4-Aryl-1,2,3-triazoles

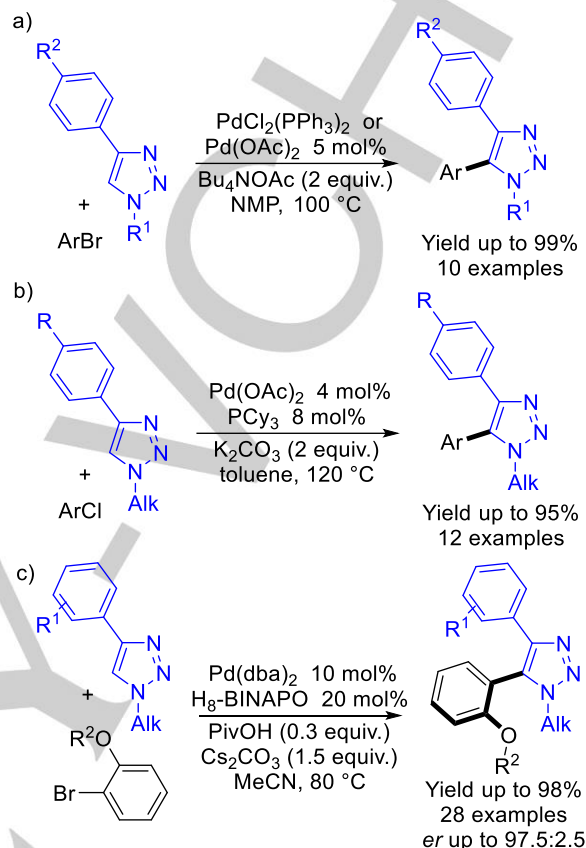
The arylation of the aryl substituent of 4-aryl-1,2,3-triazoles has been reported by Ackermann in 2010 using [RuCl₂(*p*-cymene)]₂ catalyst.^[59a,b] The monoarylated products were selectively obtained with both *ortho*- and *meta*-substituted 4-aryl-1,2,3-triazoles; whereas with phenyl or *para*-substituted aryls on the triazole ring, the two *ortho*-positions of the aryl were arylated (Scheme 33, a). In 2017, Jiang et al. reported a Pd-catalyzed direct C–H arylation of the aryl ring of 4-aryltriazoles (Scheme 33, b).^[59c] For this reaction they employed AgOAc base and trifluoroacetic acid as the solvent. The monoarylated products were selectively formed when the 4-aryltriazole derivative bearded either an *ortho*- or a *meta*-substituent on the aryl. Conversely, again the diarylated aryls were obtained with *para*-substituted aryls. The use of a silver base associated to a carboxylic acid as solvent had been previously used to control the arylation on the aryl of 1-arylpyrazole (see scheme 3). The authors proposed a possible Pd(II)/Pd(IV) mechanism for this arylation reaction. First, coordination of the 1,2,3-triazole to a Pd(II) species followed by C–H bond cleavage forms a five-membered palladacycle. Trifluoroacetate likely participates in the proton abstraction. Then, oxidative addition of ArI generates a Pd(IV) species. Finally, a reductive elimination produces the arylation product with regeneration of Pd(II).



Scheme 33. Pd- or Ru-catalyzed direct arylations of the aryl unit of 4-aryl-1,2,3-triazoles.

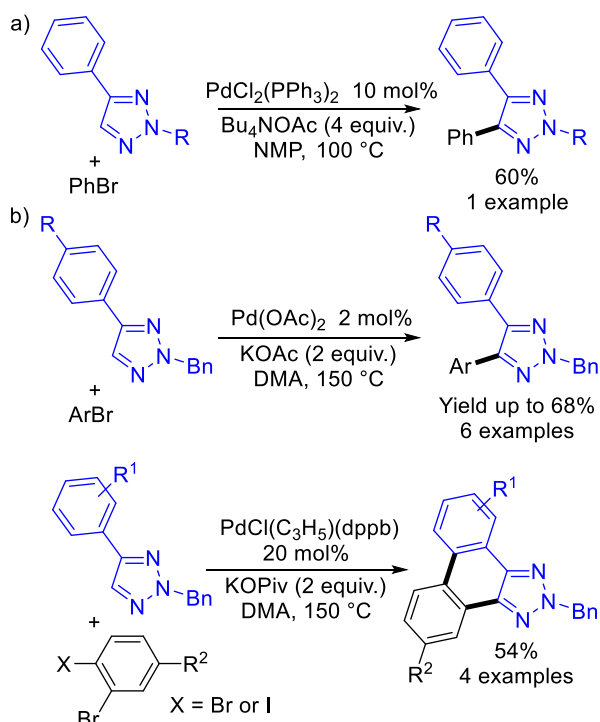
Pd-catalysis is also very effective to promote the C5-arylation of 4-aryl-1,2,3-triazoles and several procedures have been reported. The first one was described by Gevorgyan's group in 2007 who employed $\text{Pd}(\text{OAc})_2$ or $\text{PdCl}_2(\text{PPh}_3)_2$ catalysts in the presence of 2 equiv. of Bu_4NOAc and aryl bromides as aryl source (Scheme 34, a).^[25] The arylation occurred regioselectively at the C5-position of the triazole unit in high to very high yields. One year later, Ackermann et al. extended the reaction to aryl chlorides using $\text{Pd}(\text{OAc})_2/\text{PCy}_3$ as catalytic system with K_2CO_3 base (Scheme 34, b).^[26a] The reaction tolerated electron-withdrawing or -donating substituents on the aryl chloride. In 2020, Farinola et al. reported the direct arylation of 4-aryl-1,2,3-triazoles in 45–78% yields in solvent free conditions with Pd/C as heterogeneous catalyst.^[60] The same year, Baudoin, Cramer et al. described the first enantioselective arylation of 4-aryl-1,2,3-triazoles. They employed a Pd(0) complex associated to H8-BINAPO as chiral ligand to obtain the C5-arylated triazoles in excellent yields and very high enantioselectivities (Scheme 34, c).^[61] They also employed this procedure for the C5-arylation of 4-arylpyrazoles. A k_H/k_D value

indicated that the C–H bond cleavage is the rate-limiting step of this reaction. As the carboxylic acid co-catalyst had an influence on the reaction rate but not on the enantioselectivity, the authors assumed that this reaction likely operates *via* a CMD mechanism.



Scheme 34. Pd-catalyzed direct C5-arylations of 4-aryl-1,2,3-triazoles.

In 2008, Fokin et al. studied the direct arylation of a compound containing a 2-substituted 4-phenyl-1,2,3-triazole unit (Scheme 35, a).^[62a] They employed $\text{PdCl}_2(\text{PPh}_3)_2$ as the catalyst and Bu_4NOAc as the base and obtained the 4,5-diarylated triazole in 60% yield. Our group also reported a procedure for the C5-arylation of 2-substituted 4-aryl-1,2,3-triazoles (Scheme 35, b).^[62b] Using only 2 mol% of phosphine-free $\text{Pd}(\text{OAc})_2$ catalyst and KOAc as base, the 4-aryl-2-benzyl-1,2,3-triazoles were arylated at C5-position affording a wide variety of symmetrical and non-symmetrical 4,5-diaryl-2-benzyl-1,2,3-triazoles in good yields. This new C–H arylation method was applied to the synthesis of π -extended phenanthro[9,10-*d*][1,2,3]triazoles *via* Pd-catalyzed intermolecular arylation associated to an intramolecular C–H bond arylation using dihalobenzenes as reaction partners. Conversely, the arylation of the aryl unit of 4-aryl-1,2,3-triazoles has not been reported so far.



Scheme 35. Pd-catalyzed direct C5-arylations of 4-aryl-1,2,3-triazoles.

6. Conclusion

In summary, in several cases, the metal-catalyzed C-H bond functionalization for the arylation of (hetero)arenes is not limited to only one “most reactive” C-H bond of the substrates. For several aryl-substituted azoles, the use of the appropriate metal source as catalyst allowed to control the site selectivity of the C-H functionalization resulting in regiodivergent arylations. Palladium and copper catalysts are very effective to promote the direct arylation of azole rings. Conversely, the direct arylation using ruthenium and rhodium catalysts generally relies on the coordination of an heteroelement such as nitrogen to the metal which promotes the formation of a C-C bond at *ortho*-position(s) of the aryl ring of aryl-substituted azoles. Therefore, metal-catalyzed direct arylation now represents a powerful method to access substituted azoles arylated at different positions. However, many challenges remain. For several aryl-substituted azoles, only the arylation of the heteroaryl ring has been reported. Moreover, for several reactions more efficient catalysts allowing lower catalyst loadings and providing higher yields need to be discovered in order to provide more economically attractive procedures. Concerning the various mechanisms which are involved allowing to control regiodivergent arylations, several questions remain unanswered. Therefore, a better understanding of the mechanisms involved in these couplings would certainly allow to improve further the scope of such reactions.

Linhao Liu was born in P.R. China. He currently works towards a PhD degree of University of Rennes 1 under the supervision of Dr. Henri Doucet. He received a grant from the China Scholarship Council (CSC) in 2019. His work focuses on the C-H bond functionalization using palladium catalysis.



Manisha Durai was born in India. She joined the international master's program “Catalysis, Molecules and Green Chemistry” in the University of Rennes 1 (France) in 2021. She performs her master's research training with Dr. V. Guerchais and Dr. H. Doucet. Her work focuses on the C-H bond functionalization using palladium catalysis.



Henri Doucet received his PhD in chemistry working with Prof. P. H. Dixneuf and Dr. C. Bruneau at Rennes 1 University (France) in 1994. After post-doctoral appointments at Oxford university (UK) with Prof. J. M. Brown; and Nagoya university, (Japan) with Prof. R. Noyori, he moved to the University of Marseille (France) as CNRS researcher in the group of Prof M. Santelli. In 2006 he moved to Rennes 1 University. His research interests include organic synthesis by metal-catalyzed processes and green chemistry.



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Keywords: Arylation • Azoles • C-H activation • Homogeneous catalysis • Regiodivergence

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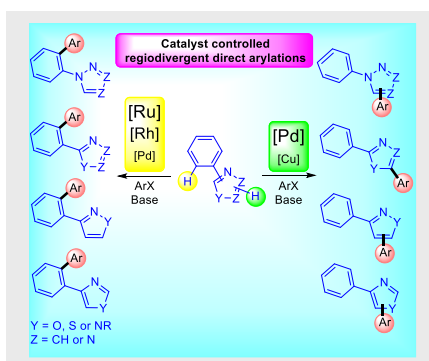
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REVIEW

Over the past decades, several examples of regiodivergent arylations of aryl-substituted azoles have been described. The nature of the metal catalyst was found to be the key factor to control the regioselectivity. In this review, we summarize the current procedures allowing to perform such regiodivergent arylations.



Linhao Liu,^[a] Manisha Durai,^[a] and Henri Doucet^{*[a]}

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**Transition-Metal-Catalyzed
Regiodivergent C-H Arylations of
Aryl-Substituted Azoles**