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Selective Csp²-H Alkynylation of Five-membered HeteroarenesFabio Bellina^{*a}, Martina La Manna^a, and Elisabetta Rosadoni^a^aDipartimento di Chimica e Chimica Industriale, Università di Pisa, Pisa, Italy

ARTICLE HISTORY

Received:

Revised:

Accepted:

DOI:

Abstract: The functionalization of a Csp²-H bond of an heteroarene with an alkyne represent one of the most attractive procedure for the late-stage functionalization of the aromatic core, due to the structural characteristics and synthetic versatility given by a triple carbon-carbon bond. The aim of this review is to cover the most significant results reported in the literature regarding the synthesis of alkynyl-substituted five-membered heteroarenes by selective direct Csp²-H alkynylation with 1-haloalkynes and analogues, or by cross-dehydrogenative alkynylation (CDA) with terminal alkynes, without making use of directing groups.



Keywords: CH activation, dehydrogenative coupling, inverse Sonogashira coupling, selectivity, heteroarenes, palladium catalyst, azoles.

1. INTRODUCTION

The functionalization of the Csp²-H bond is one of the main research topics in the world of organic chemistry today, since this bond is ubiquitously present in organic compounds and is, therefore, a potential reactive center for the simple construction of new carbon-carbon or carbon-heteroatom bonds. However, this issue is also among the most complex to be addressed, since the reactivity of C-H bonds is usually very limited due to the high energy required for their breaking (about 110 kcal mol⁻¹ for an aromatic Csp²-H).

For decades, traditional Friedel-Crafts reactions have been a fundamental pillar for the functionalization of the Csp²-H (hetero)aromatic bond, while suffering from limited general applicability since they allowed only the introduction of alkyl or acyl groups on the aromatic ring. These groups have, as is well known, not only activating or deactivating effects but also a significant influence as directing groups in orienting subsequent functionalization only in specific positions. This, as a result, limits the variety of products potentially obtainable through selective functionalization of each Csp²-H bond present on the (hetero)aromatic nucleus.

To date, most functionalizations of (hetero)aromatic systems are achieved through the use of methods that require a pre-activation of a sp² carbon atom by halogenation or metallation. Among these, the reactions of Suzuki,[1-7] Negishi,[8-10] and Migita-Stille[11-14] foresee the creation of the new C-C bond by cross-coupling of organic halides with organometallic compounds in the presence of catalysts based on transition metals.[15-17] These procedures, although often characterized by high efficiency and selectivity, have two significant disadvantages: a) the activation of both reagents, which leads to an increase in the stages of the synthetic sequence, and b) the nature and quantity of reaction waste, which is detrimental to the atom economy of the entire synthetic process.

The logical alternative to synthetic strategies based on the double pre-activation should be the development of methods that directly involves the functionalization of the σ C-H bond of one or both partners.

In the activation of a single C-H bond, a pre-activated substrate, such as an organic halide or organometallic reagent, takes part in a cross-coupling reaction involving a C-H bond of the reaction partner. Such an example, the Mizoroki-Heck alkenylation[18-20] belongs to this specific class of reactions, because it allows the formation of C-C bonds by reaction of

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(hetero)aromatic halides with alkenes. It must be noted, however, that the advantage of being able to use directly an organic reagent without first having to pre-activate it (in this case turning it into an organometallic compound) is still associated with some disadvantages, including a not always high selectivity due to the presence of multiple potentially reactive C-H bonds.

The possibility of forming new σ carbon-carbon bond through the double activation of two distinct carbon-hydrogen bonds through an oxidative cross-coupling reaction promoted by transition metals, represents, at least ideally, the best synthetic approach. This class of reactions, which takes also (more correctly) the name of cross-dehydrogenative coupling (CDC), [21-24] turns out to be very attractive, since no pre-activation stage of reagents, such as the halogenation or metalation of the carbon atoms involved in the formation of the new bond, is necessary. This naturally leads not only to an economic advantage, since synthetic stages are less because fewer reagents are used, but also to an ecological benefit, since potentially toxic waste is reduced. However, these undeniable advantages can be associated with low selectivity, particularly in intermolecular cross-couplings, so accurate optimization of the entire reaction system (coupling partner, catalyst, additives, oxidants, solvent, temperature and reaction time) is necessary to ensure the desired efficiency and selectivity.

The development of methods for the activation of Csp²-H (hetero)aromatic bonds is of particular relevance in the pharmaceutical field, where such approaches can be advantageously used in a synthetic strategy called Late-Stage Functionalization (LSF). The concept of using the functionalization of C-H bonds to obtain several analogues of a complex molecule in the last synthetic stage was first proposed in 1973 by the Breslow and co-workers [25] but only recently, with the advent of new procedures for the functionalization of C-H bonds operating under mild conditions and that can tolerate a wide variety of generally sensitive functional groups present in potentially active molecules and natural products, the LSF approach can be widely applied in drug discovery. [26, 27] According to Cernak and co-workers, [26] LSF protocols follow two distinct approaches, defined as *directed* and *innate*. *Directed* reactions achieve the desired selectivity through the use of directing groups or by exploiting steric hindrance, and also through molecular recognition. As regards *innate* reactions, the selectivity is obtained on the basis of the inherent different reactivity of the different C-H bonds of the coupling partners. In this case, the synthetic protocol is optimized in order to promote the reactivity of the C-H bond which is intrinsically more reactive based on its specific electronic properties (for example, the more acidic C-H bond).

Among the cross-coupling reactions involving Csp²-H (hetero)aromatic bonds potentially useful for LSF-based synthetic approaches, undoubtedly the alkynylation is one of the most interesting due to the structural characteristics and synthetic versatility given by a triple carbon-carbon bond. [28-35]

In this review we will then analyze *innate* LSF procedures that allow the preparation of alkynyl-substituted heteroarenes by selective alkynylation of heteroaromatic Csp²-H bonds. The choice to specifically examine the protocols involving 5-membered heteroarenes lies both in the general presence of these

nuclei as privileged scaffolds in natural products, pharmaceuticals and organic materials, and in the *innate* differentiation among the different C-H bonds induced by the presence of one or more heteroatoms.

2. DIRECT ALKYNYLATION WITH 1-HALOALKYNES OR GEM-DIHALOALKENES

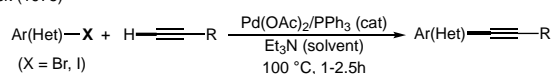
Thanks to its rigidity, its extraordinary electronic properties and the numerous methods available for its functionalization, the triple carbon-carbon bond of alkynes has always been one of the most important functional groups in organic chemistry. More generally, alkynes are important synthetic sources and structural elements in both material science and biological chemistry. [36] As a result, it is essential to have efficient and flexible methods for the construction of triple bonds in any position of a complex molecule, or alternatively, valid methods for the transfer of this important functional group.

If we wanted to functionalize a molecule by creating a new Csp²-Csp bond using a terminal alkyne, a textbook would certainly suggest converting it into the corresponding alkynilide by treatment with an appropriate base (via deprotonation, thanks to the relative high acidity of the terminal Csp-H bond), and then making it react with an appropriate organic electrophile. It is in fact possible, through the use of a transition metal catalyst, to obtain the alkynylation of (hetero)aromatic halides by in situ formation of acetylide anions in catalytic amounts. Specifically, in 1975 Cassar [37] and Heck [38] independently published two procedures for Pd-catalyzed alkynylation of aromatic or alkenyl halides in the presence of organic or inorganic bases (Eq. 1 and 2, Scheme 1).

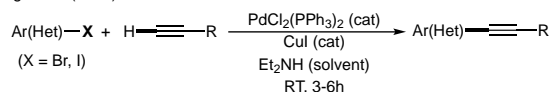
(1) Cassar (1975)



(2) Heck (1975)



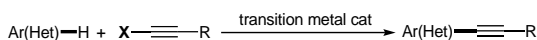
(3) Sonogashira (1975)



Scheme 1. Pd-catalyzed classical alkynylation reactions of (hetero)aryl halides, according to Cassar, [37] Heck, [38] and Sonogashira. [39]

A short time later, Sonogashira and co-workers showed how the addition of a catalytic amount of CuI salt as a co-catalyst significantly accelerated the reaction rate (Eq. 3, Scheme 1). [39] These conditions, now generally known as Sonogashira cross-coupling, see an organic halide react with a terminal alkyne in the presence of a transition metal catalyst, generally based on Pd, a Cu (I) salt as co-catalyst, and an amine. [40-42]

Recently, the development of a complementary strategy, called "direct alkynylation" or even "inverse Sonogashira coupling", which involves the direct alkynylation of Csp²-H bonds of (hetero)arenes with alkynyl halides (Scheme 2) has gained much interest. [33, 43-49]

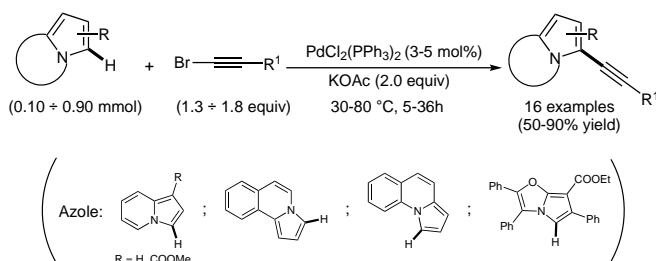
**Scheme 2.** Direct alkynylation or “inverse” Sonogashira coupling.

This approach, which, among other things, dramatically reduces the formation of by-products resulting from the homocoupling of the alkyne typical of classical Sonogashira,[40-42] is in all respects a reaction of functionalization of Csp²-H (hetero)aromatic bonds. Alkynyl halides are the main and certainly the most logical choice for the realization of this type of coupling. However, the sp-hybridization of the triple bond gives low reactivity to these reagents, and it is only with the introduction of the catalysis by transition metals that they have shown their full potential.

The following paragraphs summarize the most significant results obtained in the field of direct alkynylation of heteroarenes, classifying them according to the nature of the catalytically active transition metal.

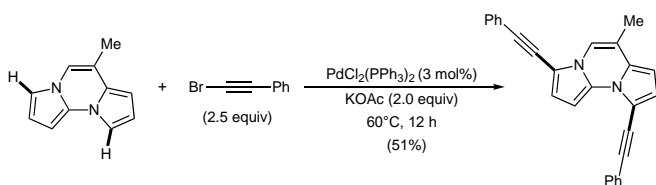
1.1. Palladium-catalyzed direct alkynylation

In 2007 Gevorgyan and co-workers developed a protocol for the direct alkynylation of *N*-fused azoles with bromoalkynes.[50] In the presence of PdCl₂(PPh₃)₂ as the catalyst precursor, KOAc as the base in toluene at 80 °C, electron-rich indolizine, pyrroquinoline, pyrroloisquinoline, pyrrolooxazole, and bis-pyrrolo-pyrimidine were regioselectively alkynylated with bromoalkynes, furnishing the required derivatives in 56-98% isolated yields (Scheme 3).

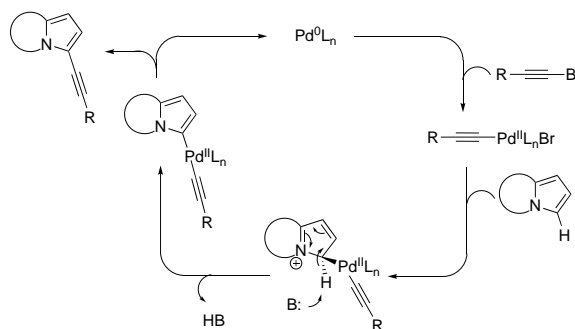
**Scheme 3.** Gevorgyan's protocol for the Pd-catalyzed direct alkynylation of azoles.[50]

This alkynylation reaction also demonstrated a remarkable tolerance toward functional groups at the bromoalkyne. Indeed, bromoalkynes possessing alkyl, aryl, alkenyl, TMS, and ester groups, were nearly equally efficient in direct alkynylation (Scheme 3). In contrast, chloro and iodo alkynes resulted scarcely efficient when compared to their bromo counterparts, providing only trace amounts of the required alkynylated heteroarenes.

Notably, 6-methyldipyrrolopyrimidine underwent double fold alkynylation with excess alkynyl bromide to furnish the required bis-alkynylated compound in 51% isolated yield (Scheme 4).

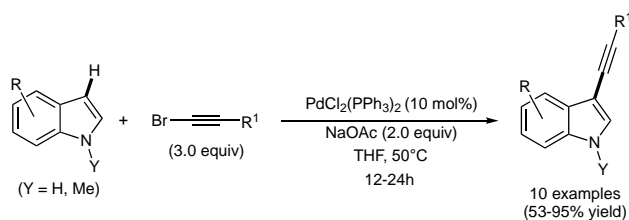
**Scheme 4.** Pd-catalyzed double alkynylation of 6-methyldipyrrolopyrimidine.[50]

Taking into account that the alkynylation regioselectively occurred at the most electron-rich C3-position of the fused azoles, and that a kinetic isotope effect of 1.15 was observed when the alkynylation was carried out with ethyl indolizine-2-carboxylate-3-*d*, the authors proposed an electrophilic substitution pathway, similarly to that previously suggested for the direct C-H arylation of electron-rich heteroarenes with aryl halides (Figure 1).[51-54]

**Figure 1.** Gevorgyan's mechanistic proposal for the Pd-catalyzed direct alkynylation of azoles.[50]

In detail, the mechanism involves a nucleophilic attack of the most electron-rich C-3 position of azole at alkynylpalladium intermediate to form an iminium intermediate. Deprotonation of the latter furnishes the Pd(II) intermediate, which upon reductive elimination produces alkynyl azole (Figure 1).[50]

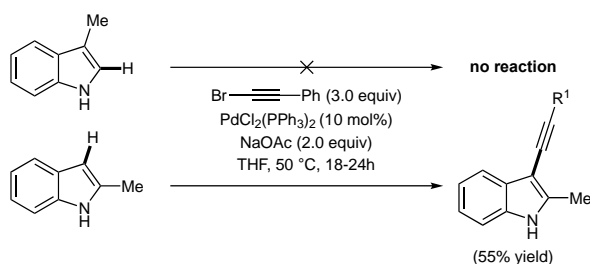
Two years later, Gu and Wang extended the PdCl₂(PPh₃)₂-catalyzed procedure developed by Gevorgyan to the regioselective C-3 alkynylation of indoles.[55] Using NaOAc as the base instead of KOAc, unprotected indoles and 1-methylindole were converted into the corresponding 3-alkynylindoles by reaction with alkynyl bromides at 50 °C in THF (Scheme 5).

**Scheme 5.** Pd-catalyzed C-3 alkynylation of indoles.[55]

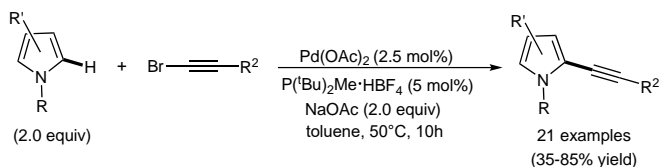
The authors evidenced that the adopted reaction conditions are insensitive to air or humidity and allow to carry out easily the coupling using unpurified THF.

Aryl- or alkenyl-substituted bromoalkynes gave the required alkynylated indoles in good isolated yields, but when the coupling was carried out using 1-bromo-1-octyne as a typical alkyl-substituted bromide the desired product was not observed, and only the 1,3-diyne derived from homocoupling of the alkynyl bromide was detected in the crude reaction mixture.

The observed C-3 regioselectivity was high (>20:1) but when C-3 was blocked (for example, in 3-methylindole), no C-2 substituted product was observed, while when C-2 was blocked (for example, in 2-methylindole), the required C-3 alkynylated indole was obtained in moderate yield (Scheme 6).

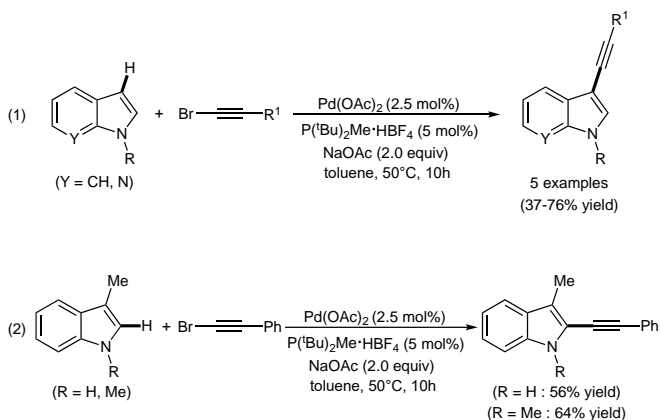
**Scheme 6.** Pd-catalyzed alkylation of 2-methylindole.[55]

As part of their efforts in developing new procedures for the regioselective synthesis of bioactive heteroarenes, Brachet and Belmont devised a mild and general method for the alkylation of pyrroles, indoles and 7-azaindole with alkynyl bromides.[56] A preliminary study made using 1-methylpyrrole and 1-bromophenylacetylene allowed to identify 2.5 mol% of $\text{Pd}(\text{OAc})_2$ with 5.0 mol% of $\text{P}(t\text{-Bu})_2\text{Me}\cdot\text{HBF}_4$ and NaOAc (2 equiv) in toluene at 50 °C for 10 h as the optimal reaction conditions for the regioselective introduction of various alkynyl residues at the C-2 position of pyrroles (Scheme 7).

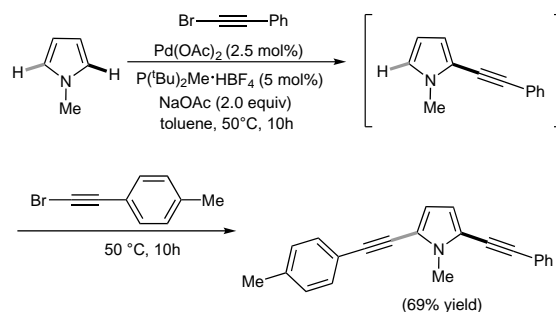
**Scheme 7.** Pd-catalyzed C-2 alkylation of pyrroles.[56]

In contrast, the authors noted that furane and thiophene were unreactive under the reaction conditions optimized for the alkylation of pyrroles, whatever the nature of the 1-bromoalkyne used.

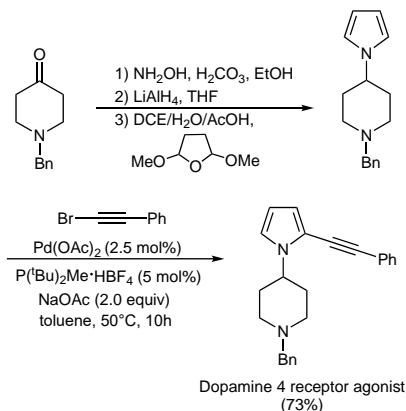
Interestingly, whereas the alkylation of selected unsubstituted indoles and 7-azaindole was obtained at their more nucleophilic C-3 position (Eq. 1, Scheme 8), an efficient C-2 alkylation was observed on C-3-substituted indoles unlike what had been previously described by Gu and Wang[55] (Eq. 2, Scheme 8).[56]

**Scheme 8.** Pd-catalyzed C-2 alkylation of indoles and 7-azaindole.[56]

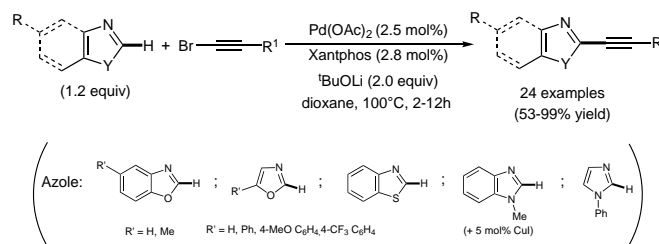
This methodology proved to be also effective for sequential one-pot double alkylation of pyrrole (Scheme 9).

**Scheme 9.** Pd-catalyzed C-2/C-5 sequential bis-alkylation of 1-methylpyrrole.[56]

The authors applied also this protocol to a short synthesis of a dopamine D-4 agonist, starting from commercially available 4-benzylpiperidine (Scheme 10).

**Scheme 10.** Synthesis of a dopamine D-4 receptor agonist.[56]

In 2010 Kim and Chang described the regioselective C-2 alkylation of several 1,3-azoles with bromoalkynes.[57] The optimized reactions conditions involved the use of $\text{Pd}(\text{OAc})_2/\text{Xantphos}$ as the catalyst system in dioxane at 100 °C, in the presence $t\text{-BuOLi}$ as the base (Scheme 11).

**Scheme 11.** Pd-catalyzed regioselective C-2 alkylation of 1,3-(benzo)azoles.[57]

The required 2-alkynylated azoles were isolated in 53-99% yield, using a range of alkyl-, alkenyl- and aryl-substituted bromoalkynes. The authors noted that the electronic nature of the aryl substituent in arylacetylenes exerted only a negligible effect on the reaction efficiency. Moreover, TIPS-substituted bromoacetylene, a precursor of terminal alkynes, was successfully reacted with all the azoles tested, giving high yields of the required C-2 products. Notably, when iodophenylacetylene was used as the reaction partner a lower yield was observed, while negligible amounts of the required 2-alkynylazoles were observed when the coupling was carried out with the analogous chlorophenylacetylene.

As regards the azoles, oxazoles, benzoxazoles, 1-methylbenzimidazole and 1-phenylimidazole resulted reactive under the optimized reaction conditions, while benzothiazole required a Cu(I) co-catalyst, CuI, when reacted with bromophenylacetylene.

On the basis of precedent reports on the C-H activation of heteroarenes, and on the negligible primary isotopic effect observed in the alkylation of *d*-labeled 5-methylbenzoxazole, the authors suggested that the electrophilic addition of the C-2 deprotonated azole to the Pd(II) acetylide complex (arising from the oxidative addition of the bromoalkyne to the Pd(0) catalyst) may be the relevant mechanistic step (Figure 2).

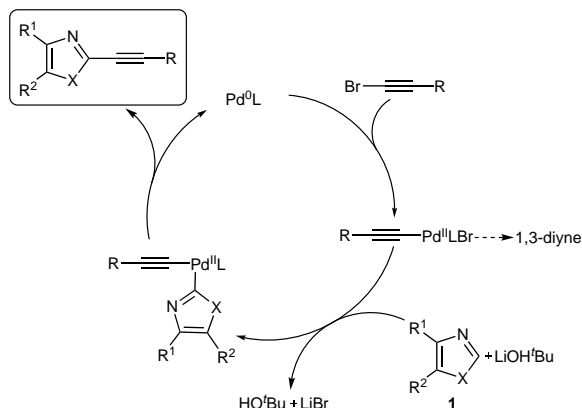
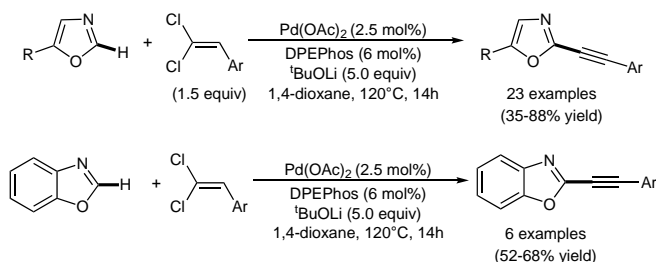


Figure 2. Plausible mechanism for the Pd-catalyzed direct C2 alkylation of azoles.[57]

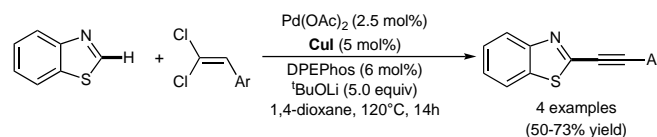
The success of the use of 1-bromoalkynes as organic electrophiles in direct alkylation reactions is also due to the mild and convenient methods that have been developed for their preparation.[43] However, these compounds are also relatively unstable, and 1,1-dihaloalkenes have recently been proposed as alkylation reagents.

In this context, through the use of moisture-stable 1,1-dichloroalkenes Ackermann and coworkers successfully performed the direct C-2 alkylation of 5-(hetero)aryloxazoles and benzoxazole using a catalytic system consisting of Pd(OAc)₂ in combination with the bidentate ligand DPEPhos, *t*-BuOLi as the base in 1,4-dioxane at 120 °C for 14h (Scheme 12).[58]



Scheme 12. Pd-catalyzed regioselective alkylation of (benzo)oxazoles with 1,1-dichloroalkenes.[58]

The Pd-catalyzed direct C-H bond alkylation of benzothiazole with 1,1-dichloroalkenes was found to be possible as well, provided that CuI was employed as co-catalyst (Scheme 13).

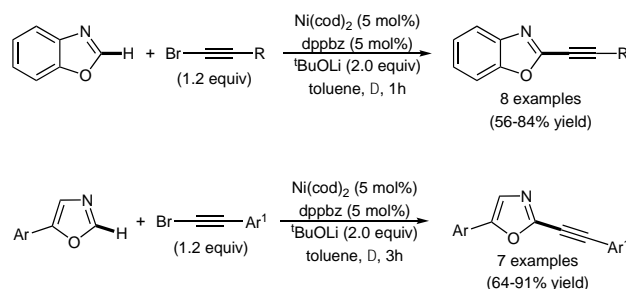


Scheme 13. Pd/Cu-catalyzed regioselective alkylation of benzothiazole with 1,1-dichloroalkenes.[58]

1.2. Nickel-catalyzed direct alkylation

The direct functionalization of C-H bonds using nickel catalyst has recently received great attention due to the lower cost of this catalysis when compared to the methodologies that use late noble transition metals such as palladium.[59-61]

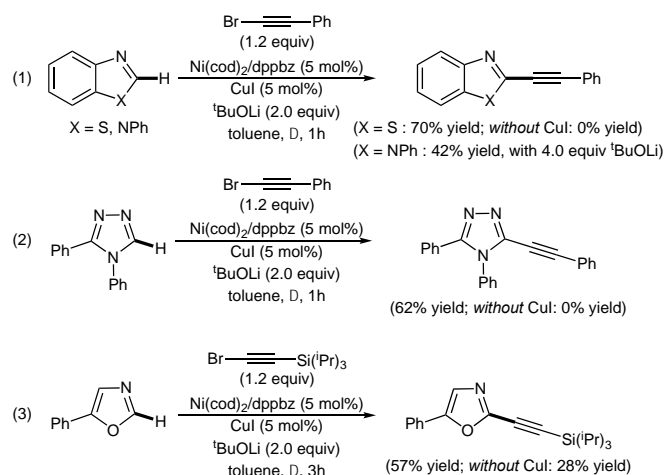
On this basis, in 2009 Miura and co-workers disclosed for the first time a procedure for the nickel-catalyzed direct alkylation of azoles with 1-alkynyl bromides. Using equimolar amount of Ni(cod)₂ and 1,2-bis(diphenylphosphino)benzene (dppbz) as the catalyst system in refluxing toluene, benzoxazole and 5-aryloxazoles were selectively alkylated at their C-2 position in the presence of *t*-BuOLi as the base (Scheme 14).[62]



Scheme 14. Ni-catalyzed direct alkylation of benzoxazoles and 5-aryloxazoles.[62]

The selected reaction conditions allowed not only the use of aryl- and alkenyl-substituted 1-alkynyl bromides as electrophilic partners, but also an otherwise scarcely reactive alkynyl bromide bearing an aliphatic substituent participated in the direct coupling.

While the standard conditions elaborated by the authors resulted ineffective in the alkylation of benzothiazole, the addition of CuI as a co-catalyst improved dramatically the yield (Eq. 1, Scheme 15). Moreover, the Ni/Cu catalyst system allowed the alkylation of 1-phenylbenzimidazole and 3,4-diphenyl-4*H*-1,2,4-triazole (Eqs. 1 and 2, Scheme 15), and improved the efficiency of the alkylation of 5-phenyloxazole with 1-bromo-tri(*i*-Pr)Siacetylene (Eq. 3, Scheme 15).



Scheme 15. Ni/Cu-catalyzed direct alkylation of azoles.[62]

As regards the mechanism, the authors suggested a Ni(0)/Ni(II) cycle that begins with the oxidative addition of the 1-bromoalkyne to Ni(0) complex, affording the corresponding Ni(II) intermediate which is then involved in the transmetalation step with 2-lithium- (or 2-copper-) azole generated in situ from the azole and the base. The reductive elimination closes the cycle regenerating Ni(0) complex and providing the required coupling product (Figure 3).

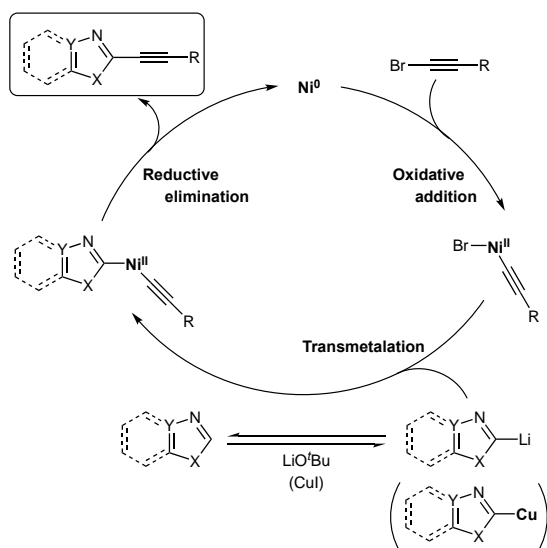
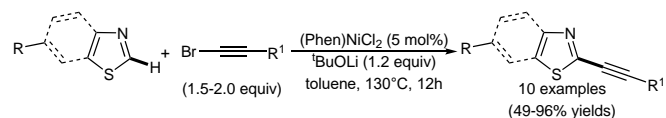


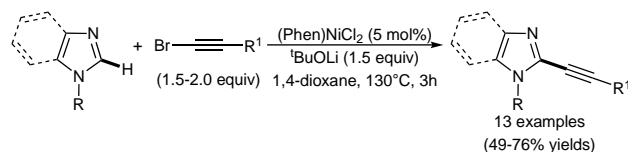
Figure 3. Plausible mechanistic pathway for the Ni/Cu-catalyzed direct alkylation of azoles, according to Miura and co-workers.[62]

In 2018 Patel and Punji reported an improved procedure for the Ni-catalyzed C-2 direct alkylation of (benzo)thiazoles, that does not require a copper co-catalysis.[63] Using the same base/solvent system developed by Miura and co-workers, i.e. *t*-BuOLi/toluene, but replacing the Ni(0)/dppbz pre-catalyst with the air stable (Phen)NiCl₂ the authors were able to efficiently obtain the required 2-alkynyl(benzo)thiazoles in moderate to good yields (Scheme 16).



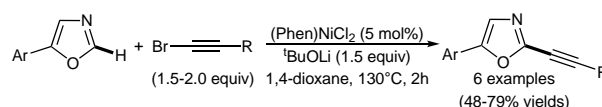
Scheme 16. Ni-catalyzed direct alkylation of (benzo)thiazoles.[63]

The use of toluene as the reaction solvent resulted to be not the best choice when (benzo)imidazoles were employed as the coupling partners. In this solvent a partial decomposition of the substrate or of the alkynylated product was observed, but better yields were obtained when the alkylation was performed in 1,4-dioxane (Scheme 17).



Scheme 17. Ni-catalyzed direct alkylation of (benzo)imidazoles.[63]

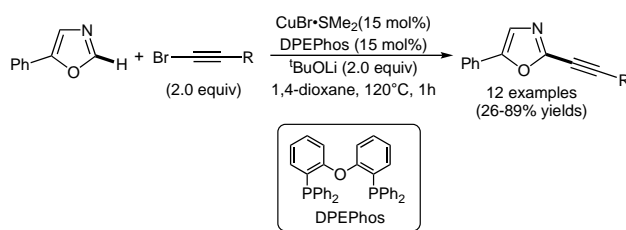
This last reaction conditions proved to work also for the C-2 alkylation of 5-aryloxazoles (Scheme 18).



Scheme 18. Ni-catalyzed direct alkylation of 5-aryloxazoles.[63]

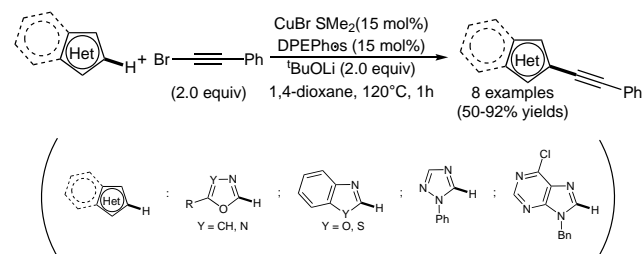
1.3. Copper-catalyzed direct alkylation

In 2009 Besselièvre and Piguel developed an efficient and general method for the direct C-2 alkylation of 5-phenyloxazole with alkynyl bromides that benefits from the minimal cost and low toxicity of copper used as the only catalyst.[64] The optimized reaction conditions involved the use CuBr·SMe₂ and bis[(2-diphenylphosphino)phenyl] ether (DPEPhos) as the catalyst system and *t*BuOLi as the base in 1,4-dioxane at 120°C (Scheme 19).



Scheme 19. Cu-catalyzed direct alkylation of 5-phenyloxazole.[64]

The same protocol was successfully applied to the regioselective alkylation of different azoles, using bromophenylacetylene as the coupling partner (Scheme 20)



Scheme 20. Cu-catalyzed direct alkylation of azoles.[64]

It is worth mentioning that azoles displaying high pK_a values (≥30),[65] such as imidazoles, resulted scarcely reactive under their optimized reaction conditions, while benzoxazoles, benzothiazoles, oxazoles and triazoles gave satisfactory

yields. The acidity of the reactive C-H bond and not the nucleophilicity of the same position hence appears to be the determining factor for the effectiveness of this Cu(I)-catalyzed coupling.

Although the authors admitted that they did not have enough information to propose a detailed mechanism, they nevertheless considered plausible the Cu(I)/Cu(III) catalytic cycle summarized in Figure 4.[64]

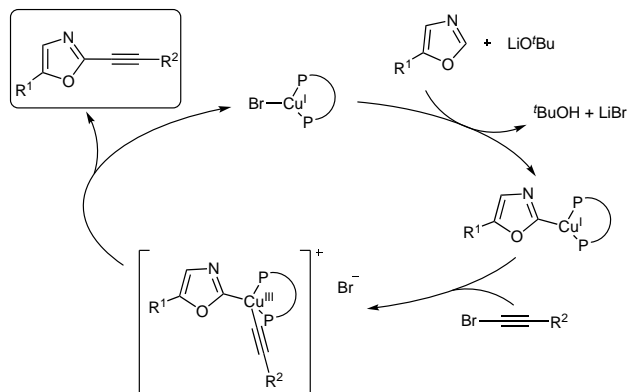
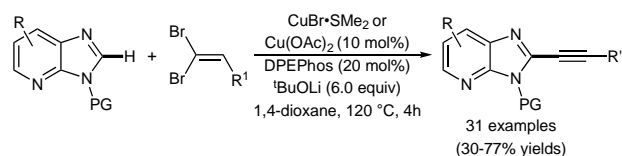


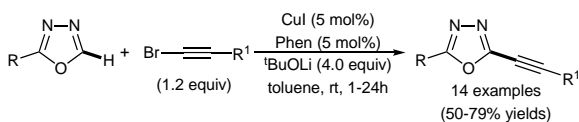
Figure 4. Plausible catalytic cycle for the Cu(I)-catalyzed direct alkylation of oxazoles, as proposed by Besselièvre and Piguel.[64]

Six years later, Piguel and co-workers extended their Cu(I)-catalyzed protocol to the direct C-2 alkylation of 3H-imidazopyridines but using stable and readily available *gem*-dibromoalkenes as the alkyne source.[66] Moderate to satisfactory isolated yields of the required coupling products were obtained using the cheap copper(I) pre-catalysts CuBr•SMe₂ or Cu(OAc)₂ (Scheme 21).



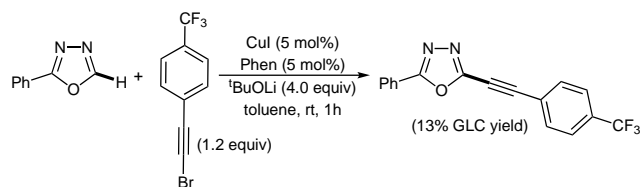
Scheme 21. Cu/DPEPhos-catalyzed direct C-2 alkylation of imidazopyridines.[66]

In 2010 Miura and co-workers reported the room temperature direct alkylation of 2-aryl- and 2-alkyl-1,3,4-oxadiazoles with alkynyl bromides in the presence of a copper(I) catalyst consisting of CuI and Phen, and using (once again) *t*-BuOLi as the base in toluene as the reaction solvent (Scheme 22).[67]



Scheme 22. Cu/Phen-catalyzed direct alkylation of 2-substituted 1,3,4-oxadiazoles.[67]

In general, satisfactory isolated yields were obtained irrespective of the C-2 substituent on the azole nucleus and of the electronic and steric nature of the bromoalkyne, with the sole exception of the coupling involving 2-phenyl-1,3,4-oxadiazole and the electron deficient 1-(bromoethynyl)-4-(trifluoromethyl)benzene, that gave the required derivative in a poor 13% GLC yield (Scheme 23).[67]

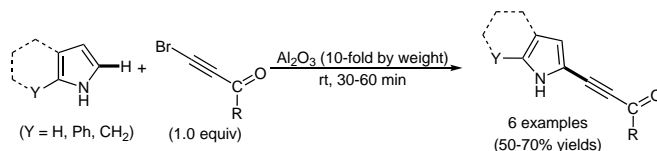


Scheme 23. Cu/Phen-catalyzed direct alkylation of 2-phenyl-1,3,4-oxadiazole with 1-(bromoethynyl)-4-(trifluoromethyl)benzene.[67]

1.4. Mechanochemical direct alkylation on metal oxides active surfaces

In the last two decades Trofimov's research team reported a series of interesting papers on the development of solvent-free procedures for the direct alkylation of pyrroles with 1-acylbromoacetylenes that made use of aluminum oxide (Al₂O₃) and other metal oxides as a solid active reaction medium.[68-70] The experimental procedures simply involved mixing the two reagents and metal oxide, and grinding the solid mixture thus obtained in a mortar at room temperature.

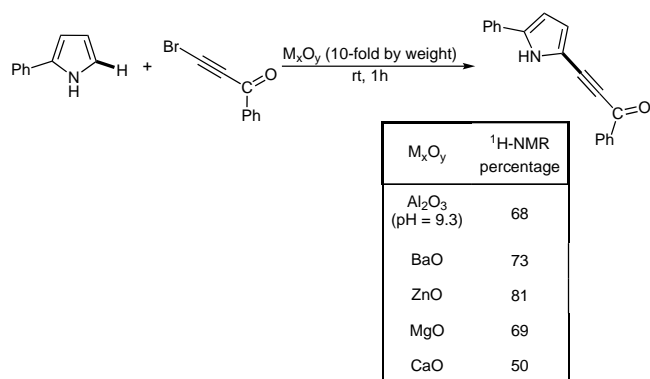
In their first paper, published in 2004, they described the regioselective alkylation of pyrrole, 4,5,6,7-tetrahydroindole and 2-phenylpyrrole with 1-acylbromoacetylenes using a 10-fold amount of Al₂O₃ (Scheme 24).[68] The reaction was carried out by grinding the solid mixture for 30-60 min at room temperature, and the required alkynylpyrroles were isolated in 50-70% yield.



Scheme 24. Trofimov's protocol for the direct C-H alkylation of azoles with acylbromoacetylenes.[68]

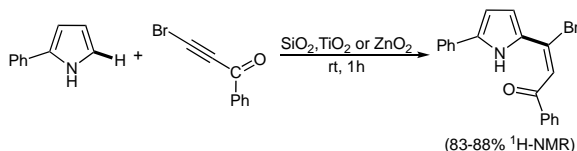
Unfortunately, when 1-bromophenylacetylene was reacted with 2-phenylpyrrole or tetrahydroindole under the same conditions summarized in Scheme 24, no coupling products were observed, and the starting materials were recovered unaltered. The authors concluded that this methodology is limited to alkynes bearing a carbonyl functional group, and this limitation was confirmed by subsequent studies.

Apart from Al₂O₃, other metal oxides proved to be active in promoting the solid-phase synthesis of alkynylpyrroles. In a study devoted to the evaluation of the efficacy of oxides of Mg, Ca, Zn, Ba, Al, Si, Ti and Zr they found that ZnO and BaO were more active than Al₂O₃ itself.[69] In fact, when 2-phenylpyrrole was grinded in a porcelain mortar for 1 h with a 10-fold amount of Al₂O₃ (pH 9.3), the percentage of the expected alkynylpyrrole in the crude reaction mixture was 68%, while when BaO or ZnO were used as solid promoters the percentages were 73% and 81%, respectively (Scheme 25).



Scheme 25. Direct alkylation of 2-phenylpyrrole promoted by metal oxides.[69]

In contrast, SiO₂, TiO₂ and ZrO₂ resulted totally ineffective in promoting the solvent-free alkylation of 2-phenylpyrrole, and the adduct deriving from the nucleophilic addition of pyrrole to the triple bond was detected as the main reaction product (Scheme 26).[69]



Scheme 26. Addition product obtained with metal oxides of Si, Ti, and Zn.[69]

As regards the plausible mechanism, through ESR studies the authors suggested that the alkylation of pyrroles with 1-acylbromoacetylenes could involve a single electron transfer (SET) step, delivering ion-radicals stabilized by the crystalline lattice of the active metal oxide surface (Figure 5).[69]

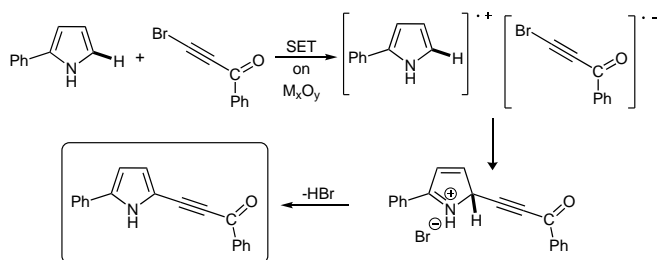
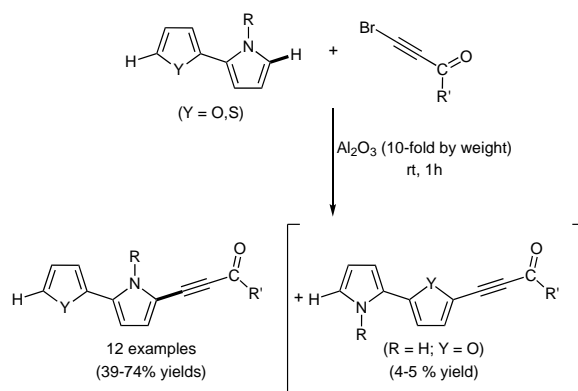


Figure 5. Plausible mechanism for the C-H alkylation of 2-phenylpyrrole, as suggested by Trofimov and co-workers.[69]

In order to check whether in addition to the pyrrole nucleus also furan and thiophene were reactive with 1-acylbromoacetylenes when grinded with solid Al₂O₃, the behavior of 2-furypyrroles and 2-thienylpyrroles was studied (Scheme 27).



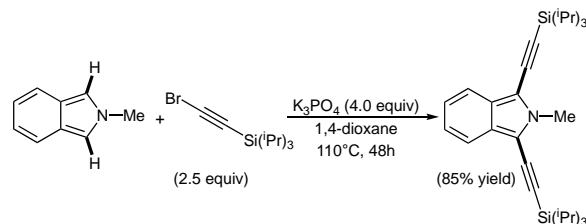
Scheme 27. Al₂O₃-Mediated C-H alkylation of 2-furypyrroles and 2-thienylpyrroles.[70]

The experimental results evidenced the higher reactivity of pyrroles ring when compared to furan and thiophene derivatives, and considering the mechanistic pathway previously suggested they are in agreement with the lower ionization potential of the pyrrole ring in respect to that of the other two heteroarenes. In fact, only the alkynylated products deriving from the alkylation of the pyrrole nucleus were obtained when 2-thienylpyrroles was used as heteroarenes. The same substitution patterns have also been observed as prevalent in the case of 2-furypyrroles, but here with the concomitant formation of products resulting from the alkylation of the furane ring in a ratio of 1:5-7 with the main products.

To conclude this paragraph it is worth mentioning that Sobenina and Trofimov published in 2020 a review dedicated to their transition metal-free “inverse Sonogashira coupling” methodology under mechanochemical conditions.[71]

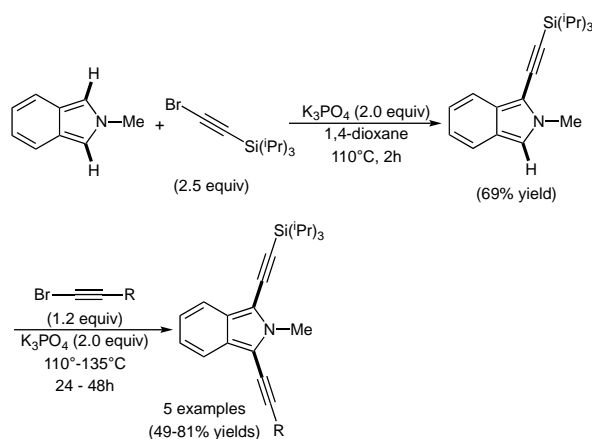
1.5. Metal-free direct alkylation

In a research dedicated to the synthesis and properties of isoindole derivatives, Ohmura, Sugimoto and co-workers found that 2-methylisoindole could be alkynylated with (bromoethynyl)triisopropylsilane simply by heating the two reactants in the presence of K₃PO₄ in dioxane, in the absence of any metal catalysts.[72] After 48h at 110 °C the double alkynylated product, i.e. 1,3-bis- (triisopropylsilyl)ethynyl-isoindole, was recovered in 85% isolated yield (Scheme 28).



Scheme 28. Metal-free cycloaddition-based formal alkylation of 2-methylisoindole.[72]

The authors also noted that the reduction of the reaction time to 2h allowed the selective formation of the 1-alkynyl substituted isoindole, which was isolated in 69% yield. The 1-alkynylisoindole thus obtained was then used in the preparation of unsymmetrical 1,3-dialkynylisoindoles by reaction with bromoalkynes (Scheme 29).[72]



Scheme 29. Synthesis of unsymmetrical 1,3-dialkynylisoindoles.[72]

Through detailed investigations it was found that the alkylation proceeds through an interesting mechanistic pathway that starts with a [4+2] cycloaddition reaction, followed by a ring-opening of the cycloadduct with elimination of HBr (Figure 6).[72]

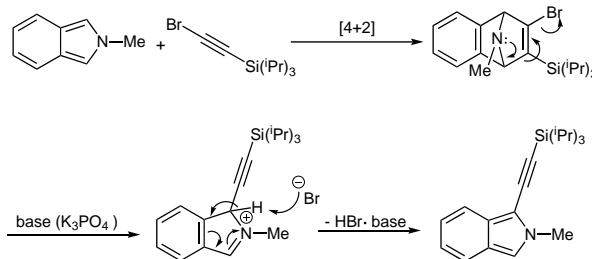


Figure 6. Proposed mechanism for the cycloaddition-based Formal C-H alkylation of isoindoles.[72]

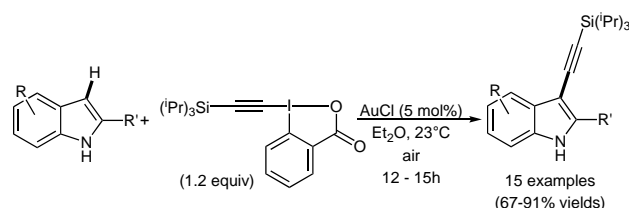
The authors suggested that the ring-opening with elimination of HBr could be probably accelerated by the β -effect of the silyl group.[73] This consideration is supported by the fact that bromoalkynes bearing phenyl or alkyl substituents did not give any C-H alkylation product, but only the [4+2] cycloaddition.

When 1-alkynylisoindole was submitted to a second alkylation, the [4+2] cycloaddition was not observed, even lowering the reaction temperature.[72]

3. DIRECT ALKYNYLATION WITH HYPERVALENT IODINE REAGENTS

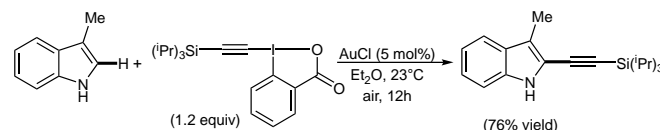
Hypervalent iodine reagents, given their high reactivity as electrophiles, are a valid alternative to organic halides as reaction partners in cross-coupling reactions.[74-76]

In 2009 Waser and co-workers described for the first time the use of this class of organic electrophiles for the direct C-H alkylation of heteroarenes.[77] In the presence of gold(I) chloride, neutral 1-[(triisopropyl-silyl)ethynyl]-1,2-benziodoxol-3(1H)-one (TIPS-EBX) was successfully reacted with indole derivatives, allowing the regioselective formation of the corresponding 3-alkynylindoles in high isolated yields (Scheme 30).



Scheme 30. Direct C3-H alkylation of indoles with TIPS-EBX.[77]

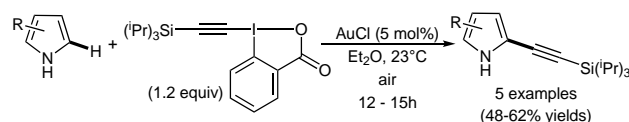
When the 3-position on the indole ring is occupied, such as in 3-methylindole, the C-2-alkynylated compound was obtained, (Scheme 31) proving the versatility of this synthetic protocol.



Scheme 31. Gold-catalyzed direct C2-H alkylation of 3-methylindole with TIPS-EBX.[77]

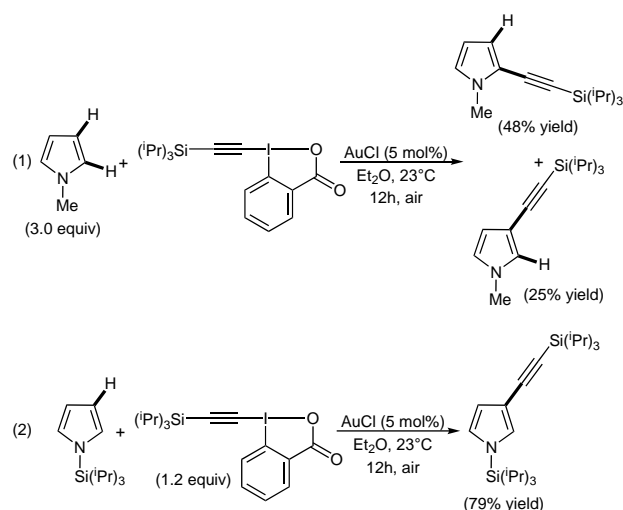
Notably, while gold catalysis revealed to be effective in promoting the C-H alkylation of indoles, no product was observed when typical Cu(I), Cu(II), Pd(II), Pt(II), Pt(IV), Fe(III), Zn(II), In(III), Yb(III) pre-catalysts were employed, and also under metal-free conditions. According to the authors, the observed relevant results could be probably related to the ability of gold salts to activate multiple unsaturated bonds.[78-82]

Free-NH pyrroles may be also reacted under gold catalysis. The coupling of pyrrole itself and substituted pyrroles with TIPS-EBX cleanly gave C-2 alkynylated derivatives in moderate isolated yields (Scheme 32).



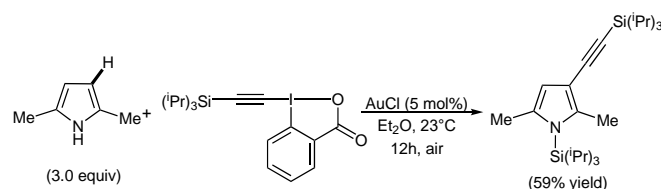
Scheme 32. Gold-catalyzed direct C2-H alkylation of pyrroles with TIPS-EBX.[77]

However, it was found that the regioselectivity is sensible to the steric hindrance when *N*-substituted pyrroles were used as coupling partners. In fact, the alkylation of 1-methylpyrrole gave with an isolated yield of 73% a mixture of 2- and 3-alkynylpyrroles in a 1.9:1 molar ratio (Eq. 1, Scheme 33) In contrast, C-3 alkylation was exclusively observed for *N*-triisopropylsilyl-protected pyrrole (Eq. 2, Scheme 33).[77]



Scheme 33. Gold-catalyzed direct C-H alkylation of *N*-protected pyrroles with TIPS-EBX.[77]

Even in the case of pyrroles when the most reactive C-2 position is occupied, the alkylation involves the less reactive C3-H bond. (Scheme 34).



Scheme 34. Gold-catalyzed direct C-H alkylation of 2,5-dimethylpyrrole with TIPS-EBX.[77]

The yields of the reactions involving pyrroles were on average lower than the similar reactions on the indole derivatives. Attributing this lower efficiency to a possible partial degradation of the highly electron-rich pyrrole nucleus by HCl generated from AuCl during the reaction, the authors found later that the simple addition of a stoichiometric amount of pyridine as acid scavenger significantly improved the isolated yields.[83] And not only were the chemical yields higher than similar reactions conducted in the absence of pyridine, but also the C2:C3 regioselectivity of the alkylation involving 1-methylpyrrole raised from 1.9:1 to 4.2:1.

The authors formulated two different plausible mechanistic hypotheses noting, however, that the data available to them did not allow to decide which of the two proposals is the most correct in their case.[77] Specifically, the first (pathway (a), Figure 7) involves an Au(I)/Au(III) catalytic cycle, while the second (pathway (b), Figure 7) considers as a key stage the gold-mediated addition of the indole to the triple bond of the hypervalent iodine species.

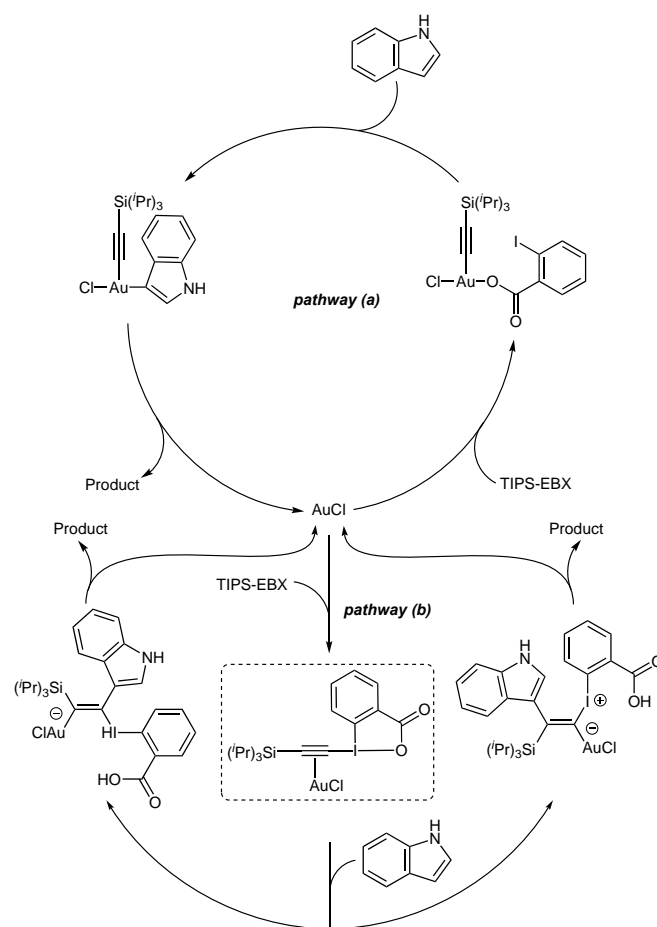


Figure 7. Waser's mechanistic proposal for the gold-catalyzed C-H alkylation of indoles with TIPS-EBX.[77]

Recently, the mechanism of the C-H alkylation of pyrroles and indoles was investigated in more details using DFT calculations, and an alternative mechanism in which iodine(III) center acts as Lewis acid better than gold(I) center in the activation of the alkyne emerged as the most feasible (Figure 8).[84]

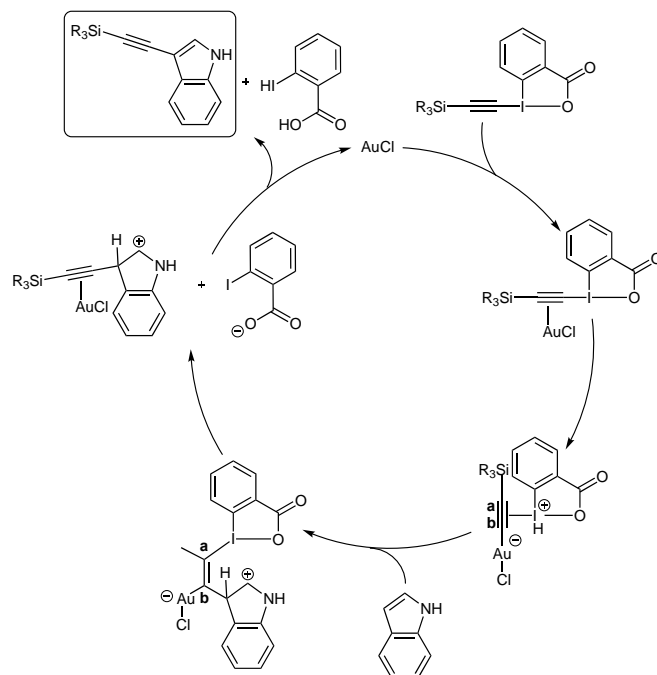
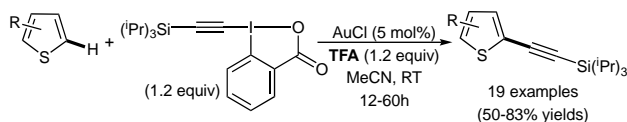


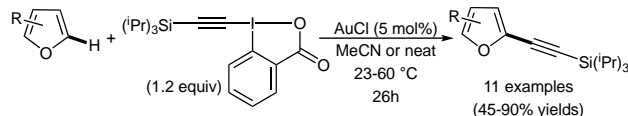
Figure 8. DFT mechanistic pathway for the gold-catalyzed alkylation of indoles.[84]

During the development of the protocol for the alkylation of indoles and pyrrole, Waser and co-workers observed that thiophenes gave only traces of the expected functionalized products. Taking into account the reported activation of EBX-based reagents by Lewis or Brønsted acids,[85-88] after a brief screening they found that carrying the coupling in the presence of 1.2 equiv of TFA in MeCN as the solvent a clean C-2 alkylation of several thiophenes was successfully achieved (Scheme 35).[89]



Scheme 35. Gold-catalyzed direct C-H alkylation of thiophenes with TIPS-EBX.[89]

However, when the same conditions were tested for the alkylation of furan, the authors observed only the decomposition of the heteroaromatic precursor.[90] Attributing the inefficiency of these conditions to the lability of the furan nucleus to the acidity caused by the presence of TFA, they noted that the alkylation could be efficiently carried out simply performing the coupling in the absence of acids. In this way, furan itself and several substituted furans were converted into their respective C-2 alkylated products by reaction with TIPS-EBX (Scheme 36).



Scheme 36. Gold-catalyzed direct C-H alkylation of furans with TIPS-EBX.[90]

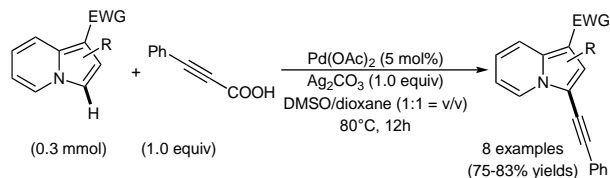
Interestingly, the coupling was performed using MeCN as the solvent, but with volatile derivatives such as furan, 2-methyl- or 2-ethylfuran the authors found more convenient to use them as solvents.[90]

4. DECARBOXYLATIVE DIRECT ALKYNYLATION

The transition metal-catalyzed decarboxylative cross-coupling has received much attention and has evolved as an advantageous alternative to the use of organometallic reagents as coupling partners.[91-97] In fact, this methodology does not make use of expensive and/or sensitive organometallic reagents and generate CO₂ without producing toxic metal halides. Moreover, carboxylic acids are in general easy to store, simple to handle, and when necessary, are accessible by means of a large number of well-established methods.[98-100]

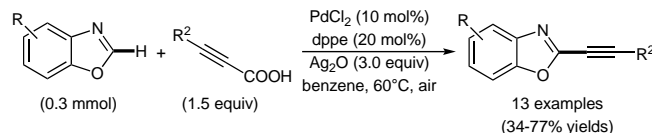
In 2012, during a study aimed at identifying new procedures for the Pd-catalyzed functionalization of indolizines, Zhao described the use of phenylpropionic acid as an effective coupling partner for the regioselective direct C3-H alkylation of substituted indolizines (Scheme 37).[101] The coupling was carried out in a 1:1 mixture of DMSO and 1,4-dioxane at 80 °C for 12 h. Through a preliminary screening of

the reaction conditions Pd(OAc)₂ resulted the best pre-catalyst, when in combination with Ag₂CO₃ as the stoichiometric oxidant (see the proposed reaction mechanism below).



Scheme 37. Palladium-catalyzed decarboxylative alkylation of indolizines.[101]

One year later Lee and co-workers described a general protocol for the palladium-catalyzed decarboxylative C-H alkylation of benzoxazoles with α,β -ynoic acids.[102] The optimized reaction conditions involved the use of PdCl₂/dppe as the catalyst system, of Ag₂O as the stoichiometric oxidant and of benzene as the solvent under air (Scheme 38).



Scheme 38. Palladium-catalyzed decarboxylative alkylation of benzoxazoles.[102]

Although the exact mechanism was not established, the authors suggested a plausible pathway that involves a double role for the Ag(I) salt (Figure 9).[102] Apart from its participation in the Pd(0)→Pd(II) re-oxidation, a process that is mandatory for closing the catalytic cycle, it is involved in the decarboxylation of the ynoic acids generating an Ag(I) acetylide that enters the main catalytic cycle by transferring the alkynyl group to palladium(II) in the transmetalation step.

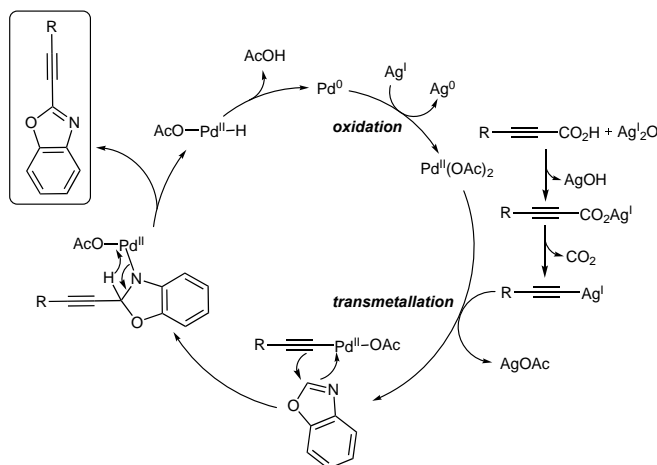
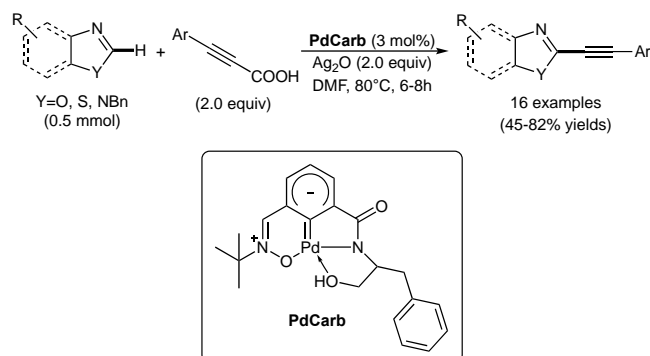


Figure 9. Suggested mechanistic pathway for the palladium-catalyzed decarboxylative alkylation of benzoxazoles.[102]

It should be noted, however, that a completely identical mechanism had already been proposed by Zhao in 2012 for the C-3 decarboxylative alkylation of indolizines.[101]

The C-2 dehydrogenative alkylation of substituted benzoxazoles was also achieved using the anionic amido carbocyclic carbene **Pd-Carb** by the research team of Likhar and Kantam.[103] In the presence of Ag₂O as the oxidant in

DMF at 80 °C under air, the reaction of 2.0 equiv of aryl propiolic acids with substituted benzoxazoles, benzothiazole, *N*-benzylbenzimidazole, and *N*-benzylimidazole gave the required alkynylated derivatives in good isolated yields (Scheme 39).



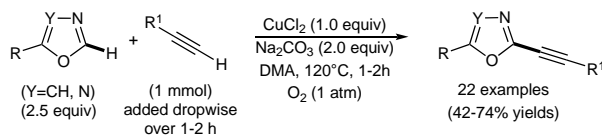
Scheme 39. Decarboxylative alkynylation of heteroarenes with arylpropionic acids promoted by the Pd-carbene complex **PdCarb**. [103]

5. CROSS-DEHYDROGENATIVE ALKYNYLATION

In the context of transition metal-catalyzed carbon-carbon bond-forming reactions by direct functionalization of C-H bonds, there is no doubt that dehydrogenative cross-couplings, although difficult to conduct, certainly represent the approach with the best atom economy. [21-24, 104] These methods, in fact, employing two different C-H bonds on the two coupling partners are highly attractive since no pre-activation, such as halogenation or metalation, is required.

This approach is particularly interesting in the alkynylation of (hetero)aromatic Csp²-H bonds, since for performing cross-dehydrogenative alkynylations (CDA) it is possible to use directly terminal alkynes without the need for preliminary activation. [24, 105-108] Activation that, on the contrary, is required by the methodologies summarized in the previous paragraphs of this review.

As part of a larger study dedicated to the development of procedures for the direct functionalization of Csp²-H bonds of heteroarenes, in 2010 Miura and co-workers described a copper-mediated protocol for the CDA of 1,3,4-oxadiazoles and oxazoles (Scheme 40). [109] The coupling was carried out in the presence of CuCl₂ and Na₂CO₃ in DMA at 120 °C under O₂ atmosphere (1 atm, balloon). To limit the formation of Glaser-type side-products, [110] DMA solutions of the terminal alkynes were added dropwise over 1-2 h to the reaction mixtures, and azoles in two portions at time 0 and after 0.5h.



Scheme 40. Copper-promoted cross-dehydrogenative alkynylation of 1,3,4-oxadiazoles and oxazoles with alkynes. [109]

In the mechanism proposed by the authors and outlined in Figure 10, O₂ should act as a stoichiometric oxidant, allowing a Cu(II)/Cu(0) catalytic cycle. [109] However, the fact that the coupling did not proceed with catalytic amounts of copper, or

when conducted under N₂, does not clarify what the real role of oxygen is in this reaction.

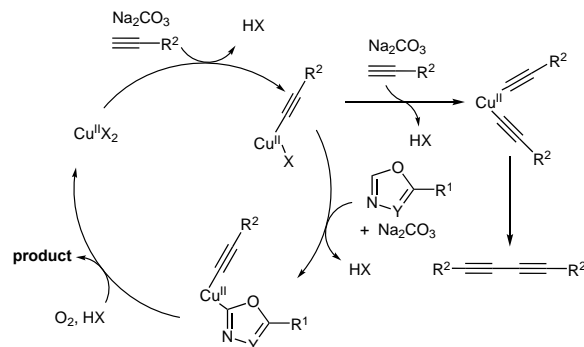
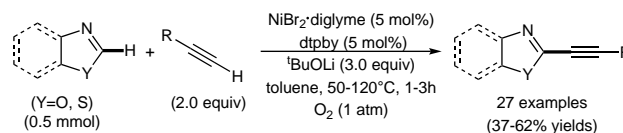


Figure 10. Miura's suggested mechanism for the Cu-mediated CDA of 1,3,4-oxadiazoles and oxazoles. [109]

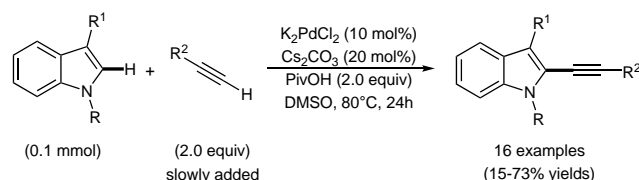
However, although this procedure allows to obtain internal heteroaryl alkynes in good isolated yields, it requires a stoichiometric amount of copper. Miura and co-workers, in the same year proposed an alternative procedure that made use of a nickel/O₂ catalytic system. [111] Such a system allowed the cross-dehydrogenative alkynylation of benzoxazoles, benzothiazoles, and oxazoles with terminal alkynes in the presence of 5 mol % NiBr₂·diglyme, 5 mol % 4,4'-(tert-butyl)-2,2'-bipyridine (dtbpy), and LiO^tBu in toluene at 100 °C under O₂ (1 atm, balloon) (Scheme 41).



Scheme 41. Nickel-catalyzed cross-dehydrogenative alkynylation of azoles with alkynes. [111]

Interestingly, the authors described an experimental procedure that differs from that previously adopted by themselves for their Cu-promoted CDA of oxazoles. In fact, all the reactants were added altogether except when ethynyltriisopropylsilane (TIPS-acetylene) was used; in this case, a toluene solution of the *azole* was slowly added to the alkyne, and not vice versa. [111]

Again in 2010, Li and co-workers described a protocol for the Pd-catalyzed dehydrogenative C-2 alkynylation of 3-substituted indoles. [112] The optimized procedure involves the use of 0.1 mmol of heteroarene and 2.0 equiv of a terminal alkyne slowly added by syringe pump to minimize the unwanted alkyne homocoupling side-products. The coupling was carried out in the presence of 10 mol% K₂PdCl₄, 20 mol% Cs₂CO₃, and 2.0 equiv of pivalic acid (PivOH) in DMSO under O₂ (1 atm) at 80 °C for 24 h (Scheme 42).



Scheme 42. Palladium-catalyzed cross-dehydrogenative alkynylation of indoles with alkynes. [112]

The proposed mechanism, summarized in Figure 11, involves as key step an electrophilic attack of the alkynylpalladium intermediate, generated by deprotonation of the terminal alkyne by the pivalate and subsequent transmetalation, to the C2-H position of the indole. The subsequent re-aromatization of the Wheland intermediate thus generated leads to the desired coupling product.

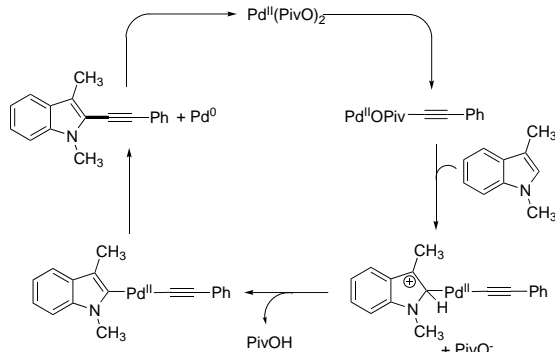
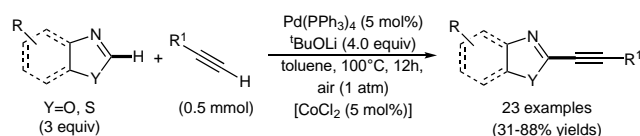


Figure 11. Palladium-catalyzed C-2 cross-dehydrogenative alkylation of 3-substituted indoles with alkynes.[112]

In 2011, Chang and co-workers reported an interesting procedure for the palladium-catalyzed aerobic dehydrogenative alkylation of azoles with terminal alkynes.[113] The peculiarity of this protocol is the use of air as the only oxidant, and it is interesting to note that very poor results were observed when organic oxidants, such as *t*-butyl hydroperoxide or phenyliodine(III) diacetate, were employed during the preliminary screening of the reaction conditions. The coupling was carried out using 3 equiv of the heteroarene, in the presence of 0.5 mmol of terminal alkyne, 5 mol% Pd(PPh₃)₄, 4 equiv of *t*-BuOLi in toluene at 100°C for 12 h (Scheme 43).

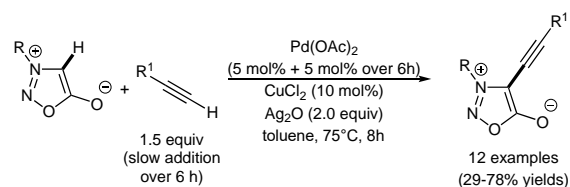


Scheme 43. Palladium-catalyzed aerobic cross-dehydrogenative alkylation of azoles with terminal alkynes.[113]

The authors observed that the reaction of phenylacetylenes substituted with electron-withdrawing substituents resulted in slightly lower yields mainly due to dimerization of the alkynes, and for this reason they were slowly added to the reaction mixtures. On the contrary, with electron-donating groups the alkylation readily took place to provide high product yields. Interestingly, when TIPSacetylene was chosen as the reaction partner, a catalytic amount of CoCl₂ was added to the reaction mixture, but its role was not clarified.

In the same year, a procedure for the palladium-catalyzed dehydrogenative alkylation of *N*-substituted sydnones was described by Larock and co-workers.[114] The optimized reaction conditions for this coupling, which are summarized in Scheme 44, deserves to be highlighted. In fact, this methodology involves the use of three distinct metal salts: Pd(OAc)₂ as the pre-catalyst, CuCl₂ as the primary oxidant of palladium and Ag₂O as a terminal oxidant. Despite this, the authors observed that it was necessary to conduct the reaction in the open air. In addition, to minimize the formation of Glaser-type side-products, the alkyne was slowly added via

syringe pump over 6 h, along with a second portion of Pd(OAc)₂.

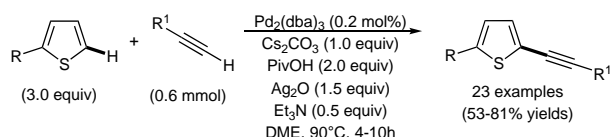


Scheme 44. Pd/Cu-catalyzed, silver-promoted cross-dehydrogenative alkylation of *N*-substituted sydnones with terminal alkynes.[114]

The second addition of palladium acetate was considered necessary because the formation of a mirror of Ag(0) during the reaction facilitated the co-precipitation of Pd(0) and, consequently, a loss of catalytic activity.

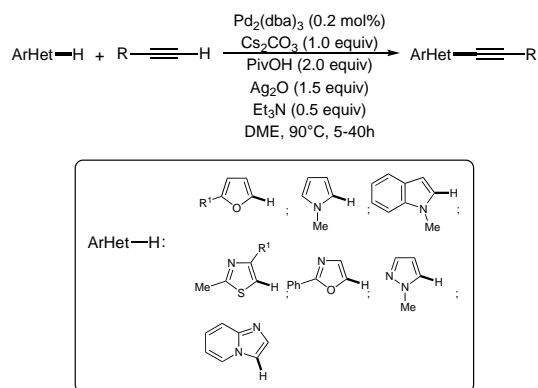
As regards the plausible mechanism, the authors suggested a classical aromatic substitution pathway involving an electrophilic palladation of the heteroaromatic nucleus by an alkynyl Pd species, generated by transmetalation between Pd(II) and a copper or silver acetylide.[114]

Silver(I) oxide is also the oxidant of choice in the palladium-catalyzed dehydrogenative alkylation procedure of substituted thiophenes with terminal alkynes, published by Su and co-workers in 2013.[115] The adopted reaction conditions are characterized by a low loading of catalyst, and involve the use of PivOH and Cs₂CO₃ as additives, in DME as the solvent at 90 °C (Scheme 45). The authors found also that the addition of a substoichiometric amount of Et₃N resulted beneficial for the coupling, but no explanation was given to clarify its role.



Scheme 45. Palladium-catalyzed cross-dehydrogenative alkylation of substituted thiophenes with terminal alkynes.[115]

The authors were pleased to find that the same reaction conditions allowed the selective C-H alkylation of substituted furans and several azoles (Scheme 46).



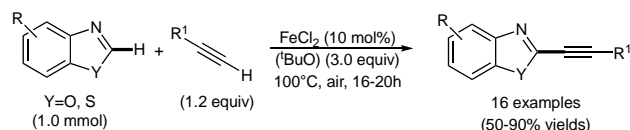
Scheme 46. Palladium-catalyzed cross-dehydrogenative alkylation of substituted furans and azoles with terminal alkynes.[115]

Among the functional groups found to be compatible with the adopted reaction conditions, it is worth noting the inertness of Csp²-I bonds which are, on the other hand, highly reactive in the classic conditions of the Sonogashira reaction. This is one

of the typical advantages of dehydrogenative couplings, i.e. the possibility of obtaining products containing carbon-halogen bonds that may be involved in further orthogonal functionalization reactions.

Finally, it should be noted that the experimental procedure described by Su and co-workers does not require the slow addition of the alkyne, which was used in a 1:3 molar ratio with the heteroarene. The authors justified this experimental choice by the plausible in situ formation of alkynylsilver derivatives which, due to their low solubility, slowly liberates the alkynyl group into the reaction system and therefore suppresses the undesired Glaser-type homocoupling side-products.[115]

Going back to 2011, Bobade and co-workers developed an efficient iron-catalyzed dehydrogenative alkylation of benzazoles with terminal alkynes.[116] The procedure does not involve the use of any metal ligands, and turns out to be very advantageous since it uses iron, the most abundant metal present on the Earth's crust, as a metal catalyst. The reaction conditions chosen to perform the coupling involved the use of 10 mol% FeCl_2 , 3.0 equiv of $(t\text{-BuO})_2$ under solvent-free conditions at 100°C in the open air (Scheme 47).



Scheme 47. Ligandless and solvent-free Fe-catalyzed alkylation of azoles with terminal alkynes.[116]

The radical mechanism postulated by the authors is summarized in Figure 12. In details, the initial reaction of t -butyl peroxide with FeCl_2 generates $\text{Fe}^{\text{III}}\text{-O}t\text{-Bu}$ and t -butyl radical. The deprotonation of an azole C(2)-H bond takes place by the action of t -butoxy radical leading to an azole radical that subsequently reacts with an in situ generated iron acetylide complex to give the 2-alkynylazole product and $\text{Fe}(\text{II})$ species.[116]

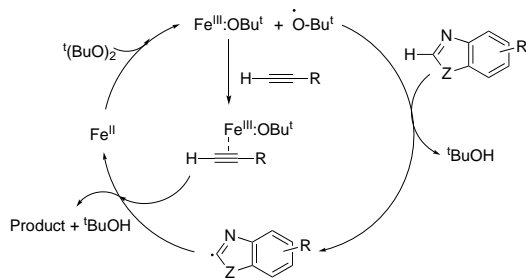
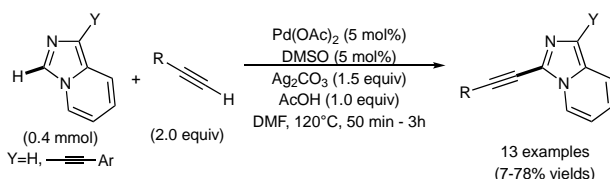


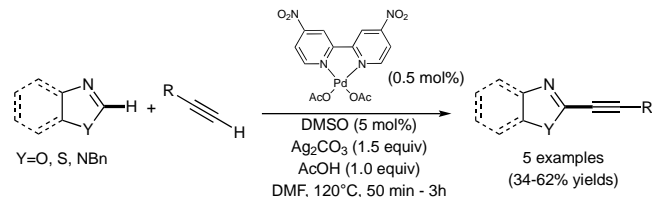
Figure 12. The radical mechanistic pathway for the Fe-catalyzed dehydrogenative alkylation of azoles with terminal alkynes, according to Bobade and co-workers.[116]

Returning to palladium-catalyzed dehydrogenative alkylation reactions, as part of a research dedicated to the identification of fluorescent organic compounds for new functional materials, Shibahara, Murai and co-worker reported in 2012 the synthesis of several 3-alkynyl- and 1,3-bis-alkynyl-substituted imidazo[1,5-*a*]pyridines (Scheme 48).[117] The coupling was carried out in the presence of 5 mol% $\text{Pd}(\text{OAc})_2$, 5 mol% DMSO as the palladium ligand,[118-120] 1.5 equiv Ag_2CO_3 , 1.0 equiv of AcOH in DMF at 120°C . Notably, the alkyne (2.0 equiv) was partly or totally added dropwise to the reaction mixture.



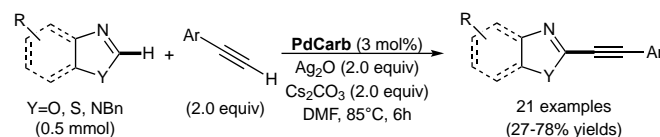
Scheme 48. Pd/DMSO-catalyzed dehydrogenative alkylation of imidazopyridine with terminal alkynes.[117]

The authors were also able to extend their procedure to the regioselective C-2 alkylation of several azoles simply replacing $\text{Pd}(\text{OAc})_2$ with its complex with 4,4'-dinitro-2,2'-bipyridine (Scheme 49).



Scheme 49. Pd/DMSO-catalyzed dehydrogenative alkylation of imidazopyridine with terminal alkynes.[117]

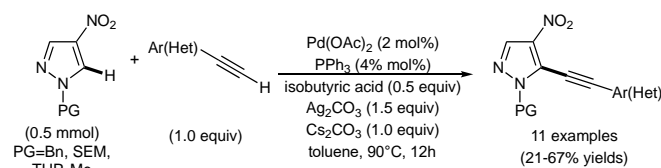
In 2015 Lokhar, Kantam and co-workers reported the application of the palladium carbene catalyst **PdCarb**, whose effectiveness in promoting the decarboxylative alkylation of heteroarenes has already been discussed (see Scheme 39), to the dehydrogenative alkylation of benzoxazoles, benzothiazole and *N*-benzyl(benzo)imidazole with terminal arylacetylenes.[103] The coupling was carried out in the presence of 2.0 equiv of Ag_2O as the oxidant and 2.0 equiv of Cs_2CO_3 in DMF at 85°C under air (Scheme 50). To minimize homocoupling byproducts, the alkyne was slowly added to the reaction mixture over 2 h.



Scheme 50. Dehydrogenative alkylation of (benzo)azoles with terminal alkynes catalyzed by the anionic/amido carbocyclic carbene Pd(II) complex **PdCarb**.[103]

In contrast with the results obtained with arylacetylenes, the reactions of benzoxazoles with aliphatic alkynes such as 1-octyne and prop-2-yn-1-ylcyclohexane did not give any coupling product.[103]

The same unsatisfactory results when aliphatic alkynes are used as coupling partners was observed in 2018 by Joo and co-workers, during a study devoted to the C-H functionalization of *N*-protected 4-nitropyrroles with terminal alkynes.[121] In fact, no product was observed when 1-methyl-4-nitropyrrole was reacted with 1.0 equiv of 1-hexyne in the presence of $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ as the catalyst system, Ag_2CO_3 as the oxidant, isobutyric acid and Cs_2CO_3 as additives, in toluene at 90°C in the open air. A similar negative result was obtained with TIPS-acetylene, while the coupling with cyclopropylacetylene gave the C-5 alkynylated pyrrole in a low 29% isolated yield. In contrast, moderate isolated yields were obtained when *N*-Bn, *N*-SEM, *N*-THP, or *N*-methyl substituted 4-nitropyrrole were reacted with (hetero)arylacetylenes (Scheme 51).[121]



Scheme 51. Dehydrogenative C-5 alkylation of *N*-protected 4-nitropyrrole with (hetero)arylacetylenes.[121]

CONCLUSION

Synthetic procedures that allow the preparation of structurally different molecular entities through the selective C-H bond functionalization of a common scaffold are the basis of the modern Late-Stage Functionalization strategies. If we add to this the synthetic versatility of a triple carbon-carbon bond, it appears clear what the importance of developing methods that allow the alkylation of C-H bonds can be.

The protocols described in this review generally require the use of palladium-based catalysts, but also Ni, Cu, Au, and Fe are also

able to promote efficiently specific alkylation reactions. However, a problem related to the use of transition metals, albeit when employed in catalytic amounts, is related to the need to carry out an accurate downstream purification to remove any traces of metal from products. To solve this issue, that is particularly severe in the field of medicinal chemistry, significant research efforts should be dedicated to the development of metal-free alkylation methods, that are substantially unknown till now. Moreover, in order to improve the efficiency of diversity-oriented procedures, in our opinion efforts should be also done to explore *non-regioselective functionalization* methods,[122] that in combination with LSF could widen the chemical space available to the medicinal chemistry for SAR studies. Specifically, procedures that allow the selective *mono*-alkylation of all heteroaromatic C-H bonds with high efficiency, excluding the formation of side-products such as multiple alkynylated derivatives or those deriving from alkyne homocoupling, a problem also common to many of the procedures discussed in this review.

REFERENCES

- [1] Pagett, A. B.; Lloyd-Jones, G. C., Suzuki-Miyaura Cross-Coupling. In *Organic Reactions*, 2019; pp 547-620.
- [2] Miyaura, N.; Suzuki, A., Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, 95 (7), 2457-2483.
- [3] Suzuki, A., Recent advances in the cross-coupling reactions of organoboron derivatives with organic electrophiles, 1995-1998. *J. Organomet. Chem.* **1999**, 576 (1-2), 147-168.
- [4] Kotha, S.; Lahiri, K.; Kashinath, D., Recent applications of the Suzuki-Miyaura cross-coupling reaction in organic synthesis. *Tetrahedron* **2002**, 58 (48), 9633-9695.
- [5] Miyaura, N., Metal-Catalyzed Reactions of Organoboronic Acids and Esters. *Bull. Chem. Soc. Jpn.* **2008**, 81 (12), 1535-1553.
- [6] Rossi, R.; Bellina, F.; Lessi, M., Highly selective palladium-catalyzed Suzuki-Miyaura monocoupling reactions of ethene and arene derivatives bearing two or more electrophilic sites. *Tetrahedron* **2011**, 67 (37), 6969-7025.
- [7] Rossi, R.; Bellina, F.; Carpita, A., Palladium Catalysts for the Suzuki Cross-Coupling Reaction: An Overview of Recent Advances. *Synthesis* **2004**, 2004 (15), 2419-2440.
- [8] Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P., Recent Developments in Negishi Cross-Coupling Reactions. *ACS Catal.* **2016**, 6 (3), 1540-1552.
- [9] Negishi, E., Magical power of transition metals: past, present, and future (Nobel Lecture). *Angew. Chem. Int. Ed.* **2011**, 50 (30), 6738-64.
- [10] Diner, C.; Organ, M. G., The Negishi Cross-Coupling Reaction. In *Organic Reactions*, 2019; pp 1-62.
- [11] Stille, J. K., The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles[New Synthetic Methods(58)]. *Angew. Chem. Int. Ed.* **1986**, 25 (6), 508-524.
- [12] Farina, V.; Krishnamurthy, V.; Scott, W. J., The Stille Reaction. In *Organic Reactions*, 2004; pp 1-652.
- [13] Mitchell, T. N., Palladium-Catalyzed Reactions of Organotin Compounds. *Synthesis* **1992**, 1992 (09), 803-815.
- [14] Farina, V., New perspectives in the cross-coupling reactions of organostannanes. *Pure Appl. Chem.* **1996**, 68 (1), 73-78.
- [15] de Meijere, A.; Diederich, F., *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Edition. Wiley-VCH: Weinheim, 2004.
- [16] Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M., Aryl-aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.* **2002**, 102 (5), 1359-470.
- [17] *Transition Metal-Catalyzed Couplings in Process Chemistry: Case Studies from the Pharmaceutical Industry*. Wiley-VCH: Weinheim, 2013.
- [18] Heck, R. F., Palladium-Catalyzed Vinylation of Organic Halides. In *Organic Reactions*, 2005; pp 345-390.

- [19] Beletskaya, I. P.; Cheprakov, A. V., The heck reaction as a sharpening stone of palladium catalysis. *Chem. Rev.* **2000**, 100 (8), 3009-66.
- [20] *The Mizoroki-Heck Reaction*. John Wiley & Sons: Chichester (UK), 2009; p 587.
- [21] Yeung, C. S.; Dong, V. M., Catalytic dehydrogenative cross-coupling: forming carbon-carbon bonds by oxidizing two carbon-hydrogen bonds. *Chem. Rev.* **2011**, 111 (3), 1215-92.
- [22] Wu, Y.; Wang, J.; Mao, F.; Kwong, F. Y., Palladium-catalyzed cross-dehydrogenative functionalization of C(sp²)-H Bonds. *Chem Asian J* **2014**, 9 (1), 26-47.
- [23] Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A., Oxidative Coupling between Two Hydrocarbons: An Update of Recent C-H Functionalizations. *Chem. Rev.* **2015**, 115 (22), 12138-204.
- [24] Bellina, F.; Perego, L. A., Aerobic Oxidative Intermolecular Cross-Coupling and Heck Reactions. In *Catalytic Oxidation in Organic Synthesis*, Muñiz, K., Ed. Georg Thieme Verlag KG: Stuttgart, 2017; pp 721-721.
- [25] Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W., Remote oxidation of steroids by photolysis of attached benzophenone groups. *J. Am. Chem. Soc.* **1973**, 95 (10), 3251-62.
- [26] Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W., The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016**, 45 (3), 546-76.
- [27] Wencel-Delord, J.; Glorius, F., C-H bond activation enables the rapid construction and late-stage diversification of functional molecules. *Nat Chem* **2013**, 5 (5), 369-75.
- [28] *Modern Acetylene Chemistry*. VCH: Weinheim, 1995.
- [29] Negishi, E.; Anastasia, L., Palladium-catalyzed alkylation. *Chem. Rev.* **2003**, 103 (5), 1979-2017.
- [30] Alonso, F.; Beletskaya, I. P.; Yus, M., Transition-metal-catalyzed addition of heteroatom-hydrogen bonds to alkynes. *Chem. Rev.* **2004**, 104 (6), 3079-159.
- [31] Toyota, S., Rotational isomerism involving acetylene carbon. *Chem. Rev.* **2010**, 110 (9), 5398-424.
- [32] Liu, C.; Zhang, H.; Shi, W.; Lei, A., Bond formations between two nucleophiles: transition metal catalyzed oxidative cross-coupling reactions. *Chem. Rev.* **2011**, 111 (3), 1780-824.
- [33] Brand, J. P.; Waser, J., Electrophilic alkylation: the dark side of acetylene chemistry. *Chem. Soc. Rev.* **2012**, 41 (11), 4165-79.
- [34] Godoi, B.; Schumacher, R. F.; Zeni, G., Synthesis of heterocycles via electrophilic cyclization of alkynes containing heteroatom. *Chem. Rev.* **2011**, 111 (4), 2937-80.
- [35] Chinchilla, R.; Najera, C., Chemicals from alkynes with palladium catalysts. *Chem. Rev.* **2014**, 114 (3), 1783-826.
- [36] *Acetylene Chemistry: Chemistry, Biology and Material Science*. Wiley-VCH: Weinheim, 2006.
- [37] Cassar, L., Synthesis of aryl- and vinyl-substituted acetylene derivatives by the use of nickel and palladium complexes. *J. Organomet. Chem.* **1975**, 93 (2), 253-257.

- [38] Dieck, H. A.; Heck, F. R., Palladium catalyzed synthesis of aryl, heterocyclic and vinylic acetylene derivatives. *J. Organomet. Chem.* **1975**, *93* (2), 259-263.
- [39] Sonogashira, K.; Tohd, Y.; Hagihara, N., A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Lett.* **1975**, *16* (50), 4467-4470.
- [40] Sonogashira, K., Development of Pd-Cu catalyzed cross-coupling of terminal acetylenes with sp²-carbon halides. *J. Organomet. Chem.* **2002**, *653* (1-2), 46-49.
- [41] Chinchilla, R.; Najera, C., The Sonogashira reaction: a booming methodology in synthetic organic chemistry. *Chem. Rev.* **2007**, *107* (3), 874-922.
- [42] Doucet, H.; Hierso, J. C., Palladium-based catalytic systems for the synthesis of conjugated enynes by sonogashira reactions and related alkynylations. *Angew. Chem. Int. Ed.* **2007**, *46* (6), 834-71.
- [43] Wu, W.; Jiang, H., Haloalkynes: a powerful and versatile building block in organic synthesis. *Acc. Chem. Res.* **2014**, *47* (8), 2483-504.
- [44] Jiang, H.; Zhu, C.; Wu, W., Reactions of Haloalkynes. In *Haloalkyne Chemistry*, Springer: Berlin, Heidelberg, 2016; pp 9-76.
- [45] Zhang, Y. H.; Shi, G. F.; Yu, J. Q., 3.23 Carbon-Carbon σ -Bond Formation via CH Bond Functionalization. In *Comprehensive Organic Synthesis II*, Elsevier: 2014; pp 1101-1209.
- [46] Gelman, D.; Shaposhnikov, I., 3.09 Coupling Reactions Between C(sp²) and C(sp) Carbon Centers. In *Comprehensive Organic Synthesis II*, Elsevier: 2014; pp 465-527.
- [47] Hirano, K.; Miura, M., C-H Activation of Heteroaromatics. In *Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries*, Dunn, P. J.; Hii, K. K. M.; Krische, M. J.; Williams, M. T., Eds. Wiley: 2013; pp 233-267.
- [48] Messaoudi, S.; Brion, J. D.; Alami, M., Transition-Metal-Catalyzed Direct C-H Alkenylation, Alkynylation, Benzoylation, and Alkylation of (Hetero)arenes. *Eur. J. Org. Chem.* **2010**, *2010* (34), 6495-6516.
- [49] Dudnik, A. S.; Gevorgyan, V., Formal inverse Sonogashira reaction: direct alkynylation of arenes and heterocycles with alkynyl halides. *Angew. Chem. Int. Ed.* **2010**, *49* (12), 2096-8.
- [50] Seregin, I. V.; Ryabova, V.; Gevorgyan, V., Direct palladium-catalyzed alkynylation of N-fused heterocycles. *J. Am. Chem. Soc.* **2007**, *129* (25), 7742-3.
- [51] Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M., Palladium-catalyzed multiple arylation of thiophenes. *J. Am. Chem. Soc.* **2002**, *124* (19), 5286-7.
- [52] Park, C. H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V., Palladium-catalyzed arylation and heteroarylation of indolizines. *Org. Lett.* **2004**, *6* (7), 1159-62.
- [53] Lane, B. S.; Brown, M. A.; Sames, D., Direct palladium-catalyzed C-2 and C-3 arylation of indoles: a mechanistic rationale for regioselectivity. *J. Am. Chem. Soc.* **2005**, *127* (22), 8050-7.
- [54] Chiong, H. A.; Daugulis, O., Palladium-catalyzed arylation of electron-rich heterocycles with aryl chlorides. *Org. Lett.* **2007**, *9* (8), 1449-51.
- [55] Gu, Y.; Wang, X.-m., Direct palladium-catalyzed C-3 alkynylation of indoles. *Tetrahedron Lett.* **2009**, *50* (7), 763-766.
- [56] Brachet, E.; Belmont, P., Palladium-Catalyzed Regioselective Alkynylation of Pyrroles and Azoles under Mild Conditions: Application to the Synthesis of a Dopamine D-4 Receptor Agonist. *J. Org. Chem.* **2015**, *80* (15), 7519-29.
- [57] Kim, S. H.; Chang, S., Highly efficient and versatile pd-catalyzed direct alkynylation of both azoles and azolines. *Org. Lett.* **2010**, *12* (8), 1868-71.
- [58] Ackermann, L.; Kornhaass, C.; Zhu, Y., Palladium-catalyzed direct C-H bond alkynylations of heteroarenes using gem-dichloroalkenes. *Org. Lett.* **2012**, *14* (7), 1824-6.
- [59] Yamaguchi, J.; Muto, K.; Itami, K., Nickel-Catalyzed Aromatic C-H Functionalization. *Top. Curr. Chem. (Cham)* **2016**, *374* (4), 55.
- [60] Khake, S. M.; Chatani, N., Nickel-Catalyzed C-H Functionalization Using A Non-directed Strategy. *Chem* **2020**, *6* (5), 1056-1081.
- [61] Harry, N. A.; Saranya, S.; Ujwaldev, S. M.; Anilkumar, G., Recent advances and prospects in nickel-catalyzed C-H activation. *Catalysis Science & Technology* **2019**, *9* (8), 1726-1743.
- [62] Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M., Nickel-catalyzed direct alkynylation of azoles with alkynyl bromides. *Org. Lett.* **2009**, *11* (18), 4156-9.
- [63] Patel, U. N.; Punji, B., A Copper- and Phosphine-Free Nickel(II)-Catalyzed Method for C-H Bond Alkynylation of Benzothiazoles and Related Azoles. *Asian Journal of Organic Chemistry* **2018**, *7* (7), 1390-1395.
- [64] Bessellievre, F.; Piguel, S., Copper as a powerful catalyst in the direct alkynylation of azoles. *Angew. Chem. Int. Ed.* **2009**, *48* (50), 9553-6.
- [65] Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X., What are the pK_a values of C-H bonds in aromatic heterocyclic compounds in DMSO? *Tetrahedron* **2007**, *63* (7), 1568-1576.
- [66] Aziz, J.; Baladi, T.; Piguel, S., Direct Alkynylation of 3H-Imidazo[4,5-b]pyridines Using gem-Dibromoalkenes as Alkynes Source. *J. Org. Chem.* **2016**, *81* (10), 4122-33.
- [67] Kawano, T.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M., Room temperature direct alkynylation of 1,3,4-oxadiazoles with alkynyl bromides under copper catalysis. *J. Org. Chem.* **2010**, *75* (5), 1764-6.
- [68] Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. b. I.; Ushakov, I. A., Ethynylation of pyrroles with 1-acyl-2-bromoacetylenes on alumina: a formal 'inverse Sonogashira coupling'. *Tetrahedron Lett.* **2004**, *45* (34), 6513-6516.
- [69] Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Vakul'skaya, T. I.; Kazheva, O. g. N.; Aleksandrov, G. G.; Dyachenko, O. A.; Mikhaleva, A. b. I., Reactions of 2-phenylpyrrole with bromobenzoylacetylene on metal oxides active surfaces. *Tetrahedron* **2008**, *64* (23), 5541-5544.
- [70] Sobenina, L. N.; Petrova, O. g. V.; Tomilin, D. N.; Gotsko, M. D.; Ushakov, I. A.; Klyba, L. V.; Mikhaleva, A. b. I.; Trofimov, B. A., Ethynylation of 2-(furan-2-yl)- and 2-(thiophen-2-yl)pyrroles with acylbromoacetylenes in the Al₂O₃ medium: relative reactivity of heterocycles. *Tetrahedron* **2014**, *70* (50), 9506-9511.
- [71] Sobenina, L. N.; Trofimov, B. A., Recent Strides in the Transition Metal-Free Cross-Coupling of Haloacetylenes with Electron-Rich Heterocycles in Solid Media. *Molecules* **2020**, *25* (11).
- [72] Ohmura, T.; Kijima, A.; Komori, Y.; Sugimoto, M., Cycloaddition-based formal C-H alkynylation of isoindoles leading to the synthesis of air-stable fluorescent 1,3-dialkynylisoindoles. *Org. Lett.* **2013**, *15* (14), 3510-3.
- [73] Jacobi, P. A.; Tassa, C., Enantioselective syntheses of ring-C precursors of vitamin B12. Substrate control. A novel Si-assisted elimination of vinyl bromides. *Org. Lett.* **2003**, *5* (25), 4879-82.
- [74] Zhdankin, V. V.; Stang, P. J., Chemistry of polyvalent iodine. *Chem. Rev.* **2008**, *108* (12), 5299-358.
- [75] Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis. In *Top. Curr. Chem.*, Wirth, T., Ed. Springer-Verlag: Berlin, 2003; Vol. 224.
- [76] Zhdankin, V. V., Organoiodine(V) reagents in organic synthesis. *J. Org. Chem.* **2011**, *76* (5), 1185-97.
- [77] Brand, J. P.; Charpentier, J.; Waser, J., Direct alkynylation of indole and pyrrole heterocycles. *Angew. Chem. Int. Ed.* **2009**, *48* (49), 9346-9.
- [78] Hashmi, A. S., Gold-catalyzed organic reactions. *Chem. Rev.* **2007**, *107* (7), 3180-211.
- [79] Gorin, D. J.; Toste, F. D., Relativistic effects in homogeneous gold catalysis. *Nature* **2007**, *446* (7134), 395-403.
- [80] Furstner, A.; Davies, P. W., Catalytic carbophilic activation: catalysis by platinum and gold pi acids. *Angew. Chem. Int. Ed.* **2007**, *46* (19), 3410-49.
- [81] Jimenez-Nunez, E.; Echavarren, A. M., Gold-catalyzed cycloisomerizations of enynes: a mechanistic perspective. *Chem. Rev.* **2008**, *108* (8), 3326-50.
- [82] Kirsch, S., Construction of Heterocycles by the Strategic Use of Alkyne π -Activation in Catalyzed Cascade Reactions. *Synthesis* **2008**, *2008* (20), 3183-3204.
- [83] Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J., Ethynyl benziodoxolones for the direct alkynylation of heterocycles: structural requirement, improved procedure for pyrroles, and insights into the mechanism. *Chem. Eur. J.* **2012**, *18* (18), 5655-66.
- [84] Ariafard, A., A Density Functional Theory (DFT) Mechanistic Study of Gold(I)-Catalyzed Alkynylation of the Indole and Pyrrole Substrates, Using a Hypervalent Iodine Reagent. *ACS Catal.* **2014**, *4* (9), 2896-2907.
- [85] Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A., Zinc-mediated formation of trifluoromethyl ethers from alcohols and hypervalent iodine trifluoromethylation reagents. *Angew. Chem. Int. Ed.* **2009**, *48* (24), 4332-6.
- [86] Allen, A. E.; Macmillan, D. W., The productive merger of iodonium salts and organocatalysis: a non-photolytic approach to the enantioselective alpha-trifluoromethylation of aldehydes. *J. Am. Chem. Soc.* **2010**, *132* (14), 4986-7.
- [87] Sreenithya, A.; Sunoj, R. B., On the activation of hypercoordinate iodine(III) compounds for reactions of current interest. *Dalton Trans* **2019**, *48* (13), 4086-4093.

- [88] Charpentier, J.; Fruh, N.; Togni, A., Electrophilic trifluoromethylation by use of hypervalent iodine reagents. *Chem. Rev.* **2015**, *115* (2), 650-82.
- [89] Brand, J. P.; Waser, J., Direct alkylation of thiophenes: cooperative activation of TIPS-EBX with gold and Brønsted acids. *Angew. Chem. Int. Ed.* **2010**, *49* (40), 7304-7.
- [90] Li, Y.; Brand, J. P.; Waser, J., Gold-catalyzed regioselective synthesis of 2- and 3-alkynyl furans. *Angew. Chem. Int. Ed.* **2013**, *52* (26), 6743-7.
- [91] Rodríguez, N.; Goossen, L. J., Decarboxylative coupling reactions: a modern strategy for C-C-bond formation. *Chem. Soc. Rev.* **2011**, *40* (10), 5030-48.
- [92] Larrosa, I.; Cornella, J., Decarboxylative Carbon-Carbon Bond-Forming Transformations of (Hetero)aromatic Carboxylic Acids. *Synthesis* **2012**, *44* (05), 653-676.
- [93] Gooßen, L. J.; Gooßen, K., Decarboxylative Coupling Reactions. In *Inventing Reactions*, 2012; pp 121-141.
- [94] Park, K.; Lee, S., Transition metal-catalyzed decarboxylative coupling reactions of alkynyl carboxylic acids. *RSC Advances* **2013**, *3* (34).
- [95] Wei, Y.; Hu, P.; Zhang, M.; Su, W., Metal-Catalyzed Decarboxylative C-H Functionalization. *Chem. Rev.* **2017**, *117* (13), 8864-8907.
- [96] Baudoin, O., New approaches for decarboxylative biaryl coupling. *Angew. Chem. Int. Ed.* **2007**, *46* (9), 1373-5.
- [97] Goossen, L. J.; Rodríguez, N.; Goossen, K., Carboxylic acids as substrates in homogeneous catalysis. *Angew. Chem. Int. Ed.* **2008**, *47* (17), 3100-20.
- [98] Ogliaruso, M. A.; Wolfe, J. F., *Synthesis of Carboxylic Acids, Esters and Their Derivatives* (1991). John Wiley & Sons Ltd: New-York, 1991.
- [99] Patai, S., *Carboxylic Acids and Esters* (1969). John Wiley & Sons Ltd.: New York, 1969.
- [100] *Three Carbon-Heteroatom Bonds: Acid Halides; Carboxylic Acids and Acid Salts*. Georg Thieme Verlag: Stuttgart, 2006; Vol. 20a.
- [101] Zhao, B., Pd-catalyzed C-3 functionalization of indolizines via C-H bond cleavage. *Org. Biomol. Chem.* **2012**, *10* (35), 7108-19.
- [102] Kim, J.; Kang, D.; Yoo, E. J.; Lee, P. H., Palladium-Catalyzed Decarboxylative C-H Alkylation of Benzoxazoles with α,β -ynoic Acids. *Eur. J. Org. Chem.* **2013**, *2013* (35), 7902-7906.
- [103] Parsharamulu, T.; Vishnuvardhan Reddy, P.; Likhar, P. R.; Lakshmi Kantam, M., Dehydrogenative and decarboxylative C-H alkylation of heteroarenes catalyzed by Pd(II)-carbene complex. *Tetrahedron* **2015**, *71* (13), 1975-1981.
- [104] *From C-H to C-C Bonds: Cross-Dehydrogenative-Coupling*. The Royal Society of Chemistry: Cambridge, UK, 2015; Vol. 26.
- [105] Panda, B., Joy and Challenges of Alkylation of Arenes and Heteroarenes through Double C-H Functionalizations. *Asian Journal of Organic Chemistry* **2020**, *9* (4), 492-507.
- [106] Zhang, J. S.; Liu, L.; Chen, T.; Han, L. B., Cross-Dehydrogenative Alkylation: A Powerful Tool for the Synthesis of Internal Alkynes. *ChemSusChem* **2020**, *13* (18), 4776-4794.
- [107] Zhang, C.; Li, N.; Li, X.; Chang, H.; Liu, Q.; Wei, W., Progress in Transition-Metal-Catalyzed Oxidative Cross-Coupling of Terminal Alkynes. *Chinese Journal of Organic Chemistry* **2014**, *34* (1).
- [108] Torres-Moya, I.; Martín, R.; Díaz-Ortiz, Á.; Prieto, P.; Carrillo, J. R., Self-Assembled Alkynyl Azoles and Benzoazoles as Colored Optical Waveguides. *Isr. J. Chem.* **2018**, *58* (8), 827-836.
- [109] Kitahara, M.; Hirano, K.; Tsurugi, H.; Satoh, T.; Miura, M., Copper-mediated direct cross-coupling of 1,3,4-oxadiazoles and oxazoles with terminal alkynes. *Chem. Eur. J.* **2010**, *16* (6), 1772-5.
- [110] Siemsen, P.; Livingston, R. C.; Diederich, F., Acetylenic Coupling: A Powerful Tool in Molecular Construction. *Angew. Chem. Int. Ed.* **2000**, *39* (15), 2632-2657.
- [111] Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M., Nickel- and copper-catalyzed direct alkylation of azoles and polyfluoroarenes with terminal alkynes under O(2) or atmospheric conditions. *Org. Lett.* **2010**, *12* (10), 2358-61.
- [112] Yang, L.; Zhao, L.; Li, C. J., Palladium-catalyzed direct oxidative Heck-Cassar-Sonogashira type alkylation of indoles with alkynes under oxygen. *Chem Commun (Camb)* **2010**, *46* (23), 4184-6.
- [113] Kim, S. H.; Yoon, J.; Chang, S., Palladium-catalyzed oxidative alkylation of heterocycles with terminal alkynes under air conditions. *Org. Lett.* **2011**, *13* (6), 1474-7.
- [114] Wu, C.; Li, P.; Fang, Y.; Zhao, J.; Xue, W.; Li, Y.; Larock, R. C.; Shi, F., Pd-catalyzed oxidative coupling of monosubstituted sydnones and terminal alkynes. *Tetrahedron Lett.* **2011**, *52* (29), 3797-3801.
- [115] Jie, X.; Shang, Y.; Hu, P.; Su, W., Palladium-catalyzed oxidative cross-coupling between heterocycles and terminal alkynes with low catalyst loading. *Angew. Chem. Int. Ed.* **2013**, *52* (13), 3630-3.
- [116] Patil, S. S.; Jadhav, R. P.; Patil, S. V.; Bobade, V. D., Ligand and solvent-free iron catalyzed oxidative alkylation of azoles with terminal alkynes. *Tetrahedron Lett.* **2011**, *52* (43), 5617-5619.
- [117] Shibahara, F.; Dohke, Y.; Murai, T., Palladium-catalyzed C-H bond direct alkylation of 5-membered heteroarenes: a well-defined synthetic route to azole derivatives containing two different alkynyl groups. *J. Org. Chem.* **2012**, *77* (12), 5381-8.
- [118] Zierkiewicz, W.; Privalov, T., A Theoretical Study of the Essential Role of DMSO as a Solvent/Ligand in the Pd(OAc)₂/DMSO Catalyst System for Aerobic Oxidation. *Organometallics* **2005**, *24* (24), 6019-6028.
- [119] Steinhoff, B. A.; Stahl, S. S., Mechanism of Pd(OAc)₂/DMSO-catalyzed aerobic alcohol oxidation: mass-transfer-limitation effects and catalyst decomposition pathways. *J. Am. Chem. Soc.* **2006**, *128* (13), 4348-55.
- [120] He, C. Y.; Fan, S.; Zhang, X., Pd-catalyzed oxidative cross-coupling of perfluoroarenes with aromatic heterocycles. *J. Am. Chem. Soc.* **2010**, *132* (37), 12850-2.
- [121] Ha, H.; Shin, C.; Bae, S.; Joo, J. M., Divergent Palladium-Catalyzed Cross-Coupling of Nitropyrroles with Terminal Alkynes. *Eur. J. Org. Chem.* **2018**, *2018* (20-21), 2645-2650.
- [122] Guariento, S.; Biagetti, M.; Ronchi, P., Non-regioselective functionalization: an underestimate chemical diversity generator in medicinal chemistry. *Future Med Chem* **2021**.