Metal-catalyzed C–H functionalization processes upon "click"-triazole assistance

Itziar Guerrero,[a] and Arkaitz Correa*[a]

Dedication ((optional))

Abstract: The functionalization of otherwise unreactive C–H bonds holds great promise for reducing the reliance on existing functional groups while improving energy efficiency and atom-economy. One of the most powerful strategies exploits chelation assistance through reversible coordination with metal catalysts. This microreview summarizes the most recent advances on the use of 1,2,3-triazoles as versatile directing groups in the field of C-H functionalization. The main feature relies on the modular and straightforward assembly of the required triazoles upon "click" chemistry and hence such procedures constitute practical synthetic tools of utmost importance for the late-stage diversification of "click compounds", which are prevalent moieties in drug discovery and material science.

1. Introduction

The recent years have witnessed a revolution in the field of C–H functionalization, thus becoming a significant discipline within the realm of organic chemistry. Owing to their high atom-economy and sustainable character, direct C–H functionalization processes[1] have certainly changed the landscape of organic synthesis, hence enabling the design of unprecedented tactics upon innovative bond disconnections and offering streamlining syntheses. Transition metal catalysis constitutes a powerful technique for building up molecular complexity through the efficient conversion of ubiquitous C–H bonds into diverse functional groups. Given the wide variety of C–H bonds often present in an organic molecule, a prime issue of those reactions relies on achieving high control of the regioselectivity. One of the most practical avenues involves the introduction of a Lewis basic functional group, commonly named directing group (DG), which upon coordination with the metal catalyst can lower the energy barrier for the cleavage of a specific C–H bond.[2] In general, the latter occurred through the formation of a thermodynamically stable five- or six-membered metallacycle intermediate and allows for the selective activation of its proximal *ortho* C–H bond.

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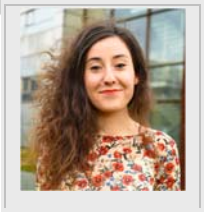
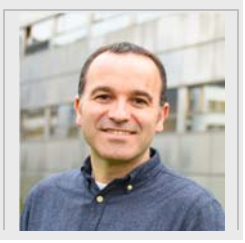


Itziar Guerrero was born in Donostia in 1993. She received her B.Sc. degree from the University of the Basque Country (UPV/EHU) in 2015. She performed the undegraduate Thesis as ERASMUS student in the University of Strathclyde under the supervision of Prof. Colin Gibson working in the synthesis of pyrrolopyrimidines. Later on, she performed the Master Thesis under the supervision of Prof. J. M. Aizpurua at UPV/EHU. She is currently doing her Ph.D. under the supervision of Dr. A. Correa at UPV/EHU. She is working on the development of catalytic methods for the assembly of α-amino carbonyl compounds and 1,2,3-triazoles upon C–H functionalization reactions.



Arkaitz Correa was born in Bilbao in 1979. He studied chemistry at the University of the Basque Country (UPV/EHU), where he completed his PhD studies in 2006 under the guidance of Prof. Esther Domínguez. Along that time, he did a short stay with Prof. Ben L. Feringa at the University of Groningen. In 2007, he undertook his first postdoctoral studies with Prof. Carsten Bolm at RWTH Aachen University (2007–2008). Subsequently, he joined the group of Prof. Ruben Martin at ICIQ (Tarragona) as a postdoctoral fellow (2008–2010). In 2010, he joined a collaborative project with Bayer CropScience at the CSIC under the supervision of Prof. J. M. Lassaletta. From april 2011 to march 2014, he went back to the group of Prof. Ruben Martin at ICIQ as a "Juan de la Cierva" associate researcher. In April 2014, he started his independent career at UPV/EHU as a "Ramón y Cajal" fellow. His current research interests include sustainable catalysis within the field of C−H functionalization as well as peptide and heterocyclic chemistry.

However, additional synthetic steps to both install and cleave the required DG in the substrate and product, respectively, are serious drawbacks, which often diminish the practicality of the chelation assistance strategy.[3] Importantly, when the DG itself can play a key role in further applications of the resulting compounds versatile, yet elegant, "late-stage" functionalization approaches can be devised.[4] In this respect, a plethora of molecules with relevant activity in medicinal or agrochemistry incorporate Lewis basic heterocycles as key frameworks,[5] which exhibit inherent ability to bind with a metal catalyst. As a result, the use of *N*-containing heterocycles as efficient DGs offers new synthetic opportunities of paramount importance within the "late-stage" functionalization of organic compounds of high structural complexity. Therefore, expanding the scope of the latter remains

a critical challenge of tremendous impact in the field of C−H functionalization.

Although 1,2,3-triazole scaffold does not occur in Nature, based on its high hydrogen bonding capability, metabolic stability, and amide bioequivalence, it is a privileged core in distinct applied areas such as crop protection, molecular biology, drug discovery and material sciences.[6] In this light, its unique molecular architecture is crucial in a vast array of bioactive peptidomimetics, compounds with important biological activities or even powerful ligands in asymmetric catalysis.[7] Likewise, they are highly promising moieties for supramolecular interactions[7d] (Figure 1).

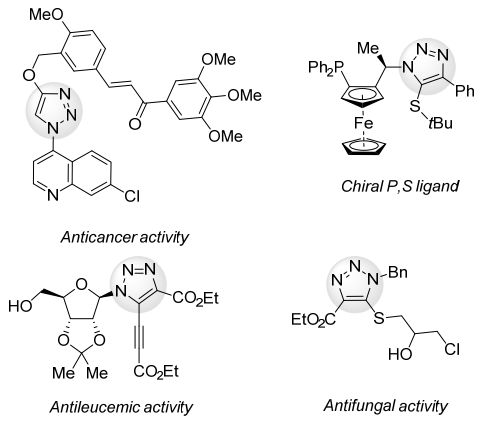


Figure 1. Relevant triazole-containing compounds.

One of the most practical methods for the assembly of 1,2,3-triazoles is often referred to as a “click process”,[8] featuring a Cu-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) to deliver 1,4-disubstituted triazoles.[9] In particular, 4-aryl 1,2,3-triazoles resulting from the atom-economical CuAAC stand out as ideal substrates to develop novel C−H functionalization events. The latter represent powerful techniques for the chemoselective late-stage derivatization of “click compounds”.[9c] However, competitive functionalization of the heterocyclic core constitutes a major drawback to be overcome. In fact, metal-catalyzed functionalizations selectively occurring at the heterocyclic acidic C−H bond are well-documented[10] and are beyond the scope of this microreview. The following review will cover the literature from 2009 up to may 2018 and its goal is to highlight the latest developments on the use of simple “click” 1,2,3-triazoles as well as triazole-containing amides as versatile mono- and bidentate DGs, respectively, in the field of C-H functionalization (Figure 2). The main achievements in this area of expertise have been categorized according to the nature of the bond formed within the oxidative process.

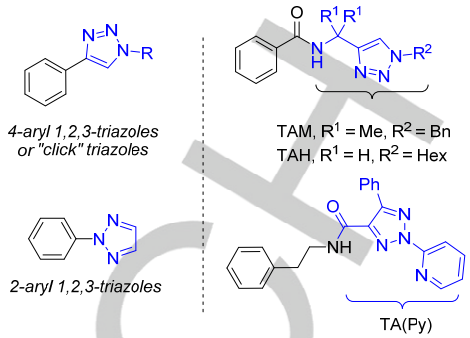


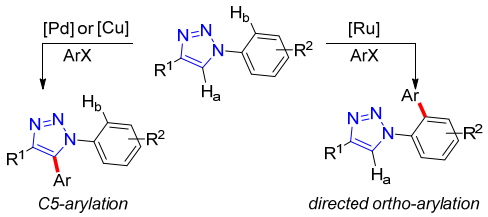
Figure 2. 1,2,3-Triazole containing DGs.

2. C–C Bond-Forming Reactions

In this section, metal-catalyzed *ortho*-C−H functionalizations where a carbon-moiety is introduced in arenes, alkenes or even alkanes upon 1,2,3-triazole assistance will be disclosed.

2.1. C–H Arylations

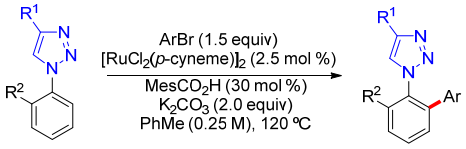
In connection with their studies in Ru-catalyzed direct arylations,[11] in 2008 the Ackermann group introduced for the first time the 1,2,3-triazole heterocyclic scaffold as a modular and practical DG in the field of C(sp^2)–H arylations.[12] Unlike previous reports on the direct arylation of 1-aryl 1,2,3-triazoles where the use of either Pd or Cu catalysts led to the functionalization of the heterocyclic C_5–H bond upon an electrophilic activation-type pathway,[10] the use of Ru catalyst enabled the selective directed C–H arylation to proceed exclusively at the arene ring (H_a *vs* H_b, Scheme 1).



Scheme 1. Regioselectivity of direct arylations in 1-aryl 1,2,3-triazoles.

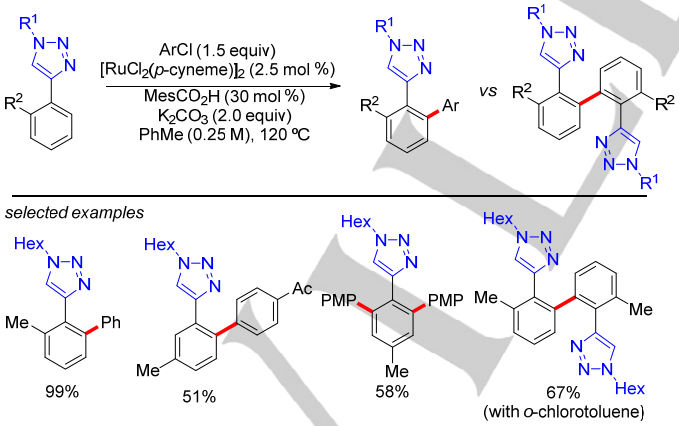
In particular, the use of [$RuCl_2$(*p*-cymene)]$_2$ as catalyst in combination with substoichiometric amounts of sterically hindered 2,4,6-trimethylbenzoic acid ($MesCO_2H$) in toluene as solvent allowed the conversion of aryl bromides into the corresponding arylated compounds in 63-97% yields (Scheme 2). Not only aryl bromides, but a more challenging heteroaryl bromide could be efficiently coupled with the corresponding 1-aryl 1,2,3-triazole derivatives. Interestingly, oxazolines, pyridines and pyrazoles were shown as efficient DGs for the direct arylation under the same reaction conditions. The success of the selective monoarylation was limited to the use of *ortho*-substituted substrates, where a sole C–H bond was available. Although *in-*

depth mechanistic studies were not performed at that early stage, by analogy with related processes the authors assumed a concerted cyclometalation-deprotonation pathway as the more plausible reaction mechanism.



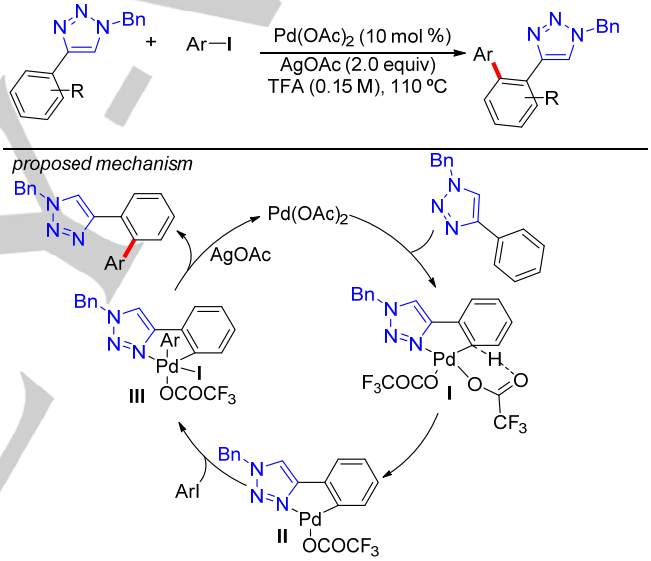
Scheme 2. Ru-catalyzed direct arylation with ArBr.

Shortly thereafter, they reported that the use of an *in situ* formed Ru complex derived from the electron rich PCy_3 as supporting ligand facilitated the employment of inexpensive, yet challenging, aryl chlorides.[13] Whereas selective monoarylation was achieved again by using *ortho*- or even *meta*-substituted arenes, 1-aryl 1,2,3-triazoles with various accessible C(sp^2)−H bonds could selectively underwent either the diarylation process by using excess of aryl bromides or the monoarylation reaction when using less reactive aryl chlorides. Later on, they demonstrated the robustness and utility of the method for the functionalization of related 4-aryl 1,2,3-triazoles.[14] Notably, the reaction conditions previously optimized for the conversion of aryl bromides were found applicable for the successful coupling of aryl chlorides and "click" triazoles. In those cases, the *ortho* and *meta*-substituted arenes delivered preferentially the monoarylated compounds and, conversely, *para*-substituted substrates provided the corresponding diarylated compounds. Interestingly, the coupling of *ortho*-substituted arenes with *ortho*-substituted aryl halides resulted in the unprecedented oxidative homocoupling process where the latter served as the sacrificial hydrogen acceptor (Scheme 3).



Scheme 3. Direct arylation *vs* oxidative homocoupling.

Recently, Jiang and co-workers reported that the use of palladium catalysis can efficiently assist the arylation of 1,4-disubstituted 1,2,3-triazoles.[15] The use of $Pd(OAc)_2$ and an excess of AgOAc in trifluoroacetic acid (TFA) as solvent at 110 °C enabled the successful functionalization of a series of 4-aryl 1,2,3-triazoles with aryl iodides. Whereas the use of *ortho* or *meta*-substituted arenes resulted in the selective formation of the corresponding monoarylated products, non- or *para*-substituted substrates delivered the corresponding diarylated compounds. Unfortunately, more attractive aryl bromides and chlorides remained unreactive under the optimized conditions and the scope of the process was limited to the use of 1-benzyl 1,2,3-triazole as DG. The observed intermolecular kinetic isotope effect (K_H/K_D = 1.2) indicated that the C–H bond cleavage was unlikely to be the rate-limiting step. Based on literature precedents, they assumed a Pd(II)/Pd(IV) mechanism. Initially, the trifluoroacetate anion would assist the required proton abstraction of the arene ring to deliver the 5-membered palladacycle **II** upon selective coordination of the electron-richer N3 atom to the Pd center. Subsequent oxidative addition of the aryl iodide would deliver the Pd(IV) intermediate **III**, which upon reductive elimination ultimately furnish the arylated compound and the active Pd(II) catalyst (Scheme 4).

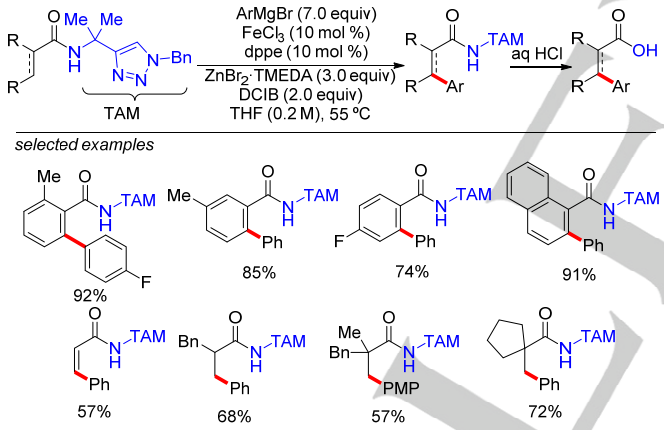


Scheme 4. Pd-catalyzed direct arylation of 4-aryl 1,2,3-triazoles.

Selective arylations of structurally related 2-aryl 1,2,3-triazoles have been also reported in the presence of Ru and Pd catalysis featuring the use of aryl bromides[16] and iodides,[17] respectively. Despite the widespread interest in medicinal chemistry of the latter triazoles, their synthesis is not as simple as their 4-aryl analogues, which are easily prepared in a modular fashion upon "click" chemistry. Accordingly, "click" triazoles stand out as privileged DGs and their use offers an added bonus from a practicality standpoint.

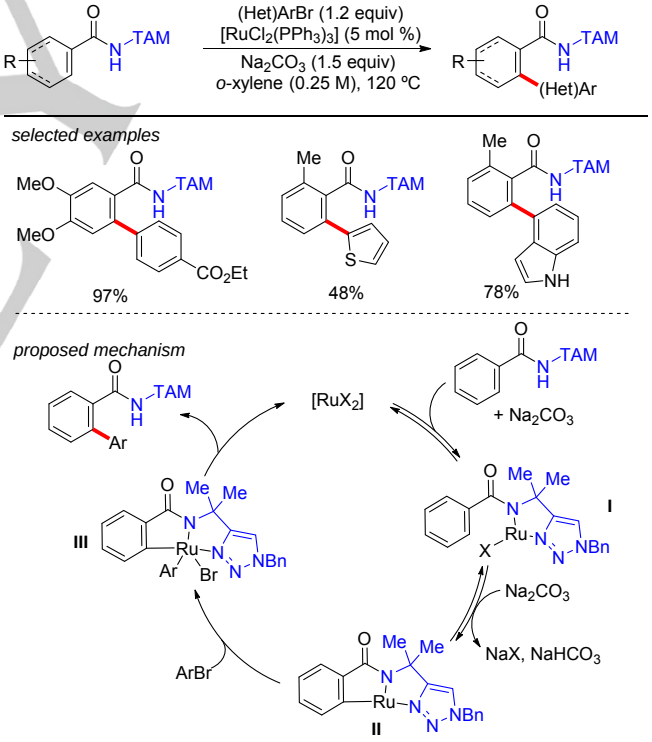
A major breakthrough in the field was achieved in 2014 by the Ackermann laboratory who developed novel triazole-based bidentate auxiliaries to assist C−H arylation reactions.[18] The latter could be forged by the CuAAC in a highly modular manner and eventually removed in a traceless fashion upon acidic treatment. Inspired by the seminal work by Daugulis[19] and Nakamura[20] on the use of 8-aminoquinoline (AQ) motif as a

powerful bidentate DG, they designed a novel family of highly versatile triazole-derived amides for the efficient arylation of arenes, alkenes and even alkanes through the activation of both C(sp^3)−H and C(sp^2)−H bonds. Control experiments revealed the superior activity of the triazolyldimethylmethyl (TAM) group, where the acidic free NH group played a crucial role in the catalyst activation mode and, conversely, the substitution pattern on the N1 atom of the triazole ring was not determinant for the process to occur as *N*-aryl as well as *N*-alkyl substituents could be tolerated. In this respect, a wide range of TAM-containing benzamides smoothly underwent iron-catalyzed arylation reactions with PhMgBr as the aryl source under similar conditions to those reported by Nakamura,[21] albeit a distinct phosphine, 1,2-bis(diphenylphosphino)ethane (dppe) was the ligand of choice. Remarkably, intermolecular competition experiments evidenced the higher activity of the TAM group *vs* the commonly employed AQ scaffold, which could be tentatively attributed to a better stabilization of the *in situ* generated low-valent iron intermediate by the TAM group. Notably, selective mono-arylation was achieved regardless of the substitution pattern of the starting benzamides and the arylation of acrylamides proceeded with excellent diastereoselectivity, thus furnishing the thermodynamically less stable *Z*-olefin as the sole product. Likewise, the TAM group was found active in the challenging arylation of otherwise unreactive C(sp^3)−H bonds and selective functionalization of the primary over the secondary benzylic C−H bonds efficiently occurred.



Scheme 5. Fe-catalyzed direct arylation of triazole-derived amides.

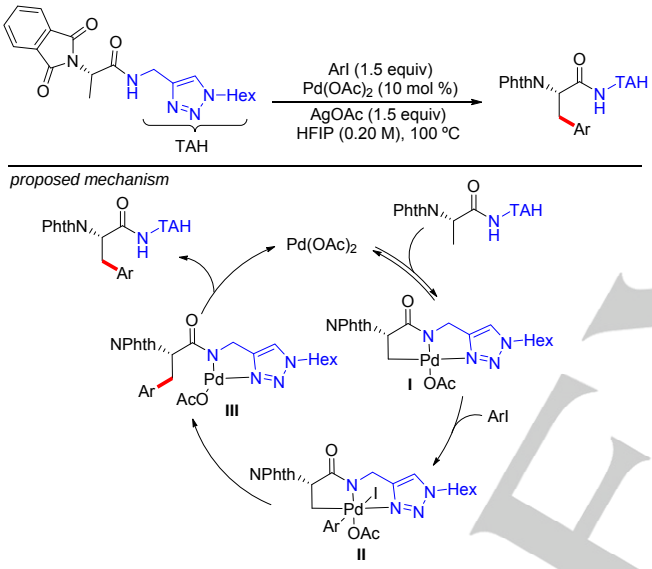
It is noteworthy that site-selective arylations were achieved by a judicious choice of the metal catalyst; whereas an Fe-based catalyst led to the arylation of benzamide directed by the bidentate TAM group, Ru-based reaction conditions led to the selective arylation of the N1-aryl ring upon a monodentate coordination mode of the triazole ring. Despite the significance of the method, the major disadvantages rely on the use of stoichiometric amounts of oxidant, expensive diphosphine ligands, and highly reactive organometallics, which can often limit the functional group tolerance. In this regard, Ackermann and co-workers further developed an improved and practical oxidant-free TAM-directed Ru-catalyzed arylation protocol, featuring the use of (hetero)aryl bromides as the convenient aryl sources.[22] Control experiments revealed the key role of the triazole unit as well as the *gem*-dimethyl substitution pattern in the benzamide backbone to ensure the efficient catalyst performance, and unlike the iron-catalyzed arylation, the use of *N*-aryl triazole-containing substrates were found unreactive under the optimized reaction conditions. Remarkably, the TAM group exhibited a superior activity to the extensively used pyridine or quinolone-based bidentate DGs. A wide variety of arenes, heteroarenes and even alkenes selectively underwent the TAM-directed *ortho*-arylation reaction, including the challenging coupling of 2-thienyl and 4-indolyl bromides (Scheme 6). Concerning the reaction mechanism, deuterium-labelling experiments provided strong support for the elementary step of C−H bond metalation being reversible in nature. On the other hand, based on the observed higher reactivity of electron-deficient benzamides along intermolecular competition experiments a simple electrophilic-type arene activation mode was ruled out. Accordingly, they proposed an initial base-assisted cyclometallation followed by oxidative addition of the aryl bromide to deliver intermediate **III**. Eventually, reductive elimination and proto-demetalation furnished the arylated product and regenerated the active Ru(II) catalyst.



Scheme 6. Triazole-assisted Ru-catalyzed *ortho*-arylation.

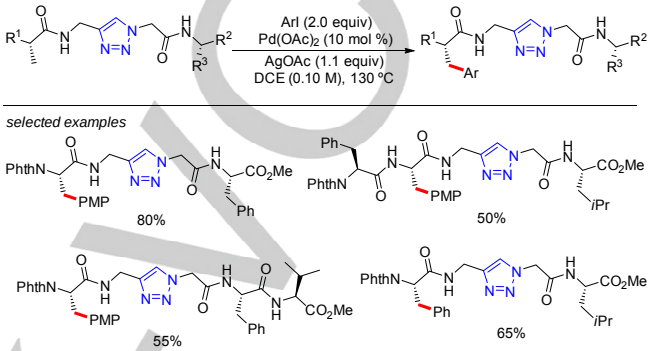
Inspired by the findings by Ackermann, in 2015 Ding and co-workers developed an efficient Pd-catalyzed C(sp^3)−H arylation of amino acid derivatives featuring the employment of a bidentate "click" triazole-containing DG.[23] The use of structurally related TAH group enabled the direct arylation of alanine derivatives with a wide range of aryl iodides under palladium catalysis;

unfortunately, heteroaryl iodides did not provide the corresponding products. Importantly, screening experiments evidenced the crucial role of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the solvent and AgOAc as the oxidant of the process. Whereas the efficient arylation of other substituted *N*-phthaloylalanine and even 3-aminoisobutyric acid derivatives were within reach, other amino acids such as 2-aminobutanoic acid or Phen derivatives did not undergo the desired direct arylation process. The utility of the method was illustrated by the performance of a gram-scale experiment in high yields (93%) and excellent enantiopurity (>96% *ee*). On the basis of literature precedents, they proposed a mechanism consisting of a TAH-directed C(sp^3)−H palladation, followed by an oxidative addition of the corresponding aryl iodide to deliver Pd(IV) intermediate **II**. Finally, reductive elimination would release the product and the active Pd(II) catalyst (Scheme 7).



Scheme 7. Triazole-assisted Pd-catalyzed arylation of amino acids.

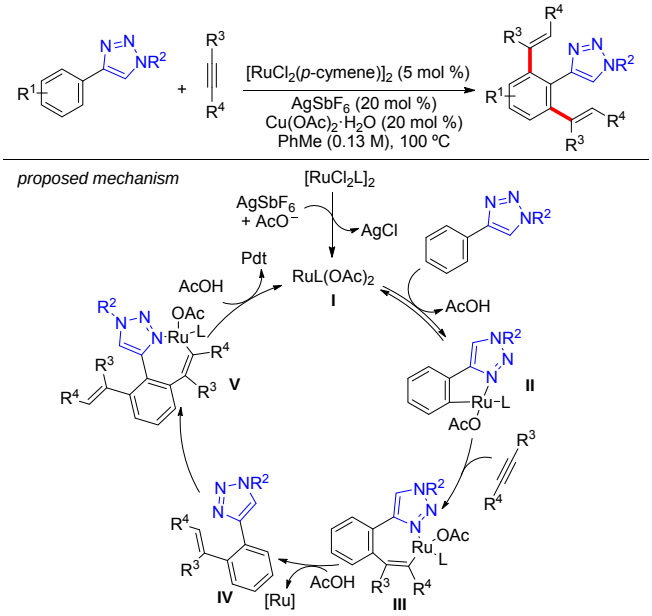
In 2016, the Ackermann group reported a TAM-assisted Pd-catalyzed arylation of benzamides with aryl iodides.[24] Unlike their previous Ru-based method,[22] both *N*-alkyl and *N*-aryl substituted triazoles efficiently directed the corresponding C(sp^2)−H arylation event. Importantly, control experiments with differently substituted benzamide compounds evidenced a clear support for a monoanionic bidentate coordination mode of the TAM group to the Pd catalyst. Prompted by the high price of silver salts, they reported alternative silver-free reaction conditions involving the use of pivalic acid as a key additive, which would presumably support the C−H activation to occur upon a carboxylate assisted concerted metalation/deprotonation (CMD) step, ambiphilic metal-ligand activation or base-assisted intramolecular electrophilic substitution-type (BIES) pathway. More recently, they have exploited the latter Pd-catalyzed arylation means for the elegant late-stage functionalization of peptides.[25] The method was successfully applied for the selective arylation of both primary and secondary C(sp^3)−H bonds, thus outperforming the method by Ding where Phen derivatives remained unreactive.[23] Notably, the arylations proceeded with excellent diastereoselectivity (d.r >20:1), which was rationalized by DFT studies, and HPLC analysis verified that the process occurred without racemization of the existing sterogenic centers. The robustness and versatility of the method was illustrated by the chemo- and positional selectivity toward the internal C(sp^3)−H arylation of a vast array of peptide compounds (Scheme 8).



Scheme 8. Triazole-assisted Pd-catalyzed arylation of peptides.

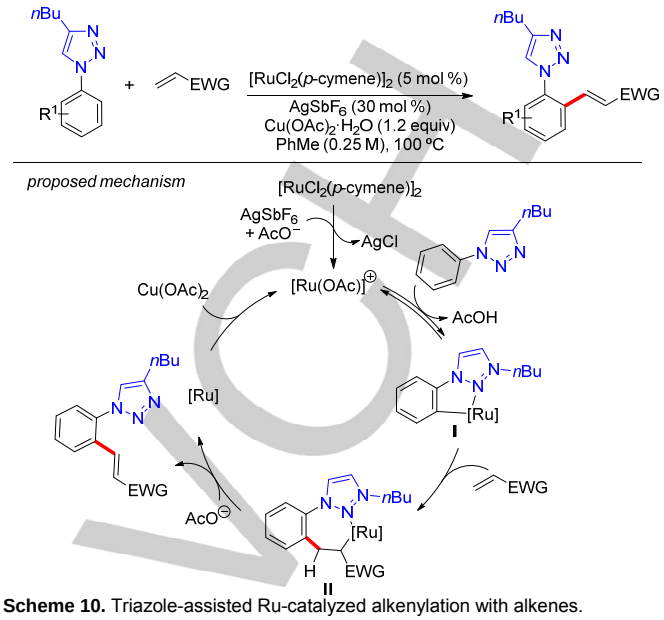
2.2. C–H Alkenylations

Transition metal-catalyzed C−H alkenylation of arenes has emerged as a convenient, yet atom-economical, alternative to the traditional Heck coupling, which involved the use of prefunctionalized substrates. Accordingly, a number of catalysts have been utilized for the directed-alkenylation of arenes with alkynes or alkenes.[26] In 2014, Liu and co-workers developed a Ru-catalyzed olefination of arenes with alkynes assisted by “click” 1,2,3-triazoles.[27] Screening experiments highlighted the key role of $AgSbF_6$ and $Cu(OAc)_2·H_2O$ to ensure the catalyst performance, upon generation of a cationic ruthenium complex. A variety of internal symmetrical diarylalkynes underwent the target dialkenylation of differently substituted 4-aryl 1,2,3-triazoles. Likewise, unsymmetrical internal alkynes regioselectively furnished the corresponding dialkenylated compounds. In contrast, terminal alkynes were not suitable coupling partners. Control experiments with D_2O evidenced that the formation of a rutenacycle upon C−H cleavage was a reversible step. Moreover, intermolecular competition studies provided a KIE value of 2.0, which indicated that the C−H cleavage may be involved in the rate-determining step. As a result, they proposed a mechanism initiated by the carboxylate-assisted, reversible cyclometalation of the triazole moiety to the *in situ* generated cationic Ru(II) complex **I**. The resulting rutenacycle **II** would undergo insertion of the alkyne into the Ru−C bond to deliver the mono-alkenylated compound **IV** through protonation of the corresponding seven-membered rutenacycle **III**. A subsequent similar reaction pathway would provide the corresponding dialkenylated product. Remarkably, slight modifications in the reaction conditions such as using stoichiometric amounts of $Cu(OAc)_2·H_2O$ allowed the use of acrylates and styrenes as alternative coupling counterparts to produce the corresponding *E* stereoisomers in yields of 65-70%.



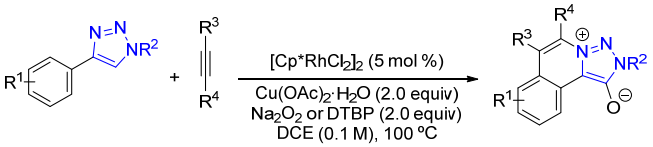
Scheme 9. Triazole-assisted Ru-catalyzed alkenylation with alkynes.

Independently, the Ackermann laboratory developed a related triazole-directed Ru-catalyzed C−H alkenylation protocol.[28] Unlike the method by Liu,[27] where the regioselectivity toward the monoalkenylation with olefins was limited to the use of *ortho*-substituted arenes thus blocking one of the C−H bonds, the method by Ackermann was found applicable to a vast array of substituted 1-aryl 1,2,3-triazoles, and even *N*-methylindole could be oxidatively coupled with the corresponding acrylate. The use of a vinyl ketone led to the corresponding alkylated product in 65% yield. Intermolecular competition experiments evidenced that electron-rich derivatives were more reactive, which supported a base-assisted internal electrophilic substitution-type metalation mode. Furthermore, the performance of the process in the presence of D_2O provided a remarkable H/D scrambling in the *ortho*-position of the recovered starting material and a significant H/D exchange on the C5−H site of the triazole. Those observations were made in the presence of $Cu(OAc)_2·H_2O$, thus constituting an strong support for an acetate-assisted C−H metalation step. Based on the mechanistic studies, they proposed a BIES as the key elemental step to provide the corresponding rutenacycle **I**. Subsequent migratory insertion with the corresponding acrylate would deliver rutenacycle **II**, which would ultimately furnish the coupling product upon β-hydride elimination. Finally, the released Ru(0) species would be then reoxidized by the copper oxidant (Scheme 10).



Scheme 10. Triazole-assisted Ru-catalyzed alkenylation with alkenes.

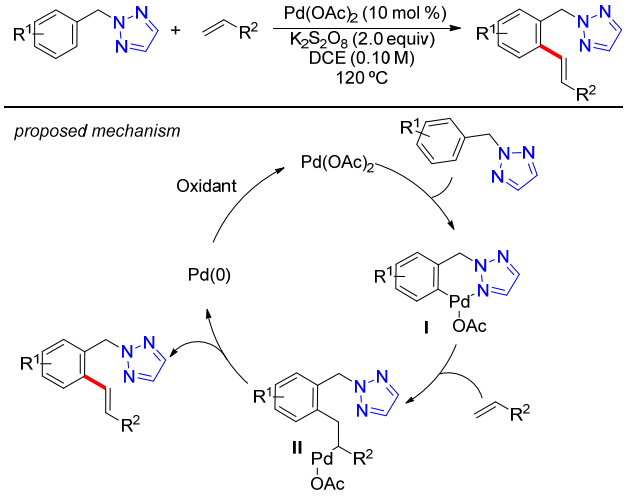
In 2015, Wu, Chen and co-workers introduced the use of Rh(III) catalysts in triazole-directed alkenylations with internal alkynes, which resulted in the unprecedented formation of mesoionic triazolo[5,1-*a*]isoquinolium compounds upon an oxidative alkenylation/annulation sequence.[29] Importantly, the judicious choice of the external oxidant was determinant for the reaction outcome; whereas the use of Na_2O_2 was found beneficial when using dialkylalkynes, di-*tert*-butyl peroxide (DTBP) was required for the conversion of arylalkynes. Interestingly, the selective dialkenylation reaction could occur in the absence of the peroxide when using aromatic internal alkynes. In a follow-up study, they demonstrated the superior activity of rhodium NHC complexes in the vinylation of a series of 4-aryl 1,2,3-triazoles and low catalyst loading of the latter were sufficient to enable the introduction of acrylates and styrenes into the corresponding "click" 1,2,3-triazoles.[30]



Scheme 11. Rh-catalyzed assembly of triazolo[5,1-*a*]isoquinolium derivatives.

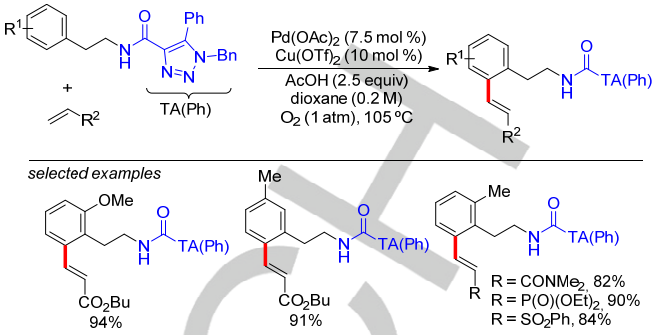
In connection with their interest in the use of 2-substituted triazole derivatives, in 2015 the Kuang laboratory reported a Pd-catalyzed *ortho*-alkenylation of 2-benzyl 1,2,3-triazoles with activated olefins such as alkyl acrylates, acrylonitrile or acrylamides.[31] A variety of arenes could be efficiently mono-functionalized with the aid of triazole-chelation assistance. Remarkably, the unique reactivity of the triazole scaffold was evidenced by the alternative use of a related pyrazole ring as the DG, which was found unreactive under the optimized conditions. Based on previous reports on Pd-catalyzed C−H functionalization reactions, they proposed a reaction mechanism where the 6-membered

palladacycle **I** would undergo an olefin insertion to produce intermediate **II**. Subsequent β-hydride elimination would then deliver the target product and Pd(0), which would be ultimately regenerated by $K_2S_2O_8$ to the corresponding Pd(II) catalyst (Scheme 12).



Scheme 12. Pd-catalyzed alkenylation of 2-benzyl 1,2,3-triazoles.

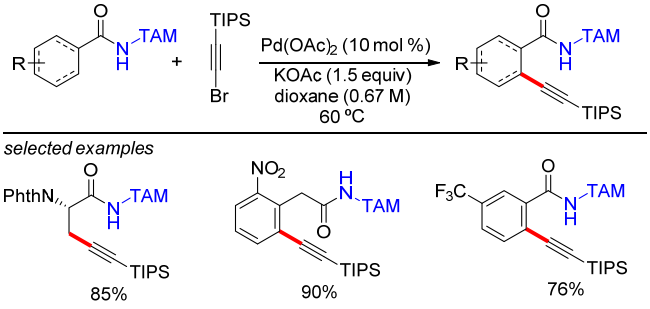
Aside from the use of monodentate 1,2,3-triazoles, Shi and co-workers successfully implemented the use removable 1,2,3-triazole-4-carboxylic acids as DGs in the Pd-catalyzed aerobic C−H olefination of arenes.[32] Owing to competitive oxidative Heck-type reactions into the heterocyclic unit, a 4,5-disubstituted triazole where the acidic triazole site was blocked was envisioned as the active DG. In particular, they utilized the triazole amide TA(Ph) as the DG for the oxidative coupling of arenes with a number of activated olefins such as acrylates, acrylamides, vinyl phosphate, vinyl sulfone or styrenes (Scheme 13). Unfortunately, α- or β-substituted alkenes failed to provide the target products. The higher efficiency of the triazole-based bidentate DG was highlighted by control experiments with other commonly used *N*-chelating groups such as quinolines, pyridines or imidazoles, which led to poor yields under the optimized conditions. Importantly, the process could be accomplished with molecular oxygen as the terminal oxidant and the use of an excess amount of alkenes resulted in the selective diolefination reaction in high yields. Prompted by early findings by the Ackermann group, they further explored the latter reaction featuring the use of TAM as the DG, where the heterocyclic C5−H site remained unblocked. Notably, a wide range of substrates successfully underwent the corresponding olefination reaction including biologically relevant estrone derivatives.[33]



Scheme 13. Pd-catalyzed alkenylation with bidentate triazole TA(Ph) as DG.

2.3. C–H Alkynylations

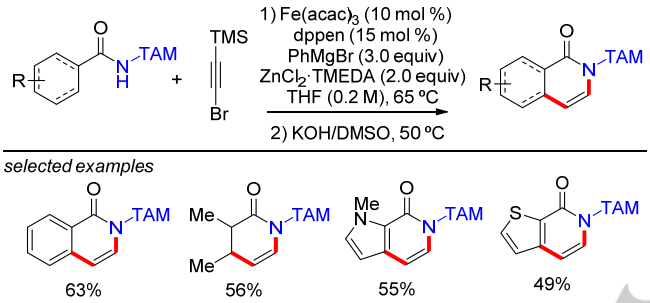
Following their interest in triazole-directed C−H functionalization processes, Shi, Chen and co-workers utilized the TAM group for the Pd-catalyzed alkynylation of C(sp^2)−H and C(sp^3)−H bonds with alkynyl bromides.[34] They first prepared a TAM-containing palladacycle, which was unambiguously characterized by X-ray crystallography, and ESI-MS analysis verified that it could successfully undergo further oxidation to the corresponding Pd(IV) intermediate upon treatment with a bromoalkyne compound. These control experiments set the stage for the optimization of the reaction conditions and accordingly a Pd-catalyzed silver-free method was developed. Remarkably, not only *N*-protected amino acids but also other cyclic substrates could be alkynylated in 70-86% yields (Scheme 14). Likewise, TAM-amides derived from phenyl acetic and benzoic acids smoothly underwent the selective mono-alkynylation process. The practicality of the protocol was demonstrated by the performance of a 2.5 mmol gram-scale synthesis of a β-alkynyl amino acid derivative without significant racemization of the existing stereocenter (95% *ee*). The main limitation relied on the alkyne scope, which was restricted to the use of 2-bromo-1-triisopropylsilyl acetylene as the coupling partner.



Scheme 14. TAM-assisted Pd-catalyzed C−H alkynylations.

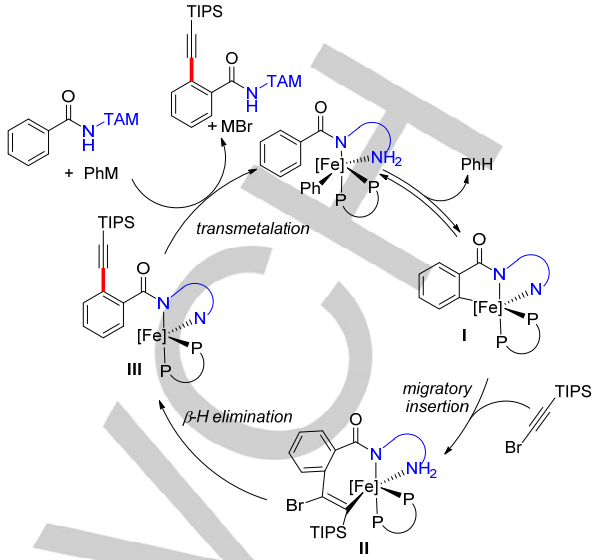
Very recently, the Ackermann laboratory has developed a practical TAM-directed Fe-catalyzed alkynylation, which can be performed in a sequential C−H functionalization/annulation manner toward the assembly of relevant heterocyclic compounds such as isoquinolones, pyridines, isoindolinones and

pyrrolones.[35] Under similar conditions reported by Nakamura, both *N*-aryl and *N*-alkyl triazole amines could serve as efficient DGs. Remarkably, arenes, heteroarenes and even alkenes underwent the corresponding alkynylation reaction in moderate to good yields. Likewise, different silicon alkynyl derivatives could be introduced into the corresponding TAM-derived benzamides, albeit bromo derivatives provided higher yields than the iodo- and chloro-analogues. Interestingly, the combination of the TAM-directed alkynylation reaction with a subsequent desilylation step under basic conditions provided a rapid, yet elegant, access to a variety of isoquinolone compounds through a regioselective 6-*endo*-dig cyclization mode (Scheme 15). On the contrary, the use of a *p*-methoxyphenyl triazole moiety led to the 2-step synthesis of isoindolinone and pyrazolone derivatives upon a distinct, regioselective 5-*exo*-dig cyclization mode.



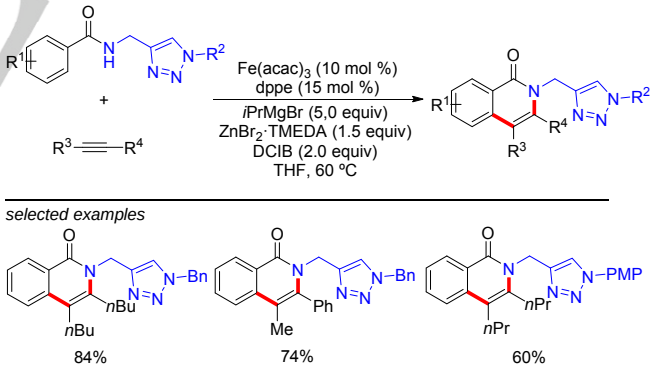
Scheme 15. TAM-assisted Fe-catalyzed tandem C−H alkynylation/annulation.

In order to gain some insights into the reaction mechanism, several experiments were conducted: 1) intermolecular competition experiments evidenced the higher reactivity of electron-deficient arenes, which could support a deprotonative σ-bond metathesis (DBM) as the key step; 2) radical traps did not inhibit the process, which may rule out a radical mechanism; and 3) the lack of KIE (K_H/K_D = 1.1) may suggest that the C−H metalation step was not kinetically relevant. Accordingly, their mechanism proposal was initiated by a reversible C−H metalation to produce the metalacycle **I**. Migratory insertion of the bromo alkyne compound would provide intermediate **II**, which upon β-bromo elimination would deliver species **III**. Finally, transmetalation with the *in situ* generate aryl zinc species would furnish the alkynylated product.



Scheme 16. Mechanism proposal for the Fe-catalyzed C−H alkynylation.

In a follow-up study, Ackermann and co-workers developed a triazole-directed Fe-catalyzed C−H functionalization/annulation process involving the use of disubstituted alkynes toward the preparation of isoquinolone derivatives.[36] Whereas the success of the previously used TAM group was partially due to the *gem*-disubstitution on the methylene backbone, the devoid of the latter was strictly required for the current tandem process. A number of symmetrical and unsymmetrical alkynes regioselectively furnished the corresponding 3,4-substituted isoquinolone derivatives.

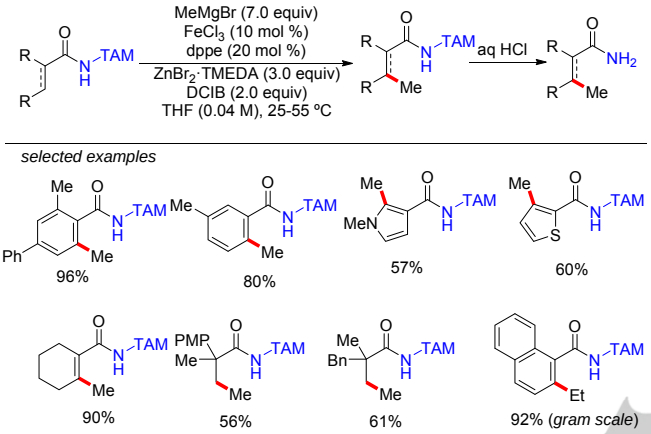


Scheme 17. Fe-catalyzed internal alkyne annulation.

2.4. C–H Alkylations

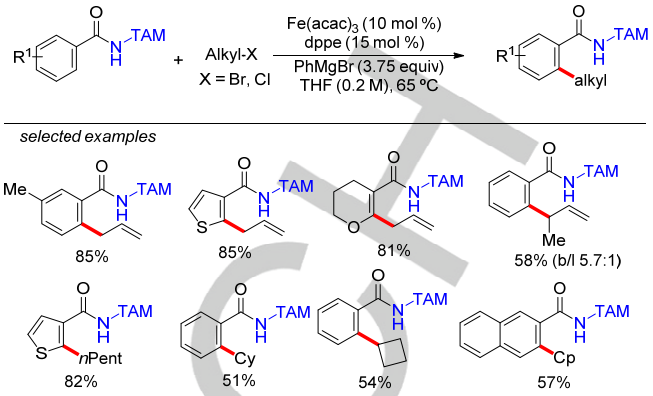
Owing to the often fast β-hydride elimination, an alkylation reaction using alkylmetal compounds has commonly been more challenging than that of arylation. In 2015, the Ackermann group reported a novel methylation procedure by TAM-assistance featuring the use of MeMgBr as the alkylating agent,[37] thus complementing studies by Nakamura and co-workers which upon picolinoyl and 8-aminoquinolyl chelation employed $AlMe_3$ as the alkyl source.[38] Control experiments with a number of amides as

the DG evidenced the mono-anionic bidentate coordination mode of the TAM auxiliary, which offered significant advantages such as its removable ease and modular installation upon "click" chemistry. The iron-based catalyst was found widely applicable for the efficient methylation of (hetero)arenes, alkenes as well as otherwise unreactive alkanes with MeMgBr. Remarkably, the chemoselective functionalization at the stronger methyl C−H bond over the activated benzylic site strongly favored an organometallic activation mode, which was also supported by the KIE of 1.8. Notably, not only methylation but also the challenging parent ethylation with β-H containing EtMgBr as the alkylating agent was within reach upon the TAM-assisted iron-catalyzed protocol.



Scheme 18. Fe-catalyzed methylation with MeMgBr.

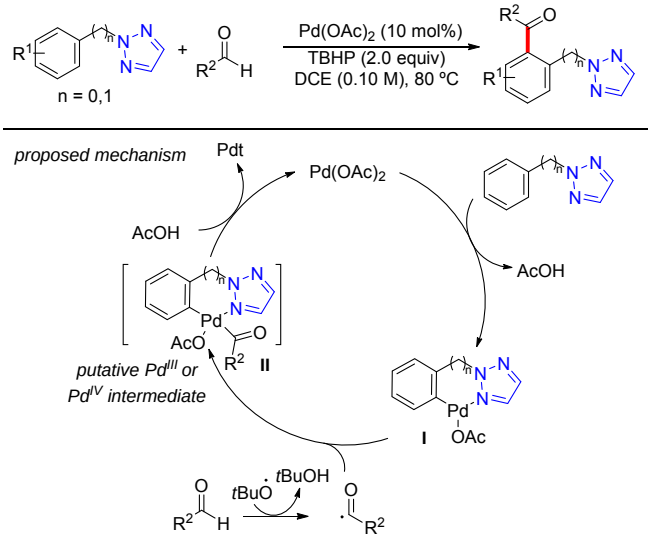
Later on, independently to the discoveries by Cook[39] and Nakamura,[40] Ackermann and co-workers devised a widely applicable method for the C–H alkylation of C(sp^2)−H bonds under triazole assistance featuring the convenient use of alkyl halides.[41] In particular, the use of $Fe(acac)_3$/dppe as catalyst system and PhMgBr as the base led to the efficient allylation of TAM-amides derived from (hetero)arenes and alkenes with allyl chloride. The use of differently substituted allyl chlorides provided the corresponding *ortho*-allylated benzamides with moderate regioselectivity (branched *vs* linear isomer, up to 5.5:1). Notably, a variety of alkyl bromides, including challenging secondary alkyl bromides were found to be competent electrophilic substrates in the alkylation of TAM-amides derived from arenes and heteroarenes. A SET mechanism was supported by the following control experiments: 1) 6-bromohex-1-ene provided the corresponding cyclized product; 2) cyclopropylmethyl bromide furnished the homoallylated product and 3) the diasteromerically pure *cis*-alkyl bromide delivered the target product with a high erosion of the stereochemistry.



Scheme 19. TAM-directed Fe-catalyzed alkylation.

2.5. C–H Acylations

In the last years a variety of functional groups bearing heteroatoms such as pyridines, amides or carboxylic acids have been utilized as the DGs in the *ortho*-acylation of arenes. In 2014, the Kuang group introduced the complementary use of 1,2,3-triazoles as monodentate DGs for the oxidative coupling of both 2-benzyl[42] and 2-phenyl triazole compounds[43] with aldehydes under palladium catalysis. In particular, a combination of $Pd(OAc)_2$ with an aqueous solution of *tert*-butyl hydroperoxide (TBHP) as oxidant enabled the regioselective *ortho*-acylation of arenes with both aromatic and aliphatic aldehydes. Based on previous studies, they proposed a reaction pathway initiated by the formation of the palladacycle **I**, which could further undergo the addition of an acyl radical, *in situ* generated from the reaction of TBHP with the corresponding aldehyde. The resulting Pd(IV) intermediate **II**, which could exist as an alternative dimeric Pd(III) species, would eventually deliver the acylated product through reductive elimination, thus regenerating the active Pd(II) catalyst.



Scheme 20. Pd-catalyzed *ortho*-acylation of 2-substituted 1,2,3-triazoles.

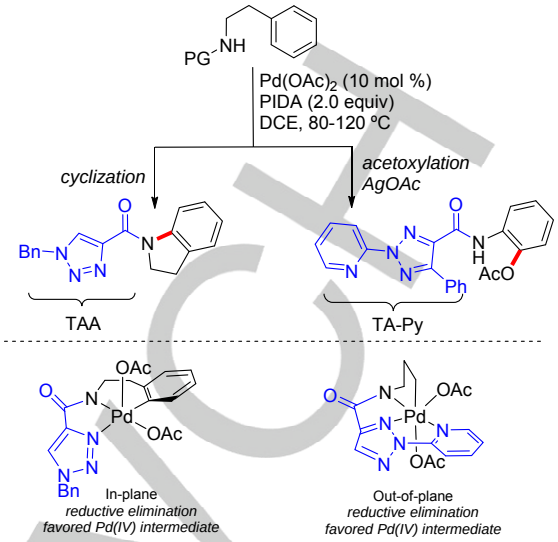
A related system was applied by the Jiang group for the *ortho*-acylation of "click" 1,4-diaryl 1,2,3-triazoles with aromatic aldehydes.[44] Unlike the method by Kuang,[43] the addition of XPhos as supporting ligand was found to significantly enhance the reaction yields. Importantly, regardless of the nature of the substitution pattern of the aryl ring the corresponding *ortho*-acylation was selectively achieved. More recently, Xie and co-workers described a related Pd-catalyzed decarboxylative acylation reaction featuring the use of arylglyoxylic acids as the acyl source.[45] In comparison with the use of 2-substituted triazoles, the practical added bonus from using 1,4-disubstituted triazoles relied on their rapid and simple assembly in a modular fashion upon "click" chemistry.

3. C–Heteroatom Bond-Forming Reactions

The direct conversion of a C–H bond into a C–heteroatom bond represents a tremendous challenge in organic synthesis. In this section, metal-catalyzed *ortho*-C−H functionalizations, where a heteroatom-containing motif is introduced in arenes, alkenes or even alkanes upon 1,2,3-triazole assistance will be disclosed.

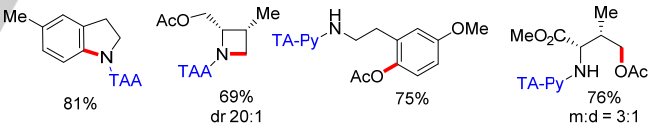
3.1. C–O Bond Forming Processes

In connection with the application of 1,2,3-triazole-4-carboxylic acids as versatile DGs in olefination reactions,[32] in 2013 the Shi group described highly selective cyclization and acetoxylation reactions under palladium catalysis.[46] Interestingly, the nature of the triazole-containing group was crucial in boosting the selectivity; whereas the use of TAA as the DG led to the cyclization products through the formation of a new C–N bond, the use of TA-Py provided the acetoxylated products upon formation of a new C–O bond (Scheme 21). The authors proposed a Pd(II)/Pd(IV) catalytic cycle where the use of TA-Py, which could behave as a tridentate DG, may force the Pd–C bond into the axial position thereby favoring the out-of-plane C–O bond-forming reductive elimination pathway. Conversely, the use of TAA as the DG would result in the formation of cyclized products through the in-plane C–N bond-forming reductive elimination mode (Scheme 21). Further computational studies by Li and co-workers indicated that the latter reaction pathways were kinetically favored.[47] However, their DFT studies revealed that the acetoxylation would likely proceed through the in-plane mode and the cyclization through an out-of-plane mode, which are contrary to the proposal by Shi. Therefore, *in depth* mechanistic studies are required to support a plausible reaction mechanism.



Scheme 21. Pd-catalyzed cyclization *vs* acetoxylation reaction.

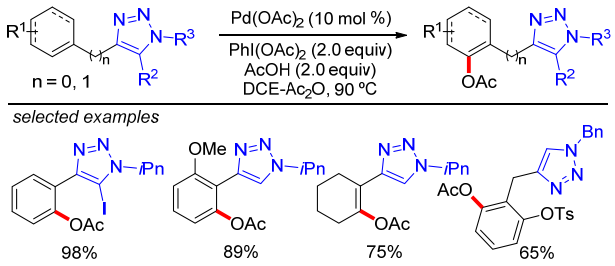
As shown in Scheme 22, TAA effectively assisted the functionalization of both C(sp^2)–H and C(sp^3)–H bonds under palladium catalysis and in the presence of $PhI(OAc)_2$ as the oxidant. Remarkably, the activation of primary over secondary C(sp^3)–H bonds was successfully achieved to yield the corresponding azetidines with high diastereoselectivity. Likewise, the use of TA-Py led to the selective acetoxylation reaction on aryl and alkyl substituted amides. Although mono-functionalization was within reach on *ortho*- or *para*-substituted arenes, the corresponding diacetoxylation could be achieved in the presence of excess of PIDA.



Scheme 22. Selected examples of cyclization and substitution reaction.

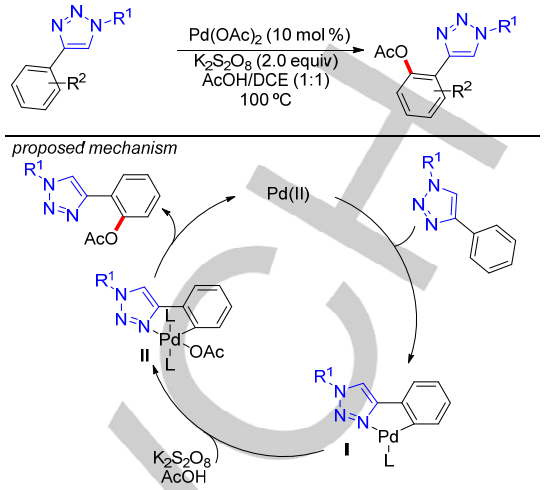
In 2016, Correa and co-workers described an alternative C(sp^2)–H oxygenation reaction featuring the use of simple "click" triazoles as monodentate DGs.[48] Notably, the corresponding mono-oxygenated arenes and even alkenes were obtained upon DG and substrate-controlled selectivity. In this regard, whereas the use of *ortho*- or *meta*-substituted arenes resulted in the exclusive formation of the corresponding mono-oxygenated compounds, substrates with two C(sp^2)–H available led to mixtures of mono and difunctionalized compounds. Interestingly, the particular use of 5-iodotriazoles resulted in the exclusive mono-oxygenation reaction, upon a DG-controlled reaction pathway (Scheme 23). The authors reasonably assumed that once the mono-oxygenation occurred, the bulky iodine atom could block the free-rotation of the aryl ring, thus hampering the formation of the

corresponding palladacycle to activate the remaining *ortho* C−H bond. Although the use of 5-iodo 1,2,3-triazoles could be an apparent synthetic limitation at first sight, the authors illustrated the ample opportunities of the resulting 5-iodo-oxygenated compounds in the assembly of fully decorated 1,2,3-triazoles upon conventional Pd-catalyzed cross-coupling techniques. Importantly, not only acetoxylations but also more challenging pivaloxylations could be accomplished by using $PhI(OPiv)_2$ as the oxidant under slightly modified reaction conditions. Shortly thereafter, Jiang and co-workers optimized the Pd-catalyzed diacetoxylation reaction of "click" triazoles by utilizing a high excess (5 equiv) of PIDA as the oxidant.[49]



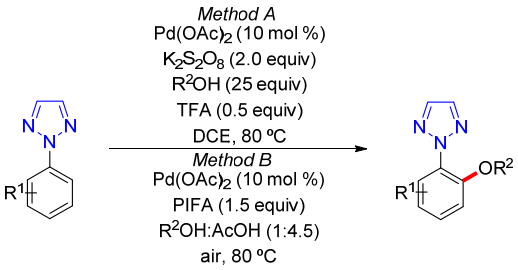
Scheme 23. Pd-catalyzed oxygenation of "click" triazoles.

In subsequent studies by the Jiang group, the regioselective mono-acetoxylation of "click" triazoles was successfully achieved by utilizing cheap $K_2S_2O_8$ as the oxidant of the process and AcOH as the acetoxy source.[50] In this regard, a number of 4-aryl 1,2,3-triazoles and even a challenging thiophene-containing compound were efficiently acetoxylated in a selective manner. The intermolecular kinetic isotope effect (K_H/K_D = 3.9) evidenced that the C−H bond cleavage may be involved in the rate-limiting step. Based on previous studies, they proposed that the electron richer N3 atom of the triazole would first coordinate to the Pd catalyst thus delivering the corresponding palladacycle **I**. Further oxidation by $K_2S_2O_8$ in the presence of AcOH would afford the reactive Pd(IV) intermediate **II**, which upon reductive elimination would ultimately furnish the *ortho*-acetoxylated product and the Pd(II) catalyst (Scheme 24). More recently, the convenient use of $Cu(OAc)_2$ instead of $Pd(OAc)_2$ in combination with PIDA as the oxidant led to the development of a more cost-efficient acetoxylation method upon the use of 1-benzyl 1,2,3-triazole as the DG.[51] Remarkably, unlike the method by Correa,[48] the use of $Cu(OAc)_2$ resulted in the selective mono-acetoxylated "click" compounds even in non-substituted arenes.



Scheme 24. Pd-catalyzed oxygenation of "click" triazoles.

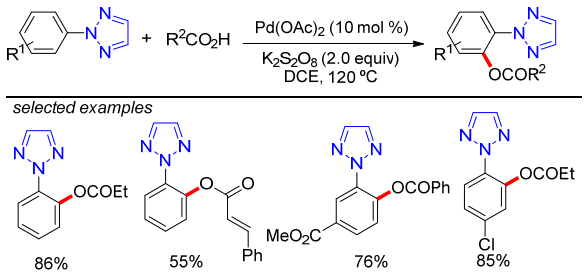
In 2014, Kuang and co-workers developed a directed Pd-catalyzed *ortho*-alkoxylation reaction featuring the use of alcohols as the oxygenated source (Scheme 25, method A).[52] A variety of acyclic and cyclic alcohols smoothly underwent the alkoxylation reaction in the presence of $K_2S_2O_8$ as the oxidant and trifluoroacetic acid as additive. Unfortunately, the challenging $C(sp^3)$–H alkoxylation upon 2-alkyl 1,2,3-triazoles could not be performed under the optimized conditions. Whereas the triazole ring selectively assisted the mono-alkoxylation reaction, the use of pyridine as the DG resulted in the exclusive dialkoxylation reaction, which highlighted the unique properties of 1,2,3-triazole scaffold. At the same time, the Shi group reported a related Pd-catalyzed aerobic *ortho*-alkoxylation of 2-aryl triazoles involving $PhI(OTFA)_2$ as the oxidant (Scheme 25, method B).[53] In both cases, a mechanism involving a Pd(II)/Pd(IV) catalytic cycle was proposed.



Scheme 25. Pd-catalyzed alkoxylation of 2-aryl 1,2,3-triazoles.

In a follow-up study, Kuang and co-workers developed a related a Pd-catalyzed oxidative coupling with numerous alkyl and aryl carboxylic acids as well as cinnamic acids to produce the corresponding acyloxylated compounds (Scheme 26).[54] Interestingly, the corresponding paladacycle was isolated and characterized by ^1H NMR, and its further oxidation to the corresponding Pd(IV) intermediate was proposed as the plausible mechanistic scenario. Eventually, C–O bond-forming reductive

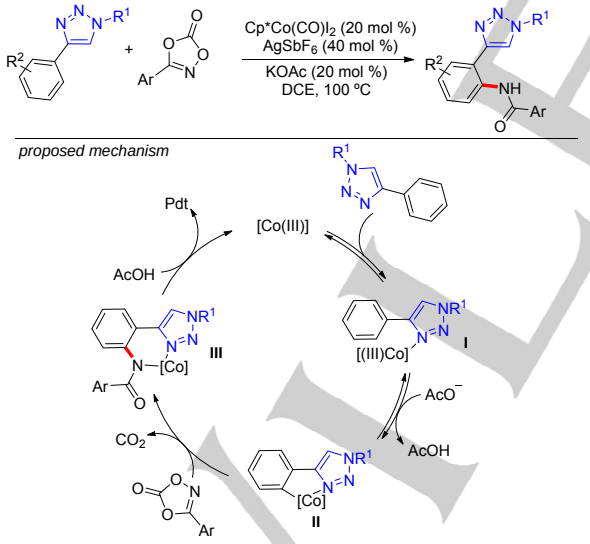
elimination would deliver the target product and the active Pd(II) catalyst.



Scheme 26. Pd-catalyzed acyloxylation with carboxylic acids.

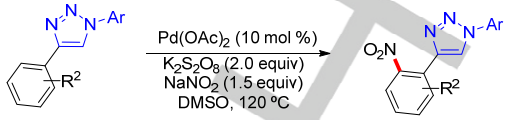
3.2. C–N Bond Forming Processes

In 2016, Chen and co-workers reported the first C(sp^2)–H amidation reaction assisted by "click" triazoles.[55] In particular, the use of a combination of a Co(III) salt along with $AgSbF_6$ enabled the amidation of 4-aryl 1,2,3-triazoles with dioxazolone derivatives. In all cases, the *N*-alkyl triazole unit efficiently directed the selective *ortho*-amidation reaction. The proposed mechanism would start by the *in situ* generation of the active cationic Co species and its further coordination with the triazole ring would deliver the cobaltacycle intermediate **II**. Subsequent coupling with the corresponding dioxazolone with concomitant release of CO_2 would afford complex **III**, which upon reductive elimination would furnish the amidated compound.



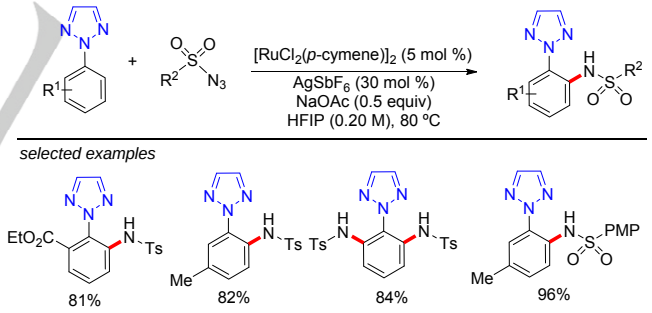
Scheme 27. Co-catalyzed amidation of "click" triazoles.

Shortly thereafter, the group of Jiang devised a Pd-catalyzed nitration reaction of arenes with $NaNO_2$ as the nitro source through triazole assistance (Scheme 28).[56] A variety of 1,4-diaryl triazoles selectively delivered the corresponding *ortho*-nitrated compounds in 60-92% yields.



Scheme 28. Pd-catalyzed nitration of "click" triazoles.

Not only practical "click" triazoles, but also 2-aryl 1,2,3-triazoles have been employed in oxidative C–N bond forming processes. In 2016, Cui, Wu and co-workers developed an Ir-catalyzed C–H sulfonamidation process assisted by 1,2,3-triazole *N*-oxides featuring the use of sulfonyl azides as the nitrogen source.[57] Interestingly, the use of sulfonyl azides produced N_2 as the sole by-product and avoided the requirement of an external oxidant, as other common nitrogen sources. Aside from triazole *N*-oxides, a few examples using the parent deoxygenated triazoles as the DG were reported; however, an *ortho*-substituted arene seemed to be required to achieve the selective mono-functionalization reaction. Later on, Wang *et al* introduced a cheaper Ru-based method for the C–H amidation of 2-aryl 1,2,3-triazoles with sulfonyl azides (Scheme 29).[58] Whereas the use of *ortho*- or *meta*-substituted arenes led to the selective *mono*-sulfonamidation process, the selective difunctionalization process was achieved when using *para*-substituted arenes in the presence of an excess of the corresponding azide.

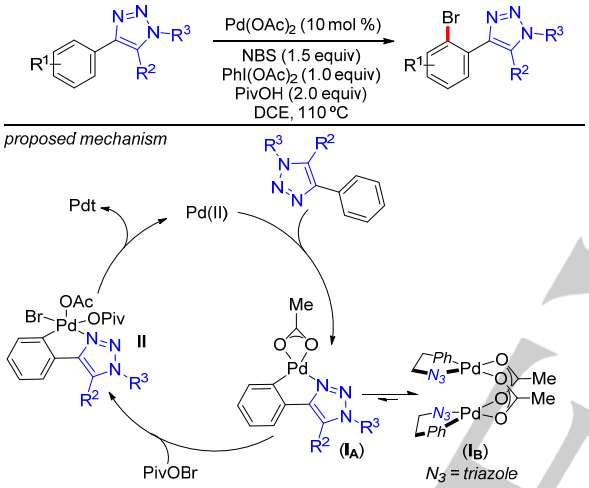


Scheme 29. Ru-catalyzed sulfonamidation of 2-aryl triazoles.

3.3. C–Halogen Bond Forming Processes

Prompted by the widespread utility of aryl halides in synthetic chemistry, in 2017 Correa and co-workers developed a novel Pd-catalyzed C(sp^2)−H halogenation of arenes directed by modular "click" triazoles.[59] Whereas electron-neutral and electron-deficient arenes selectively underwent the corresponding Pd-catalyzed triazole-directed C−H *ortho*-halogenation, electron-rich arenes were regioselectively halogenated following a distinct electrophilic aromatic substitution reaction pathway. In particular, they found that the use of *N*-bromosuccinimide together with

PivOH and $PhI(OAc)_2$ was determinant for the halogenation of "click" compounds. Control experiments as well as computational studies supported the intermediacy of pivaloyl hypobromite (PivOBr) as the most plausible *in situ* formed brominating agent (Scheme 30). Moreover, the paladacycle **I_B** was prepared and unambiguously characterized by X-ray analysis, which evidenced its bimetallic nature. Based on stoichiometric experiments and DFT studies, they proposed that the process would start by a cyclopalladation process to furnish the bimetallic species **I_B**, which was confirmed by DFT studies to be more stable than its monomeric species **I_A** and thus a dissociation could occur prior to the subsequent oxidation step. Likewise, DFT studies revealed that the oxidation step was energetically more favorable assisted by *in situ* generated PivOBr than NBS. Eventually, C−Br bond-forming reductive elimination from the monometallic Pd-intermediate **II** would afford the desired product and regenerate the active Pd catalyst.



Scheme 30. Pd-catalyzed bromination of "click" triazoles.

The Kuang group demonstrated that 2-aryl 1,2,3-triazoles could be an efficient platform for the development of appealing Pd-catalyzed C(sp^2)−H halogenation reactions.[60] Unlike the method by Correa restricted to the use of NBS,[59] other *N*-halosuccinimides led to the efficient chlorination and iodination of the corresponding arenes. Remarkably, high selectivity toward the mono-halogenation reaction was always achieved, regardless of the substitution pattern of the arene.

4. Conclusions

In this Microreview the current state of the art in the triazole-directed C–H functionalization processes has been described. Transition metal-catalyzed C–H functionalization is a rapidly evolving research area, which has become a powerful and practical means for the assembly of structurally diverse organic compounds. One of the most common approaches implies the use of a DG, which by coordination to a metal catalyst enables the selective activation of a proximal C−H bond through a cyclometalation process. In this light, although a wide variety of DGs have been effectively utilized, expanding the scope to other versatile motifs still remains a critical challenge. Owing to their prevalence in drug discovery and their modular, yet advantageous, assembly upon "click" chemistry, 1,2,3-triazoles stand out as privileged heterocyclic scaffolds. Accordingly, triazole-directed C−H functionalization reactions constitute unique tools of utmost importance for the late-stage diversification of "click compounds", thus enabling the build-up of molecular diversity in a simple fashion. Despite the advances realized, several challenges need to be addressed to render triazole-directed procedures the method of choice for the construction of those compounds in industrial environments. Firstly, C−heteroatom bond-forming reactions are still rare in the literature and mostly limited to the use of expensive transition metals. A considerable step-forward would consist in the implementation of cost-efficient base metal calatysts, thus offering new attractive, yet sustainable, synthetic perspectives. Secondly, whereas the functionalization of C(sp^2)−H bonds upon triazole assistance is well-developed, the parent processes with C(sp^3)−H bonds are comparatively less explored and limited to the use bidentate DGs. Thirdly, few advances have been made in the development of asymmetric triazole-directed reactions. Accordingly, the pursuit of novel C(sp^3)–H coupling processes which occur in an enantioselective fashion still remains an elusive goal, and it would clearly open up new synthetic opportunities of paramount chemical significance in the synthesis of complex triazole-containing compounds. As a result, we anticipate that efforts along these lines would have a significant impact on this field of expertise and we hope this microreview could encourage practitioners in the area to look into unprecedented triazole-assisted transformations.

Acknowledgements

We are grateful to MINECO (CTQ2016-78395-P) and Gobierno Vasco (IT_1033-16) for financial support. A. C. thanks MINECO for a Ramón y Cajal research contract (RYC-2012-09873). Cost-CHAOS action (CA15106) is also acknowledged.

Keywords: 1,2,3-triazole • C−H functionalization • click • *N*-heterocycle • cross-coupling

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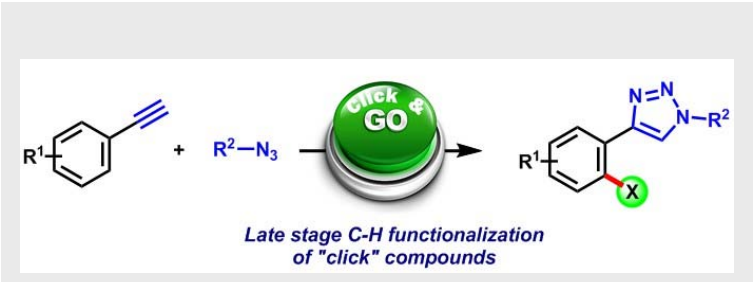

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Metal-catalyzed C–H functionalization processes upon "click"-triazole assistance

This microreview summarizes the most recent advances on the use of 1,2,3-triazoles as versatile directing groups in the field of C–H functionalization. The main feature relies on the modular and straightforward assembly of the required triazoles upon "click" chemistry and hence those procedures constitute practical synthetic tools of utmost importance for the late-stage diversification of "click compounds", which are prevalent moieties in drug discovery and material science.