Regioselective syntheses of fully-substituted 1,2,3-triazoles: the CuAAC/C–H bond functionalization nexus

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Regioselective syntheses of 1,4,5-trisubstituted 1,2,3-triazoles were accomplished by three different strategies, relying on (i) the interception of stoichiometrically formed 5-cuprated-1,2,3-triazoles, (ii) the use of stoichiometrically functionalized alkynes or (iii) catalytic C–H bond functionalizations. This perspective article summarizes progress in this research area until June 2010.

Introduction

1,2,3-Triazoles are indispensable structural motifs of compounds with increasing importance in diverse research areas, ranging from medicinal chemistry or crop protection to material sciences.[1] These heteroarenes have proved particularly valuable as genuine amide surrogates in bioactive molecules, because of their physicochemical properties (peptide isosteres), in addition to their remarkable metabolic stability.[2] While 1,2,3-triazoles are not present in naturally occurring compounds, the "amide-triazole bioequivalence" was exploited for the development of among others HIV-1 protease inhibitor **1**,[3] potential anticancer agent **2**,[4] or non-nucleoside reverse transcriptase inhibitor **3** (Fig. 1).[5]

The synthesis of substituted 1,2,3-triazoles strongly relies on Huisgen's 1,3-dipolar cycloaddition between organic azides and substituted alkynes.[6] While this technique proved to be highly versatile, the thermal conversion of unsymmetrically-substituted alkynes usually resulted in difficult to separate mixtures of regioisomers (Scheme 1).

A major advance in improving the regioselectivity, as well as reaction rate, of azide-alkyne [3+2]-cycloadditions was accomplished through the use of copper compounds as additives. Thus, Meldal and coworkers disclosed the use of copper(I) salts for regioselective 1,3-dipolar cycloadditions with terminal alkynes.[7] In contrast to thermal reactions, copper catalysis delivered the 1,4-disubstituted 1,2,3-triazoles as the sole products under exceedingly mild reaction conditions. While copper(II) salts were not

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Lutz Ackermann

Lutz Ackermann studied chemistry at the Christian-Albrechts-University Kiel, Germany, and obtained his PhD from the University of Dortmund in 2001 for research under the supervision of Alois Fürstner at the Max-Plank-Institut für Kohlenforschung in Mülheim/Ruhr. He was a postdoctoral fellow in the research group of Robert G. Bergman at the University of California at Berkeley, USA, before initiating his independent career in 2003 at the Ludwig-Maximilians-University München supported within the Emmy Noether-programme of the DFG. In 2007, he became full professor at the Georg-August-University Göttingen. His recent awards and distinctions include an ORCHEM-price (2006), a Dozentenstipendium (2007) and a JSPS fellowship (2009), as well as visiting professorships at the Università degli Studi di Milano, Italy (2007), and the University of Wisconsin at Madison, USA (2008). The development of sustainable catalytic transformations for organic synthesis constitutes one of his major current research interests.

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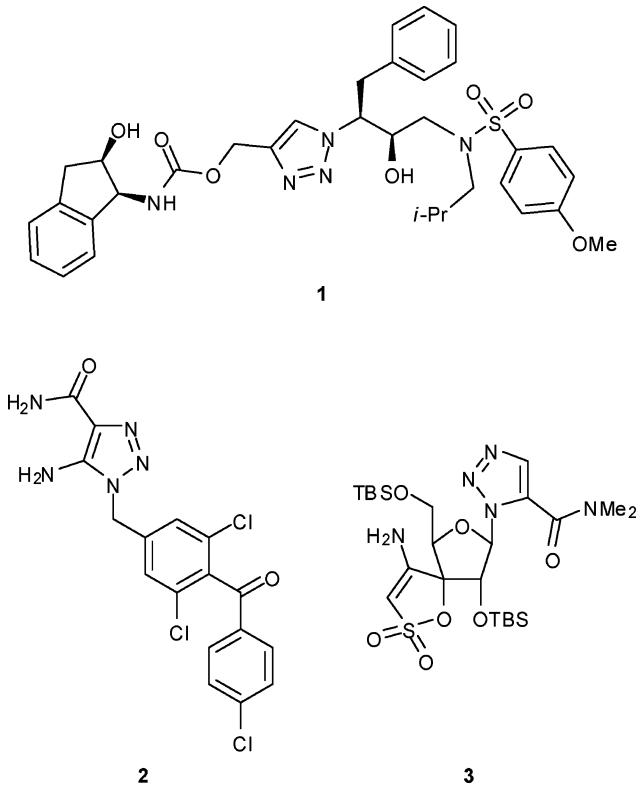
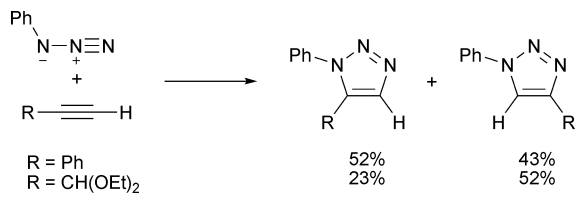
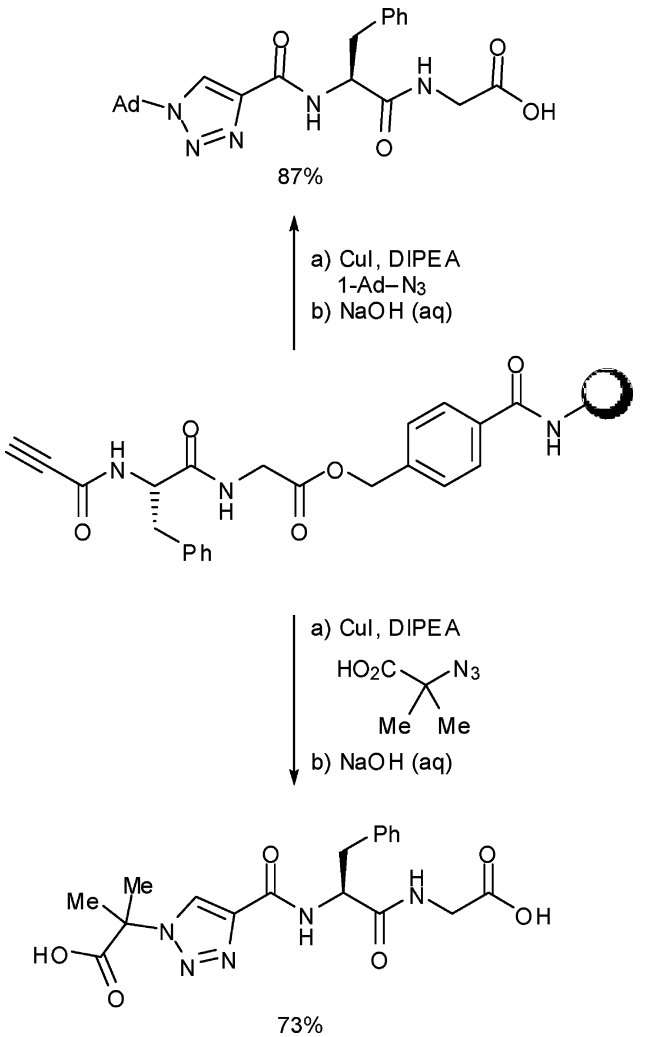


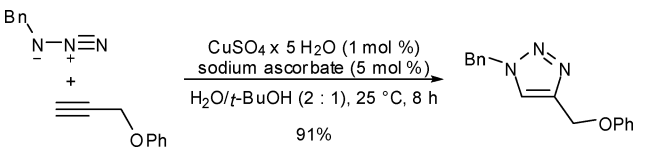
Fig. 1 Representative bioactive 1,2,3-triazoles **1–3**.



Scheme 1 Azide-alkyne [3+2]-cycloadditions.



Scheme 2 Copper-catalyzed azide-alkyne cycloaddition (CuAAC).

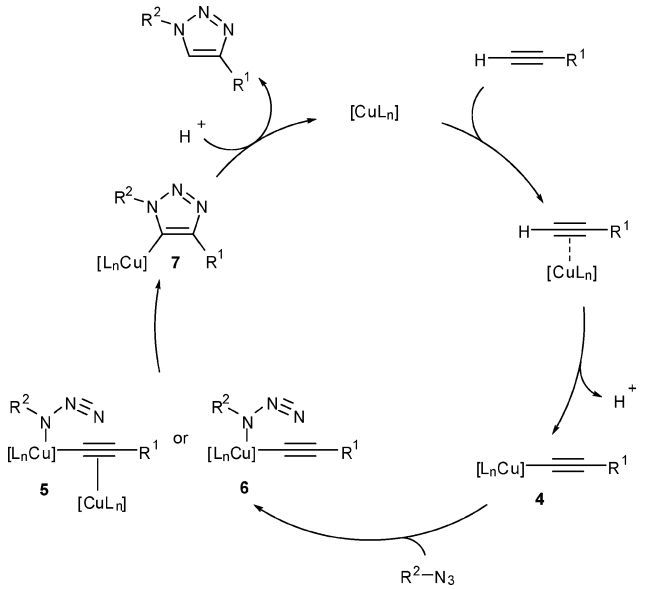


Scheme 3 CuAAC through *in situ* reduction of a copper(II) precatalyst.

catalytically competent, different copper(I) species could be employed with a catalyst loading of as low as 1 mol%. An additional asset of this pioneering work was represented by establishing procedures for solid-phase synthesis, which served as convenient access to various peptidotriazoles (Scheme 2). The catalysts' scope included primary, secondary and tertiary alkyl or aryl azides, as well as azido sugars. Further, the copper(I)-catalyzed [3+2]-azide-alkyne cycloadditions (CuAAC) displayed a remarkable chemoselectivity, in that valuable functional groups, including all amino acids, were well tolerated.

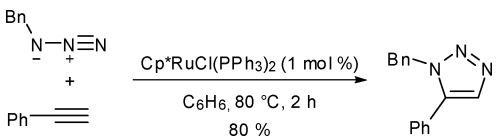
In independent studies, Sharpless, Fokin, and co-workers found a very robust catalytic system for cycloadditions between azides and terminal alkynes, which made use of a less expensive copper(II) precatalyst, along with substoichiometric amounts of sodium ascorbate for an *in situ* reduction (Scheme 3).[8] As was observed by Meldal and co-workers, this chemical ligation of azides and terminal alkynes delivered exclusively the 1,4-disubstituted 1,2,3-triazoles. Notably, the transformation could be performed in various organic solvents as well as in water. Based on its outstanding chemo- and regioselectivities this copper-catalyzed 1,3-dipolar cycloaddition reaction served as a prime example of a "click"-reaction,[9] and set the stage for various applications to post-synthetic modifications of functional molecules.[1,2]

The remarkable rate-acceleration of copper-catalyzed azide-alkyne cycloadditions (CuAAC) was attributed to a stepwise mechanism, that is initiated by the formation of copper(I) acetylide **4** (Scheme 4),[8,10] a feature being reminiscent of Sonogashira–Hagihara reactions.[11] Thereafter, the azide coordinates to copper acetylide **4**, giving rise to the formation of complexes **5** or **6**. Notably, kinetic studies revealed the rate law to be second order with respect to the copper concentration,[12] which was rationalized with the formation of *inter alia* bimetallic[13–15] copper species **5**.[12,16] Irrespective of the exact nature of these intermediates, 5-cuprated 1,2,3-triazoles **7**[17] are overall regioselectively formed.[18] Finally, metalated heterocycle **7** undergoes protonolysis, delivering the desired product and regenerating the active catalyst.



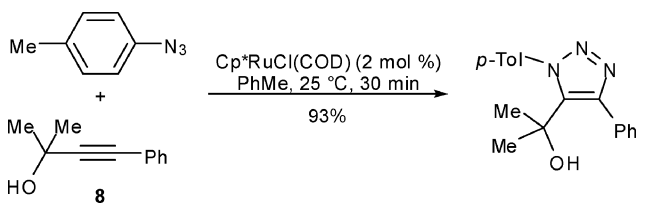
Scheme 4 Proposed catalytic cycle of CuAAC reactions.

Importantly, a complementary regioselectivity was accomplished through the use of ruthenium catalysts, which enabled the synthesis of 1,5-disubstituted 1,2,3-triazoles (Scheme 5).[19]



Scheme 5 Ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC).

In particular, the application of [Cp*RuCl]-containing complexes resulted in excellent 1,5-regioselectivities.[20] These catalysts proved broadly applicable, but protic solvents had a detrimental effect on catalytic performance. Contrary to CuAAC reactions, ruthenium catalysts allowed for the effective conversion of internal alkynes, thereby rendering mechanisms based on ruthenium acetylides unlikely to be operative. Thus, for instance, Cp*RuCl(PPh_3)$_2$ or Cp*RuCl(COD) provided access to fully-substituted 1,2,3-triazoles. Unfortunately, the desired products were obtained with high regioselectivities only when the alkynes displayed a hydrogen-bond donor directing group (Scheme 6) or when being electronically strongly biased.



Scheme 6 RuACC with internal alkyne **8** bearing a directing group.

The proposed mechanism of RuAAC reactions involves an initial oxidative coupling to form ruthenacycle **9** as key intermediate (Fig. 2).[20] Thereafter, rate-limiting reductive elimination occurs, furnishing the corresponding 1,5-disubstituted 1,2,3-triazoles.

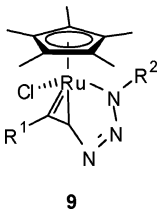
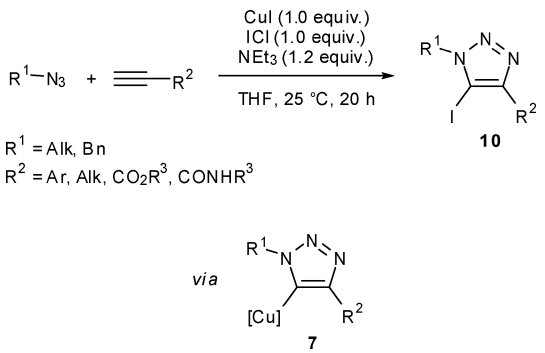


Fig. 2 Proposed key intermediate **9** of RuAAC reactions.

Despite these remarkable advances, only a few generally applicable methods for regioselective syntheses of fully-decorated 1,2,3-triazoles were until recently available. These approaches can be differentiated into (i) the interception of stoichiometrically functionalized 5-cuprated-1,2,3-triazoles, (ii) the use of stoichiometrically functionalized internal alkynes or (iii) catalytic direct C–H bond functionalization reactions. This perspective article critically summarizes this recent progress, with a particular focus on the latter research area.

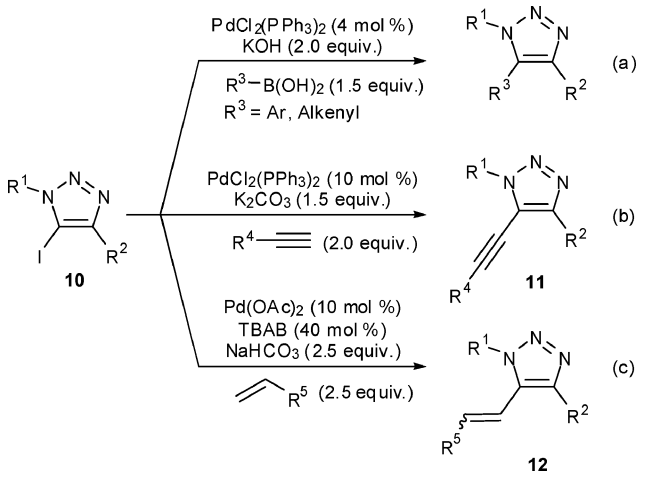
Interception of 5-cuprated 1,2,3-triazoles

5-Cuprated 1,2,3-triazoles **7** were shown to be key intermediates in azide-alkyne cycloadditions with terminal alkynes, which upon reaction with the simplest electrophile deliver 1,4-disubstituted products (Scheme 4). However, when stoichiometric amounts of copper(I) salts were employed, along with stoichiometric quantities of sufficiently reactive electrophiles, intermediates **7** could be intercepted to yield C–5-functionalized 1,2,3-triazoles **10**. Thus, a copper-mediated synthesis of fully-substituted 1,2,3-triazoles was developed through the use of ICl as trapping reagent (Scheme 7).[21] Moreover, allyl bromide and benzoyl chloride were found to be possible electrophilic substrates.



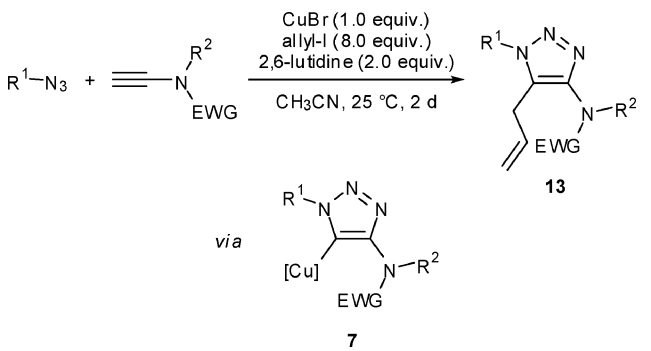
Scheme 7 Copper-mediated synthesis of 5-iodo-1,2,3-triazoles **10** using ICl as electrophile.

With an efficient synthesis of 5-iodo-1,2,3-triazoles **10** in hand, Wu, Chen and Deng illustrated their potential as substrates for palladium-catalyzed cross-coupling reactions.[22] Hence, aryl- and alkenyl-substituted boronic acids served as nucleophiles for Suzuki–Miyaura reactions with electrophiles **10** to yield fully-substituted products (Scheme 8, a). Furthermore, palladium-catalyzed (b) Sonogashira–Hagihara and (c) Mizoroki–Heck reactions gave rise to the 5-alkynylated or 5-alkenylated products **11** and **12**, respectively.



Scheme 8 Palladium-catalyzed cross-couplings with 5-iodo-1,2,3-triazoles **10**.

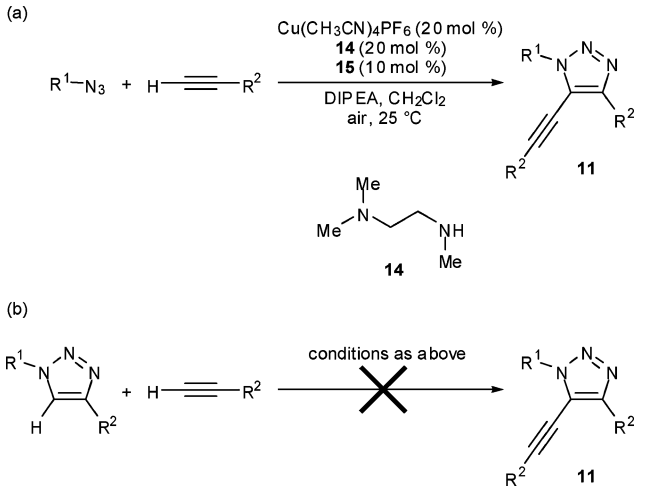
Additionally, Hsung and coworkers established the feasibility of copper-mediated [3+2] cycloaddition with ynamides (Scheme 9), and demonstrated the use of the thus formed triazoles **13** as precursors for ring-closing diene or enyne metathesis reactions.[23] Again, intermediates **7** were generated with stoichiometric quantities of copper(I) salts, and were directly reacted with allyl iodide. Unfortunately, a large excess of the electrophile turned out to be mandatory to ensure satisfactory yields, and strictly anhydrous reaction conditions were required to avoid ynamide hydrolysis.



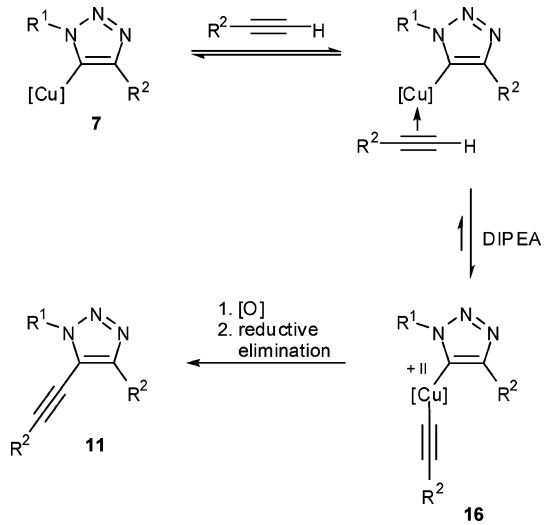
Scheme 9 Copper-mediated synthesis of 5-allylated products **13**.

During studies on the diversification of resin-bound alkynes, Porco and coworkers serendipitously observed the remarkable formation of 5-alkynylated-1,2,3-triazoles **11** in CuAAC under an atmosphere of air (Scheme 10, a).[24] Specifically, $Cu(CH_3CN)_4PF_6$, in combination with *N*,*N*,*N*′-trimethylethylenediamine (**14**) as ligand and cocatalytic amounts of 4-methoxymorpholine *N*-oxide (NMO, **15**), gave rise to the optimal catalytic system. Importantly, mechanistic studies revealed that the corresponding 1,4-disubstituted triazoles did not deliver alkynylated products **11** (Scheme 10, b), thus ruling out a catalytic C–H bond activation manifold.

Given that an initial oxidative Glaser homocoupling of the terminal alkynes was also shown not to be operative, the authors proposed the oxidative transformation to proceed *via* formation of 4-cuprated-1,2,3-triazole **7** and copper(II)-species **16** as key intermediates (Scheme 11).



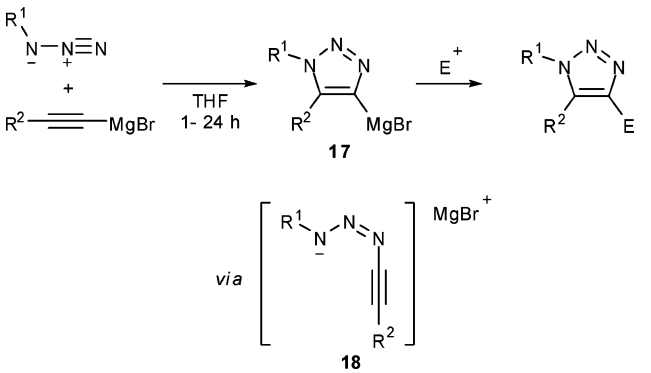
Scheme 10 Oxidative synthesis of 5-alkynylated-1,2,3-triazoles **11**.



Scheme 11 Proposed mechanism for formation of 5-alkynylated-1,2,3-triazoles **11**.

Stoichiometrically functionalized alkynes

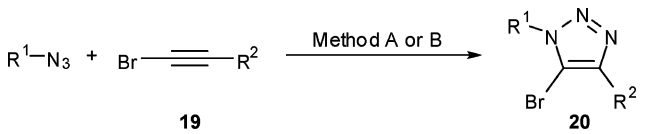
C–4-Metallated 1,2,3-triazoles **17** were obtained through non-catalytic transformations of organic azides with metallated acetylides[25,26] (Scheme 12).[27,28] The thus formed Grignard reagents



Scheme 12 Non-catalytic formation of 4-magnesiated-1,2,3-triazoles **17**.

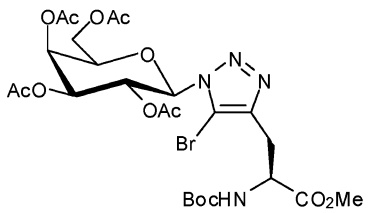
17[29] could be directly reacted with various electrophiles, such as D_2O, I_2, CO_2 or carbonyl-containing organic compounds. Improved reactivities of electron-deficient azides were rationalized with an initial nucleophilic attack of the metallated acetylide on the terminal nitrogen atom of the azide to form salt **18**, which in turn explained the observed regioselectivities.

In 2005, Rutjes and coworkers showed that easily-accessible 1-bromoalkynes **19** are viable substrates for CuAAC reactions, providing access to 5-bromo-1,2,3-triazoles **20** (Scheme 13).[30] The remarkably broad scope of this CuAAC was among others highlighted with the selective synthesis of triazole-linked glycopeptide **21**. Furthermore, bromo-metal exchange reactions on heteroarene **20**, along with subsequent reactions with various electrophiles, constituted a highly modular approach to fully-substituted 1,2,3-triazoles.



19 **20**

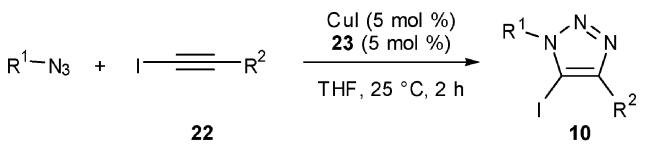
Method A: CuI (5 mol %), $Cu(OAc)_2$ (5 mol %), THF, 50 °C.
Method B: CuBr (20 mol %), $Cu(OAc)_2$ (20 mol %), THF, 50 °C.



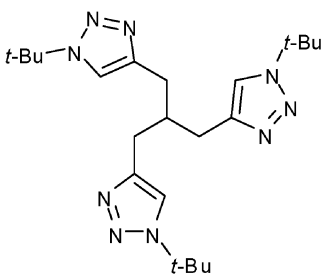
21: 65%

Scheme 13 CuAAC with bromo-alkynes **19**.

Furthermore, 1-iodoalkynes **22** were found to be viable substrates for CuAAC reactions, provided that amines were present in either stoichiometric or catalytic quantities.[31] In particular, the use of tris((1,2,3-triazolyl)methyl)amine TTTA (**23**) as ligand reduced the formation of undesired byproducts (Scheme 14). The significant rate acceleration achieved with ligand **23** allowed for



22 **10**

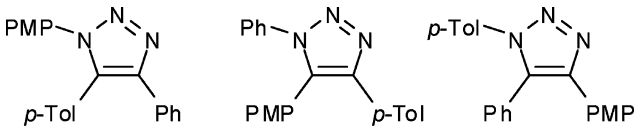


TTTA (**23**)

Scheme 14 CuAAC reactions with 1-iodoalkynes **22**.

reactions to be performed at ambient reaction temperature with a low catalyst loading. Importantly, various functional groups were tolerated, and reactions could be performed in protic solvents as well. Further, the authors disclosed an efficient synthesis of 1-iodoalkynes **22** using *N*-iodomorpholine, which was exploited for a one-pot, two-step synthesis of 5-iodo-1,2,3-triazoles **10**.

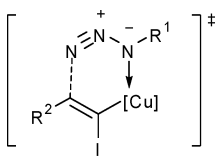
The synthetic utility of the iodo-CuAAC reaction was showcased by its combination with palladium-catalyzed Suzuki–Miyaura cross-coupling reactions within a one-pot procedure. Thereby, 1,4,5-triaryl-1,2,3-triazoles were prepared (Fig. 3), with a regiocontrol that is beyond the scope of both thermal or ruthenium-catalyzed cycloadditions.



73% 71% 70%

Fig. 3 Products of iodo-CuAAC/Suzuki–Miyaura reaction sequence.

While detailed mechanistic studies on iodo-CuAAC reactions are as of yet not available, the authors suggested transition state model **24** (Fig. 4).[31a] However, more recently strong evidence was provided for an initial formation of copper acetylides, common intermediates of conventional CuAAC with terminal alkynes (Scheme 4).[10,15]

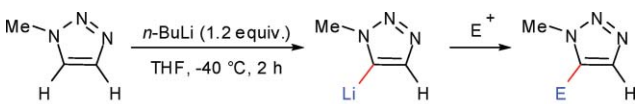


24

Fig. 4 Proposed transition state model **24** for CuAAC with 1-iodoalkynes **22**.

Catalytic C–H bond functionalizations

Regioselective syntheses of fully substituted 1,2,3-triazoles through 1,3-dipolar cycloadditions were thus far largely limited to either the use of stoichiometric amounts of copper salts in AAC reactions, or stoichiometrically halogenated or metalated alkynes. On the contrary, the combination of CuAAC reactions of terminal alkynes with direct C–H bond functionalizations on the thus generated 1,4-disubstituted triazoles offers an attractive alternative. In this context it is noteworthy that stoichiometric metalations of 1,2,3-triazoles were well established,[32] as illustrated by the deprotonation of *N*-methyl-1,2,3-triazole (**25**) depicted in Scheme 15. These reactions were accomplished with strong lithium bases, such as *n*-BuLi, LDA or LiTMP, and notably proceeded



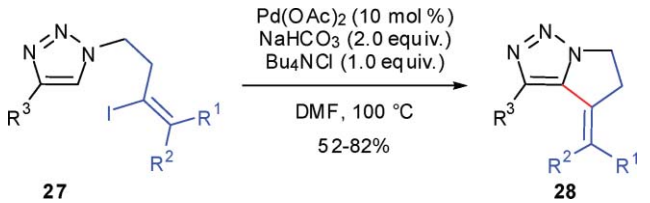
25 **26**

Scheme 15 Stoichiometric lithiation with a strong base.

with excellent regioselectivities to provide the 5-lithiated-1,2,3-triazole **26**.[33]

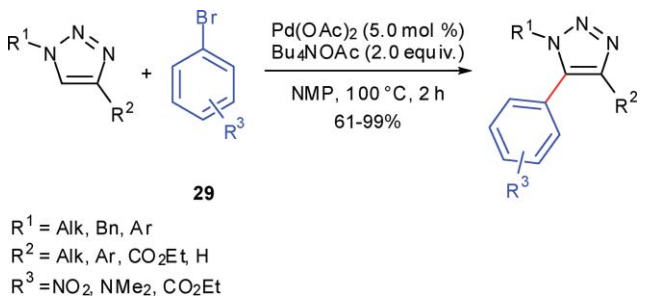
Unfortunately, the use of strongly basic lithium reagents calls for a protection and deprotection of all electrophilic and acidic functional groups. A more sustainable strategy is therefore represented by transition-metal-catalyzed direct C–H bond functionalizations[34] of 1,2,3-triazoles under mild reaction conditions.

Palladium-catalyzed $C(sp^2)$–$C(sp^2)$ bond formations on 1,2,3-triazoles **27** through C–H bond cleavages were achieved with alkenyl iodides in an intramolecular fashion (Scheme 16).[35] Thereby, pyrrolo[1,2-*c*]triazoles **28** were obtained with inexpensive $Pd(OAc)_2$ as catalyst, along with tetra-butylammonium chloride as additive. However, only tetra-substituted alkenes **27** could be employed as substrates, since β-eliminations to form the corresponding alkynes occurred otherwise preferentially under the basic reaction conditions.



Scheme 16 Intramolecular palladium-catalyzed direct alkenylation.

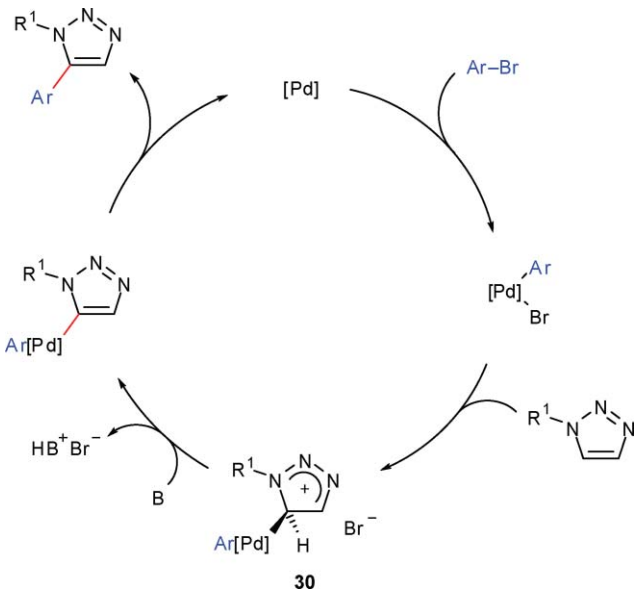
Palladium-catalyzed direct functionalizations of C–H bonds on triazoles were not restricted to entropically favorable cyclization reactions. Indeed, both 1,4-disubstituted and *N*-mono-substituted 1,2,3-triazoles[36] were efficiently functionalized with aryl bromides **29** (Scheme 17).[37] Different palladium(0) and palladium(II) precursors could be used as catalysts, when employing tetrabutylammonium acetate as additive. Importantly, the direct arylations proceeded smoothly to furnish C–5 functionalized products, while tolerating a variety of functional groups.



Scheme 17 Palladium-catalyzed intermolecular direct arylations with aryl bromides **29**.

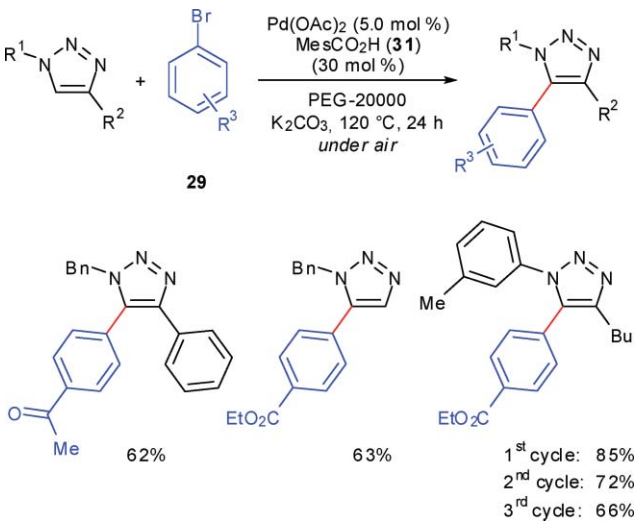
Notably, a lack of a kinetic isotope effect ($k_H/_D = 1.0$) and DFT calculations supported an electrophilic activation-type mechanism (Scheme 18). Thus, the suggested mechanism comprises initial oxidative addition of the aryl bromide to a palladium(0) catalyst, followed by electrophilic activation of the electron-rich heteroarene to furnish intermediate **30**. Subsequent deprotonation and final reductive elimination deliver the C–5-arylated triazoles and regenerate the active catalyst.

Thus far, most protocols for metal-catalyzed direct arylations through C–H bond cleavages were lacking operational simplicity,[38]



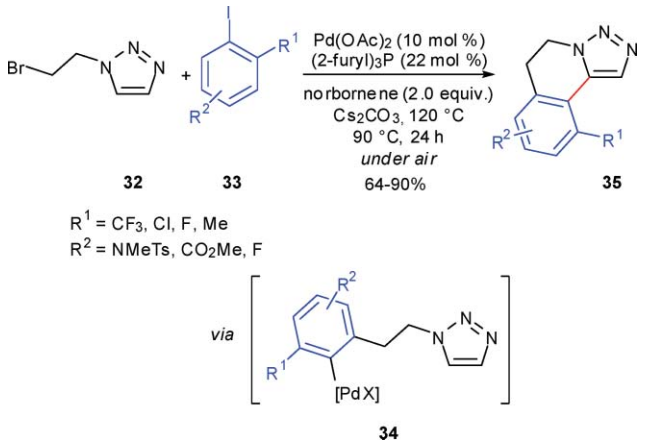
Scheme 18 Proposed mechanism for palladium-catalyzed direct arylations of 1,2,3-triazoles.

in that potentially hazardous organic solvents and/or vigorous anaerobic reaction conditions proved to be mandatory. However, during studies on more sustainable reaction media for C–H bond functionalizations, we found that a palladium catalyst derived from carboxylic acid $MesCO_2H$ (**31**) enabled direct arylations of 1,2,3-triazoles in nontoxic polyethylene glycol (PEG).[39] Specifically, PEG-20000 was found to be optimal for reactions under an atmosphere of air, and gave rise to a broadly applicable palladium catalyst (Scheme 19). Notably, these studies also allowed for the development of a first recyclable transition-metal catalyst for direct arylations.



Scheme 19 Direct-arylations under air in PEG-20000 with a recyclable palladium catalyst.

A palladium-catalyzed intramolecular direct arylation of 1,2,3-triazoles served as the key step of a remarkable Catellani[40–42] reaction. Hence, Laleu and Lautens disclosed the chemoselective conversion of *N*-mono-alkylated starting materials **32** with aryl



Scheme 20 Catellani reactions involving intramolecular direct arylations.

iodides **33**, which proceeded through proposed palladium(II) intermediate **34** (Scheme 20).[43]

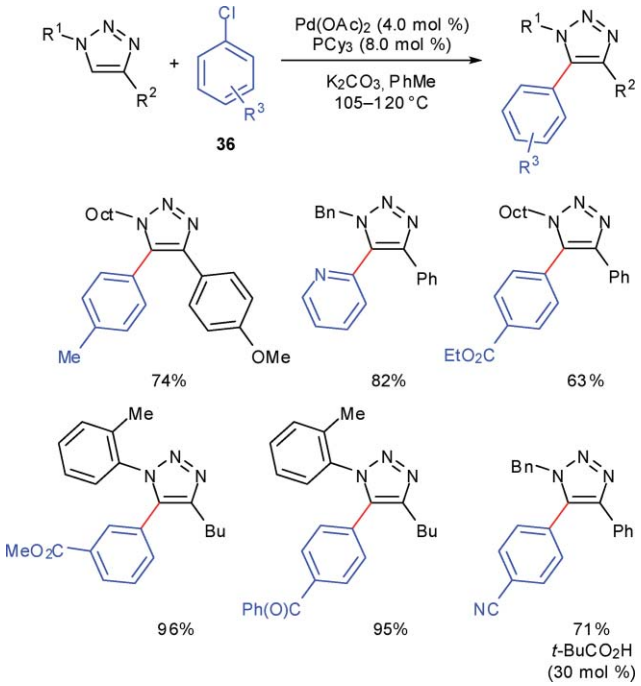
Independent studies by Yorimitsu and Oshima[44] as well as Ackermann[45] and co-workers highlighted that less expensive, but more difficult to activate aryl chlorides **36**[46,47] could be employed as electrophilic arylating reagents likewise. In this context, Yorimitsu, Oshima and Iwasaki exploited microwave irradiation for direct arylations of 1,4-disubstituted-1,2,3-triazoles, which required a reaction temperature of 250 °C (Scheme 21).[44] Notably, these transformations were conceived to occur due to a non-thermal microwave effect.

Scheme 21 Direct arylations under microwave irradiation.

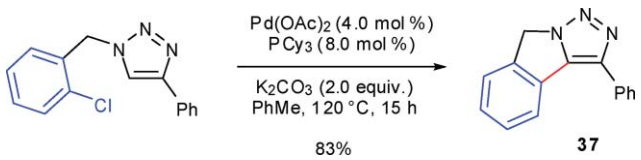
However, convenient thermal direct arylations of 1,4-disubstituted-1,2,3-triazoles were also viable with inexpensive aryl chlorides **36** under mild reaction conditions (Scheme 22).[45] Among a variety of ligands, a catalyst derived from an electron-rich tertiary phosphine provided the best results. The optimized catalytic system displayed a broad substrate scope, which notably included Lewis-basic N-heteroaryl chlorides **36**. Both *N*-aryl and *N*-alkyl-substituted 1,2,3-triazoles were converted with high catalytic efficacy to afford fully-decorated triazoles in high yields. Interestingly, in select reactions with aryl chlorides **36** displaying electron-withdrawing substituents, a more effective catalyst was obtained with substoichiometric amounts of pivalic acid[48] as additive.[45] Further, the catalytic system enabled direct arylations with aryl bromides **29**, and intramolecular competition experiments suggested the following order in reactivity of leaving groups in the electrophiles: Br > Cl > OTs.

The optimized protocol was not restricted to intermolecular transformations, but allowed also for the synthesis of annulated 1,2,3-triazole **37** (Scheme 23).[45]

Aryl tosylates **38** or mesylates are desirable electrophiles in cross-coupling chemistry, since they can be prepared from readily



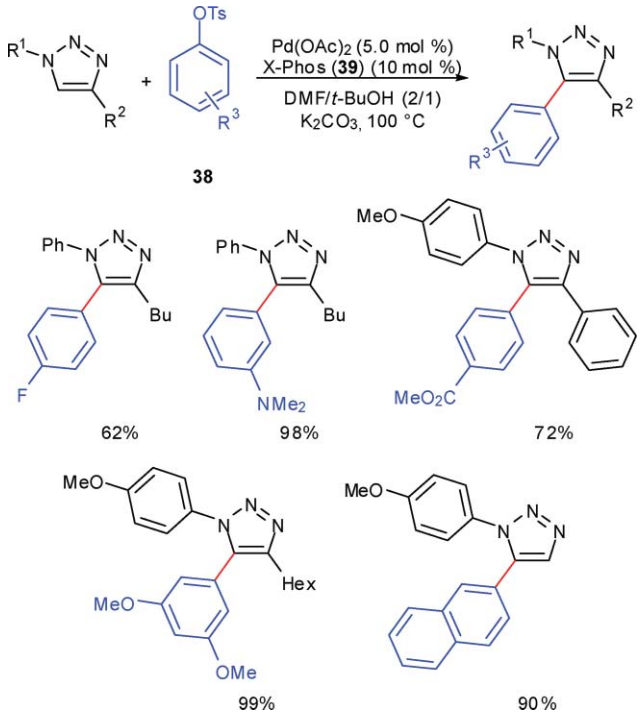
Scheme 22 Direct arylations of 1,2,3-triazoles with aryl chlorides **36**.



Scheme 23 Intramolecular direct arylation with an aryl chloride.

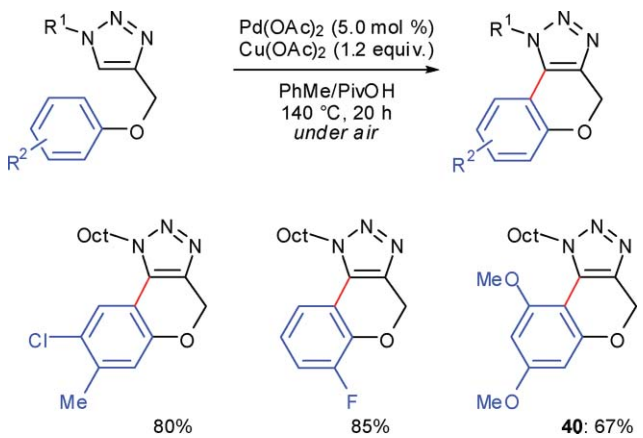
available, yet inexpensive starting materials. These sulfonates are more convenient to handle than are aryl triflates, because they are highly crystalline and stable towards hydrolysis. However, their outstanding stability translates into a significantly reduced reactivity in metal-catalyzed coupling reactions. As a result, generally applicable methodologies for traditional cross-coupling reactions with organometallic nucleophiles have been developed only in recent years.[49] We, on the contrary, devised reaction conditions for palladium-catalyzed[50] direct arylations of simple (hetero)arenes with moisture-stable aryl tosylates **38** and mesylates.[51,52] Particularly, a catalytic system generated from phosphine-ligand X-Phos (**39**) enabled effective direct arylations of 1,2,3-triazoles with various functionalized electron-deficient electrophiles **38** (Scheme 24). Likewise, the catalyst was applicable to electron-rich aryl tosylates **38**, which are thus electronically-deactivated for oxidative additions. Furthermore, the selective synthesis of 1,4,5-triaryl-1,2,3-triazoles was conveniently realized. As to the mechanism, it is noteworthy that *N*-mono-substituted triazoles were selectively functionalized at position C–5, which could be rationalized with an electrophilic activation manifold or a dependence on C–H bond acidity.

While intermolecular direct arylations of 1,2,3-triazoles with aryl (pseudo)halides proceeded in a highly regioselective fashion, they strongly relied on prefunctionalized arylating reagents. During studies on intramolecular direct arylations of 1,2,3-triazoles,[45] we became interested in developing oxidative[53] direct arylations of these heteroarenes with simple arenes. As a result



Scheme 24 Direct arylations with aryl tosylates **38**.

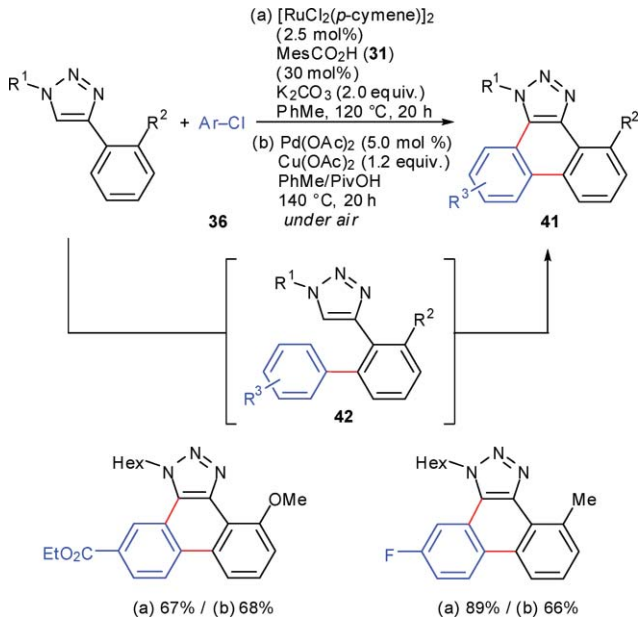
of our efforts, palladium-catalyzed dehydrogenative arylations were accomplished under ambient pressure of air, provided that $Cu(OAc)_2$ was present as sacrificial oxidant (Scheme 25).[54] Notably, this protocol enabled among others the synthesis of tetra-*ortho*-substituted biaryl **40**.



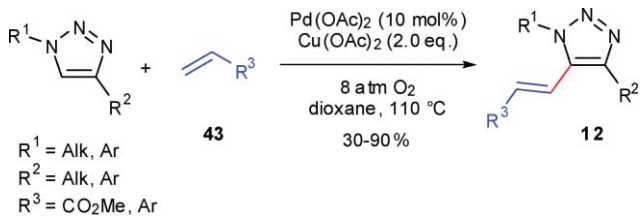
Scheme 25 Dehydrogenative direct arylations.

Moreover, the palladium-catalyzed oxidative arylation set the stage for a modular sequential synthesis of heteroannulated phenanthrenes **41** consisting of two mechanistically distinct direct C–H bond functionalizations (Scheme 26).[54] Thus, a ruthenium-catalyzed[55,56] directed arylation of 4-aryl-substituted 1,2,3-triazoles[57,58] furnished biphenyl **42**, thus exploiting the triazole as Lewis-basic directing group. This enabled efficient dehydrogenative arylations, delivering differently-substituted phenanthro[9,10-*d*]triazoles **41**.[54]

A related approach was independently exploited by Jiang and co-workers for intermolecular Fujiwara–Moritani alkenylations of 1,2,3-triazoles with terminal conjugated alkenes **43** (Scheme 27).[59] Here, palladium-catalyzed dehydrogenative alkenylations were accomplished with $Cu(OAc)_2$ as terminal oxidant, albeit with satisfactory efficacy only under 8 atm of an O_2 atmosphere.



Scheme 26 Sequential synthesis involving two mechanistically distinct C–H bond functionalizations.



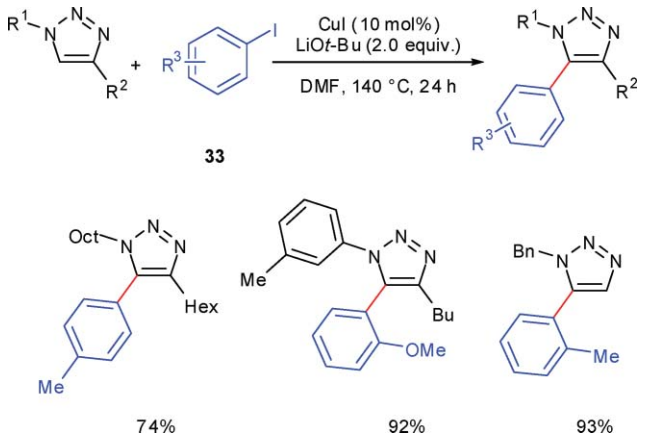
Scheme 27 Fujiwara–Moritani alkenylation with alkenes **43**.

Palladium-catalyzed direct C–H bond functionalizations of 1,2,3-triazoles were not limited to $C(sp^2)$–$C(sp^2)$ bond formations. Indeed, Fagnou and Lapointe reported on a palladium-catalyzed[60] direct benzylation,[61] which was achieved with an *in situ* generated complex derived from mono-phosphine ligand **44** (Scheme 28).[62,63] Notably, the presence of cocatalytic amounts of pivalic acid turned out to be beneficial, indicating a deprotonative metalation[34] reaction manifold.

Scheme 28 Palladium-catalyzed direct benzylation.

The CuAAC/C–H bond functionalization nexus

Thus far, all catalytic direct C–H bond functionalizations of 1,2,3-triazoles required the use of palladium complexes as catalysts. However, particularly the use of inexpensive copper compounds for catalytic C–H bond functionalizations is highly attractive, considering (i) their cost-effective nature, and (ii) their use in CuAAC for the assembly of 1,2,3-triazoles. Consequently, we set out to devise reaction conditions for highly modular syntheses of 1,4,5-trisubstituted 1,2,3-triazoles directly from terminal alkynes and NaN_3 through the use of a single copper catalyst. Therefore, we first probed various copper(I) compounds for direct C–H bond functionalizations on isolated 1,2,3-triazoles. We were pleased to observe that copper-catalyzed[64,65] direct arylations of 1,2,3-triazoles through C–H bond cleavages could be accomplished with aryl iodides **33** as arylating reagents, provided that LiO*t*-Bu served as the base (Scheme 29).[66]

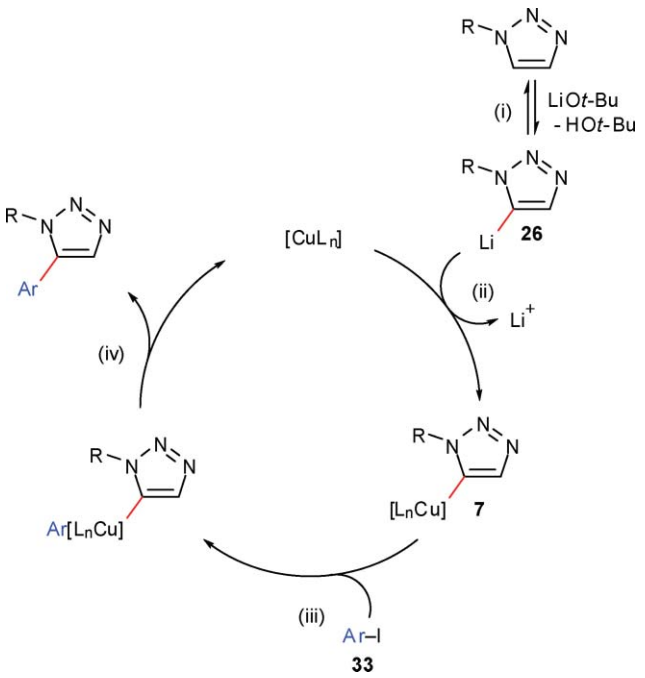


Scheme 29 Copper-catalyzed direct arylations.

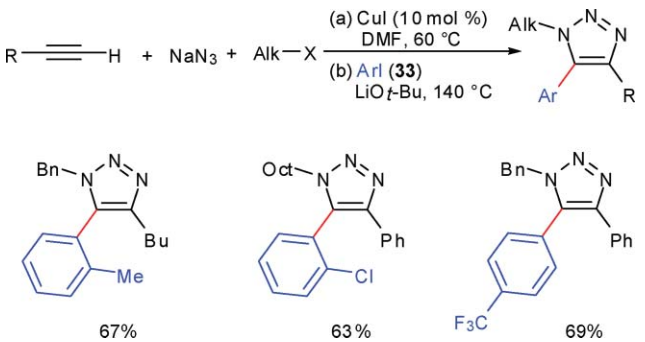
A probable working mode for these copper-catalyzed direct arylations consists of (i) initial *in situ* deprotonation with the base LiO*t*-Bu,[32,33] (ii) lithium-copper transmetalation, (iii) activation of the aryl iodide **33** and (iv) final reductive elimination (Scheme 30).[67] Given the deprotonation-based mechanism, the regioselectivity of the overall transformation is likely governed by C–H bond acidity.

With reaction conditions for copper-catalyzed direct arylations of 1,2,3-triazoles in hand, we explored the assembly of fully-substituted derivatives directly from NaN_3 employing a single inexpensive copper catalyst for two mechanistically distinct transformations. As a result, we disclosed a modular sequential synthesis of 1,2,3-triazoles through a chemo- and regioselective one-pot, four-component coupling (Scheme 31).[66] Overall, an inexpensive copper catalyst thus allowed for the assembly of 1,4,5-trisubstituted 1,2,3-triazoles through a sustainable CuAAC/direct arylation sequence. Notably, this catalytic multicomponent reaction involved the selective formation of one C–C and three C–N bonds.

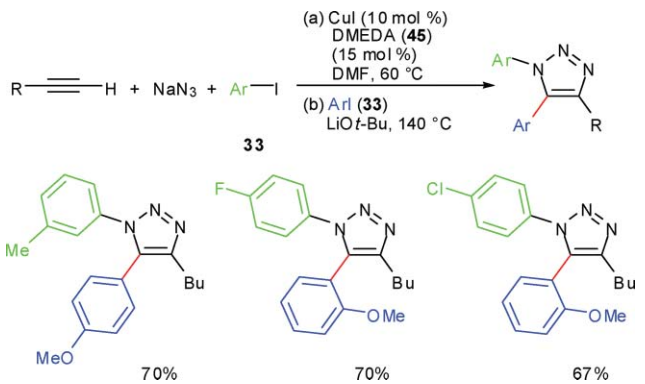
While simple CuI served as catalyst for the preparation of *N*-alkyl-substituted 1,2,3-triazoles, the synthesis of the corresponding *N*-aryl analogues required the use of DMEDA (**45**) as stabilizing ligand for the initial formation of aryl azides from NaN_3 and aryl iodides **33** (Scheme 32).



Scheme 30 Proposed mechanism for copper-catalyzed direct arylations.



Scheme 31 One-pot CuAAC/C–H bond functionalization sequence.

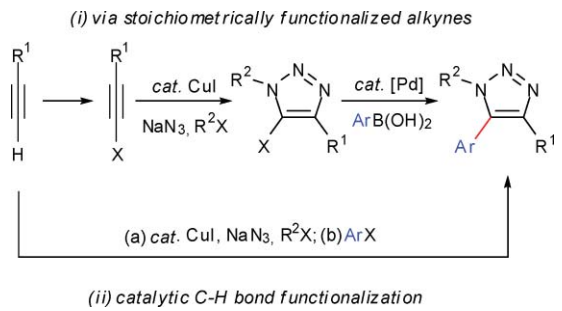


Scheme 32 CuAAC/C–H bond functionalization sequence for the synthesis of *N*-aryl-1,2,3-triazoles.

Conclusions and outlook

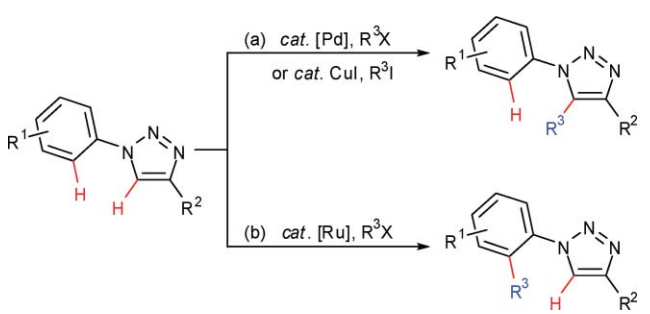
In recent years, 1,2,3-triazoles have found various valuable applications in the post-synthetic modification of functional molecules. Particularly, copper-catalyzed Huisgen azide-alkyne-cycloadditions (CuAAC) have matured to being indispensable

tools for the regioselective preparation of 1,4-disubstituted-1,2,3-triazoles. However, recently focus has shifted towards the development of generally applicable syntheses of 1,4,5-trisubstituted derivatives, for which three strategies were devised. First, the interception of 5-cuprated-1,2,3-triazoles with electrophiles was accomplished, provided that stoichiometric amounts of copper salts were employed. Second, stoichiometrically functionalized, *i.e.* magnesiated or halogenated, alkynes could be converted to fully-decorated 1,2,3-triazoles. Third, and finally, a highly sustainable approach exploited the nexus of CuAAC reactions with atom-economical C–H bond functionalizations. Specifically, palladium-catalyzed direct arylations, alkenylations and benzylations of 1,2,3-triazoles were viable, even with inexpensive aryl chlorides or aryl tosylates. Moreover, a single inexpensive copper catalyst could be employed for two mechanistically distinct transformations. Thus, simple CuI served as catalyst for a one-pot sequence comprising CuAAC reactions and C–H bond arylations. Thereby, 1,4,5-trisubstituted-1,2,3-triazoles could be directly accessed from terminal alkynes and NaN_3 in a highly modular fashion (Scheme 33).



Scheme 33 Strategies for catalytic syntheses of fully-substituted 1,2,3-triazoles.

With respect to post-synthetic modifications of functional molecules, the chemoselectivity of C–H bond functionalizations offers an additional valuable asset for the practitioner. Thus, the judicious choice of the transition-metal catalyst enables either the direct functionalization of the electron-rich heteroaromatic moiety itself (Scheme 34, a), or allows for its use as Lewis-basic directing group (b).



Scheme 34 Complementary chemoselectivities of late transition-metal–catalyzed direct C–H bond functionalizations.

Considering the increasing practical importance of 1,2,3-triazoles in synthetic chemistry, along with the sustainable nature of C–H bond functionalizations, we believe that methods for regioselective preparations of 1,4,5-trisubstituted triazoles will exert an additional stimulus to this rapidly evolving research area.

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