A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Silver-Free C–H Activation: Strategic Approaches towards Realizing the Full Potential of C–H Activation in Sustainable Organic Synthesis

Authors: Arup Mondal and Manuel van Gemmeren

To be cited as: *Angew. Chem. Int. Ed.* **2022**, e202210825

Link to VoR: https://doi.org/10.1002/anie.202210825

WILEY-VCH

10.1002/anie.202210825

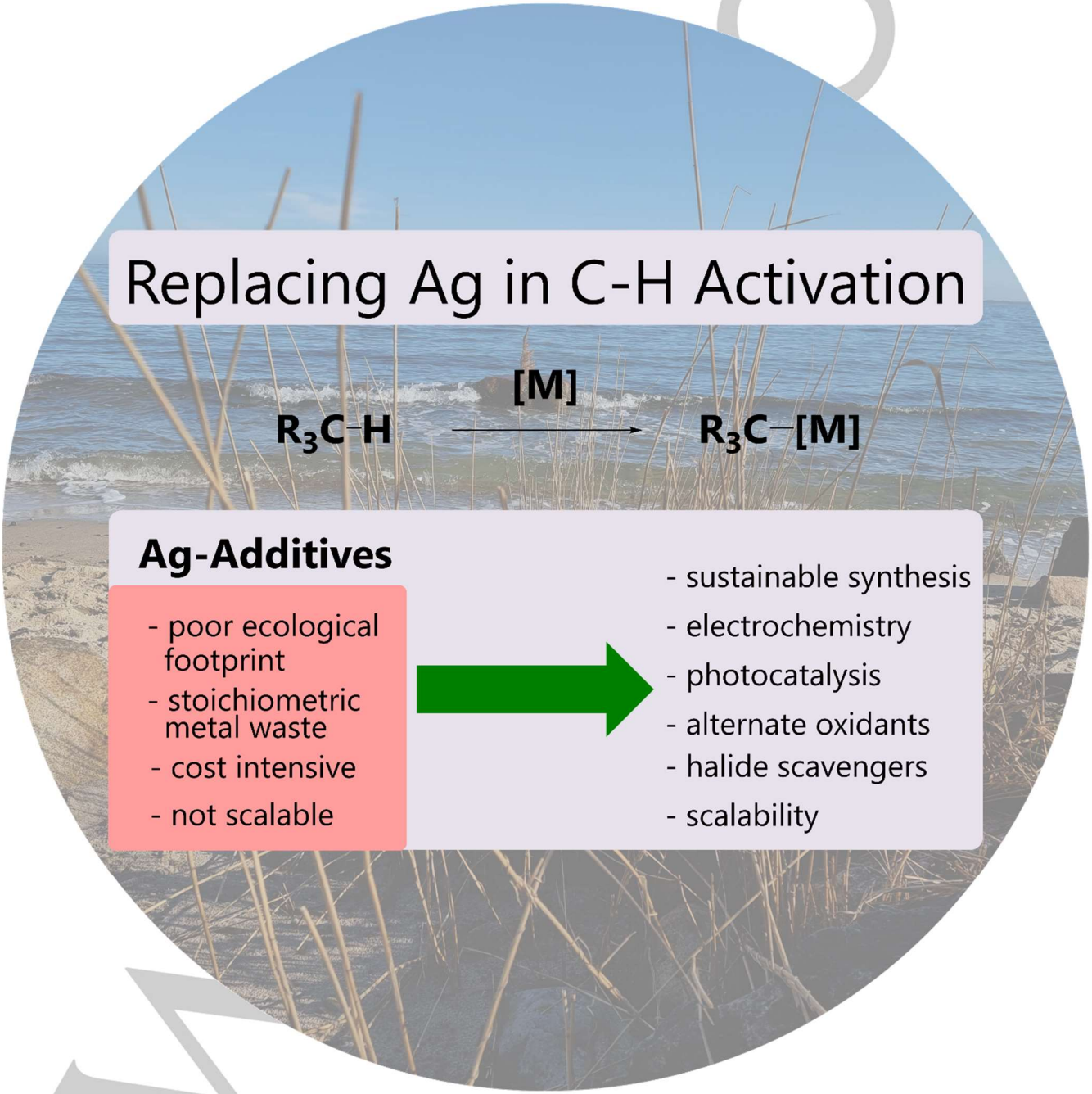
WILEY-VCH

REVIEW

Silver-Free C–H Activation: Strategic Approaches towards Realizing the Full Potential of C–H Activation in Sustainable Organic Synthesis

Arup Mondal,[b] and Manuel van Gemmeren*[a]

Dedicated to Professor Frank Glorius on the occasion of his 50th birthday



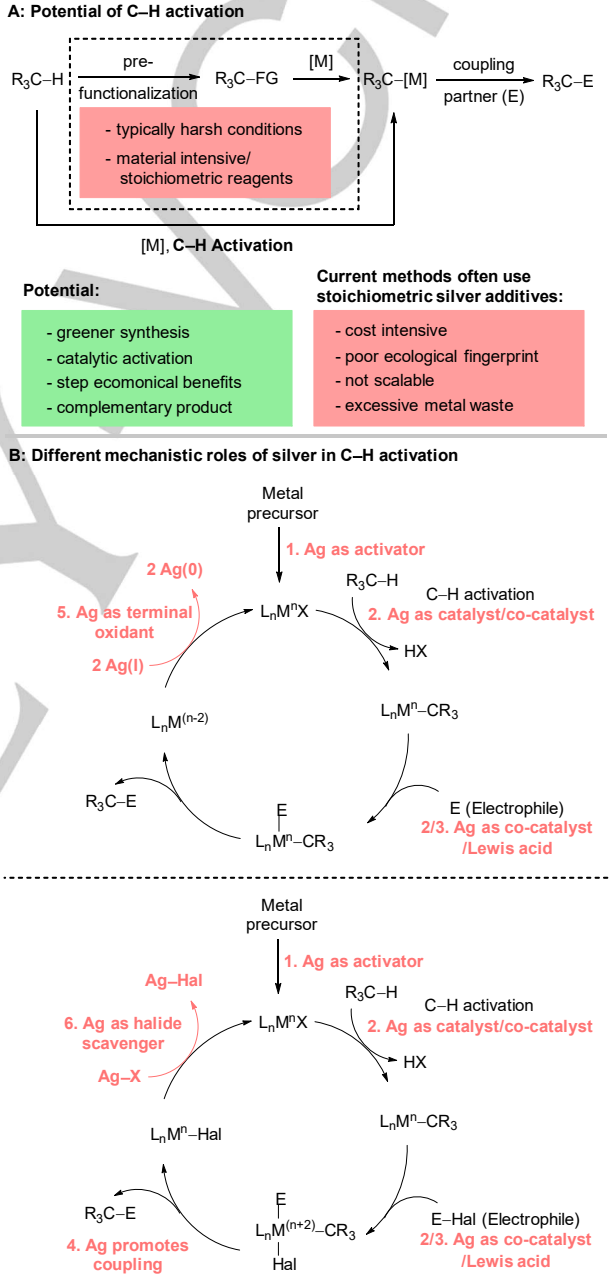
[a] Prof. Dr. Manuel van Gemmeren
Otto-Diels-Institut für Organische Chemie
Christian-Albrechts-Universität zu Kiel
Otto-Hahn-Platz 4, 24118 Kiel (Germany)
E-mail: vangemmeren@oc.uni-kiel.de
[b] Dr. Arup Mondal
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstraße 36, 48149 Münster (Germany)

Abstract: The activation of carbon-hydrogen bonds is considered as one of the most attractive techniques in synthetic organic chemistry because it bears the potential to shorten synthetic routes as well as to produce complementary product scopes compared to traditional synthetic strategies. However, many current methods employ silver salts as additives, leading to stoichiometric metal waste and thereby preventing the full potential of C–H activation to be exploited. Therefore, the development of silver free protocols has recently received increasing attention. Mechanistically, silver can serve various roles in C–H activation and thus, avoiding the use of silver requires different approaches based on the role it serves in a given process. In this review, we present the comparison of silver-based and silver-free methods. Focusing on the strategic approaches to develop silver-free C–H activation, we provide the reader with the means to develop sustainable methods for C–H activation.

1. Introduction

Over the past decades, the transition metal catalyzed activation and functionalization of C–H bonds has been recognized as one of the key strategies towards sustainable method development in organic synthesis.[1] The ability of building complex molecules from simple hydrocarbon feedstock is inherently more step-economical compared to traditional cross-coupling approaches and often complementary product scopes can be accessed (**Scheme 1A**).[2] In practice, many methods for C–H activation have been developed that use silver salts as additives together with the catalytically active transition metal.[3,4,5] Despite their effectiveness, these protocols automatically fall far short from the promise C–H activation holds in the context of sustainable organic synthesis. Thus, the development of silver-free C–H activation is a key step towards the sustainability and scalability of such methods. Importantly, silver is often not fundamentally required for the methods to work, as evidenced by studies that through various strategies avoid the use of silver-additives. In this review, we will compare representative methods for C–H activation that employ stoichiometric silver-salts with related processes that function without such additives. We will highlight general approaches towards the development of silver-free C–H activation processes, based on the role silver plays within the respective methodologies. The discussion will aid the reader to identify and apply pathways towards sustainable and scalable C–H activation that do not require stoichiometric silver salts.

1.1. Mechanistic roles of silver in C–H activation



Scheme 1. A: Potential of C–H activation. **B:** Mechanistic roles of silver in C–H activation.

The roles silver can adopt in transition metal-catalyzed C–H activation have been studied in various experimental and computational studies and have recently been summarized in the literature.[5,6] The most common roles are shown in **Scheme 1B**.

Silver can serve to generate the active species from metal precursor (1), as catalyst or co-catalyst in the C–H activation step (often by forming bi- or multi metallic M-Ag complexes)[4,7] (2), as a Lewis acid (increasing the electrophile reactivity) (3), it can promote the coupling step, (4) serve as the terminal oxidant to regenerate the active catalyst (5), or as a halide scavenger (6).
In some of these roles, namely for the generation of the active catalyst, when serving as "catalyst/co-catalyst" or as a Lewis acid" silver is employed in a catalytic amount. Additionally, when the silver is part of the active principle, no generalizable strategy can be proposed to replace it. In contrast, the role as "terminal oxidant" or "halide scavenger" requires the use of silver salts in stoichiometric amounts. Herein, we will focus on these cases, where stoichiometric quantities of silver are used and the impact of avoiding silver is maximal. These will be presented structured by the mechanistic roles of silver and the strategies used to replace the stoichiometric silver additives.

2. Silver as Oxidant

Conceptually, the replacement of the silver as an oxidant requires an alternative path to remove electrons from the metal and regenerate the active species. This has been achieved using photochemistry, electrochemistry, other oxidants, and redox-active directing group (DG). In the next sub-chapters, we will describe these techniques and compare them with corresponding most closely related silver-based methods. It should be noted that in addition to the silver-based methods and the silver-free variants discussed here, methods have often been reported that rely on other stoichiometric metal salts (e.g. Cu(II)-salts) as oxidants and which sometimes strongly resemble the silver-free methods. While we focus on the comparison of silver-based and silver-free variants, the existence of such studies will be highlighted when appropriate to provide further context.

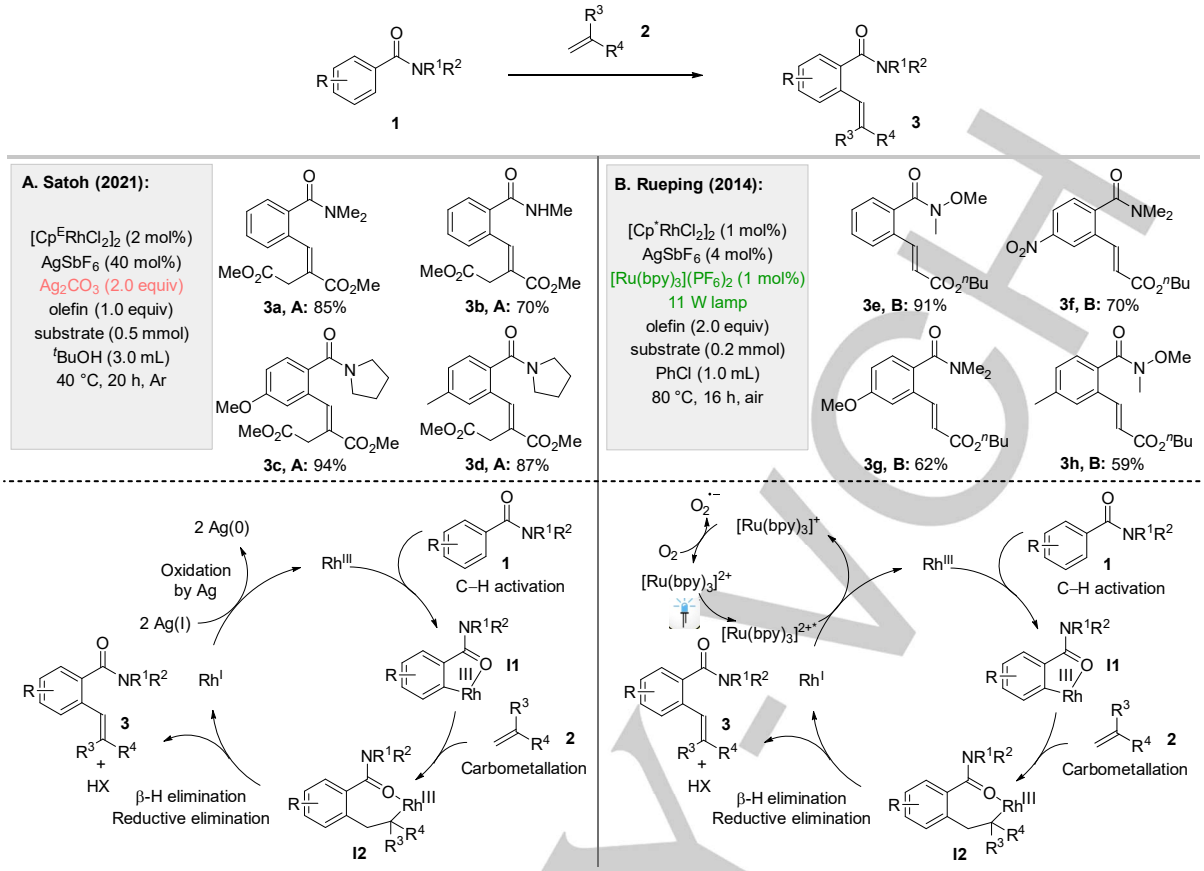
2.1. Approaches employing photochemistry

In recent years, photoredox catalysis has been applied intensively in electron-transfer reactions, including cases where the photoredox process was used to alter the catalysts oxidation state.[8] This concept has been extended to C–H activation/ functionalization processes.[9,10,11]
The coupling of benzamide derivatives and olefins via Rh-catalysis constitutes an attractive synthetic goal. To this end, the group of Glorius reported such a coupling using $Cu(OAc)_2$ as stoichiometric oxidant in 2010.[12] An analogous method suitable for Weinreb amides was reported by Wang and coworkers in 2013.[13]
In 2021, Satoh and coworkers reported a related Rh-catalyzed *ortho*-C–H olefination of benzamide derivatives using silver carbonate as stoichiometric oxidant (**Scheme 2A**).[14] The substrate is C–H activated by Rh(III) to form intermediate **I1**, which, after carbometallation and β-hydride elimination, generates the product. A reductive elimination process produces Rh(I), which is oxidized by silver to regenerate the Rh(III). The authors showed different substituents on the directing nitrogen are well-tolerated under the reaction conditions (**3a-d**) giving access to the corresponding *ortho*-olefination products with high efficiency. Similarly, an electron-donating methoxy and methyl group (**3c** and **3d** respectively) can form the *ortho*-isomer exclusively with respect to the DG. This protocol can be compared with a silver-free process previously reported by Rueping and coworkers (**Scheme 2B**).[15] The authors employed $[Ru(bpy)_3](PF_6)_2$ as a photocatalyst in combination with a suitable light source and achieved the same overall transformation. Importantly, the protocol employed 4 mol% $AgSbF_6$ for the initial activation of the Rh-catalyst. During the re-oxidation step, the excited state of the photocatalyst oxidizes Rh(I) to Rh(III). The reduced photocatalyst is then oxidized by oxygen to close the photocatalytic cycle. The authors did not observe a significant impact on the yield by changing the weakly coordinating PF_6 counter anion to the more strongly coordinating Cl presumably due to the presence of the $AgSbF_6$ activator. However, increasing the electron density through sequential introduction of ^{t}Bu groups on the bipyridine backbone of the photocatalyst led to a drop-in yield. Changing Ru to Ir led to complete suppression of the conversion. These observations suggest that the reduction potential of the photoredox catalyst is a crucial parameter in the recycling of the active Rh catalyst. Generally, the use of a photocatalyst to re-oxidize the catalytically active metal requires that the reduction potential of $M^{(n+2)}/M^n$ is lower than the one of the excited photocatalyst. Importantly, when judging the feasibility of such a process, it needs to be considered that the reduction potentials of the metal catalysts depend strongly on the properties of the ligand, solvent, temperature in a given reaction and can differ drastically from the values tabulated for the simple metal

Arup Mondal was born in West Bengal, India (in 1995). After receiving the B.Sc. degree in Chemistry from University of Calcutta, he moved to Indian Institute of Technology Bombay, where he obtained the M.Sc. degree in Chemistry. He then joined the organic chemistry institute of Westfälische Wilhelms-Universität Münster to pursue his doctoral studies. As a part of the master and doctoral thesis, he worked in the area of ligand controlled C–H activation reactions. After receiving a Doctoral degree in Natural Sciences (in 2022), he currently works at the California Institute of Technology as a DFG Walter-Benjamin postdoctoral fellow. Dr. Mondal is interested in the field of catalysis, photochemistry and enantioselective method developments.

Manuel van Gemmeren, studied chemistry in Freiburg, before joining the group of Prof. Benjamin List at the Max-Planck-Institut für Kohlenforschung for his doctoral studies (completed in 2014). After postdoctoral studies in the group of Prof. Rubén Martín at the ICIQ in Tarragona, he started an independent research group at the WWU Münster in 2016. Since 2022 he is Professor for Organic Chemistry at Kiel University. Research in the van Gemmeren Lab focusses on the development of novel synthetic methods that enable challenging transformations to proceed with catalyst-controlled reactivity and selectivity.

10.1002/anie.202210825



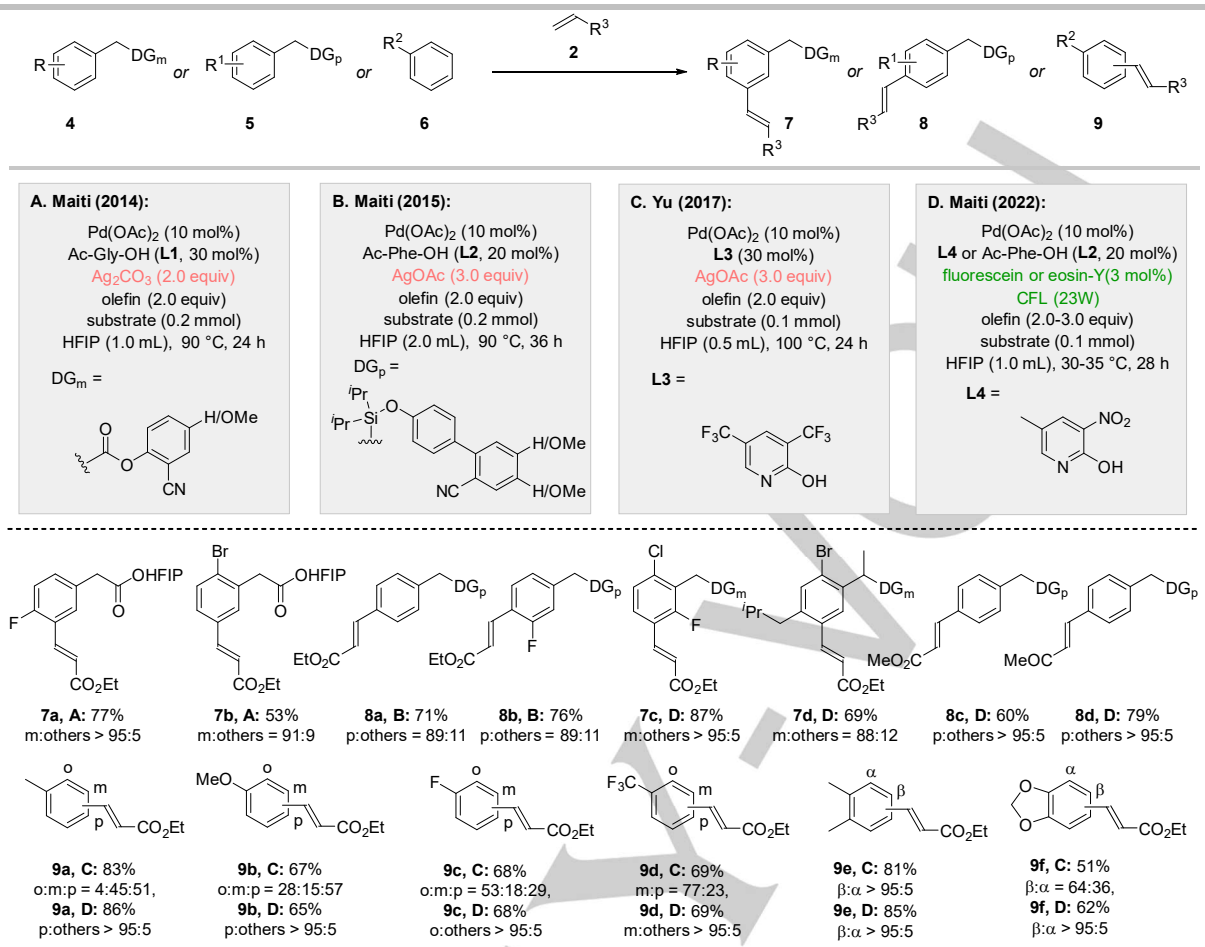
Scheme 2. A: *Ortho*-C–H olefination with Ag.[14] **B:** Complementary stoichiometric Ag-free transformation.[15]

ions. In the present case, the reduction potential of Rh(III/I) typically varies in the reange from –0.1 to +0.1 V_{SCE}, whereas that of excited sate of Ru-based photocatalyst is +0.77 V_{SCE},[16] indicating its suitability for the re-oxidation step. The authors employed different substituents on nitrogen (**3e-h**) as well as electron-withdrawing nitro (**3f**), and electron-donating methoxy and methyl groups (**3g**, **3h**) on the arene moiety and achieved *ortho*-selective functionalization with excellent efficiency.

In this context, a Ru-catalyzed *ortho*-C–H olefination of phenol derivates (with pyridine as the DG) reported by the Rueping group represents another case study of employing photocatalyst to regenerate the active catalyst.[17]

The Pd-catalyzed oxidative C–H olefination of arenes, known as Fujiwara-Moritani reaction, is known to often employ stoichiometric additives as terminal oxidant.[18] In 2014, Maiti and coworkers (based on the original report by Yu[19]) developed a nitrile-containing template with a carboxylate linker to activate the *meta* position preferentially (**Scheme 3A**).[20] The protocol employed two equivalents of silver salts and produced olefination products with excellent *meta* selectivity (**7a, 7b**). Related methods employing stoichiometric silver additives have been studied extensively.[21] A comparable silver-free method was reported by Maiti and coworkers in 2022 and employed fluorescein or eosin-Y as photocatalyst together with a suitable light source in place of silver (**Scheme 3D**).[22] Substituents like halogens and alkyl-groups are well-tolerated under the reaction conditions (**7c**, **7d**) giving excellent *meta* selectivity. In 2015, Maiti and coworkers reported a silyl ether linked D-shaped template to reach to the *para* position of arenes (**Scheme 3B**).[23] In subsequent studies, the efficiency of the template was shown to increase by placing suitable substituents on the biphenyl template part.[24] The original protocol employed three equivalents of silver acetate and can delivers products with high *para* selectivity (**8a**, **8b**). The same group again replaced the silver in the same photocatalytic study mentioned above (**8c** and **8d**).[22] In 2017, Yu and coworkers reported an arene limited non-directed C–H olefination, where the authors employed a pyridine-based ligand (**L3**) on the palladium catalyst and three equivalents of silver acetate to induce the desired transformation (**Scheme 3C**).[25] In a contemporary study, van Gemmeren and coworkers addressed the same synthetic challenge employing a dual-ligand based catalyst system and stoichiometric silver additive.[26] Once again, Maiti et al., reported a silver-free variant based on photocatalysis (**Scheme 3D**).[22] The authors proposed that the C–H activation step is Pd-catalyzed and aided by visible light, while the photocatalyst itself does not play a role in this step. Considering that the reduction potential of Pd(II/0) typically varies from –0.2 to +0.4 V_{SCE},[27] the excited state of the photocatalyst is able to oxidize Pd(0) to Pd(II). The reduced photocatalyst is then oxidized by oxygen to close the photocatalytic cycle. Both the protocols by Yu and Maiti tolerated a wide range of functional groups providing the corresponding olefinated arenes. Mono-substituted arenes with methyl (**9a**), methoxy (**9b**), fluoro (**9c**), and trifluoromethyl (**9d**) as substituents formed the olefinated products efficiently. The regioselectivity was determined by a combination of steric and electronic properties in Yu's system, whereas in Maiti's study electronic effects dominate the regioselectivity patterns, as evidenced by the formation of products **9a** and **9b** with para:others selectivities of >95:5.

10.1002/anie.202210825



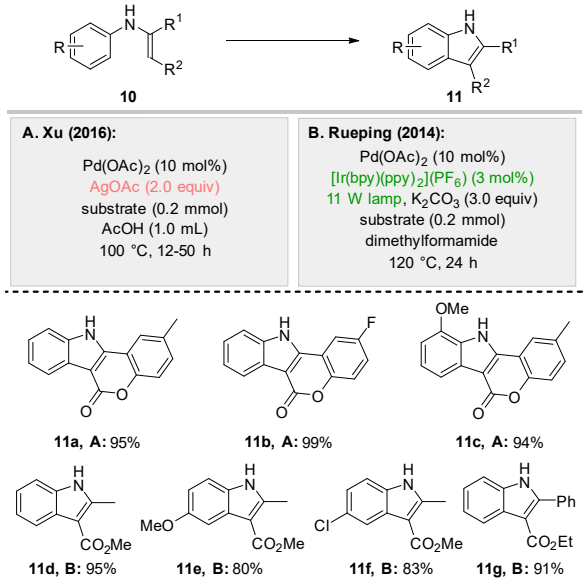
Scheme 3. A: *Meta*-C–H olefination with Ag.[20] **B:** *Para*-C–H olefination with Ag.[23] **C:** Non-directed C–H olefination with Ag.[25] **D:** Ag-free methods for C–H olefination using photochemistry.[22]

These effects were found to be consistent when di-substituted arenes (**9e**, **9f**) were tested under both reaction conditions.

The indole motif is one of the most common building blocks among natural products and bioactive compounds.[28] Following reports on the Pd-catalyzed indole synthesis with stoichiometric Cu-oxidants,[29] in 2016, Xu and coworkers reported an analogous, silver-based C–H activation of olefin and arene to form the indole motif (**Scheme 4A**).[30] The authors employed two equivalents of silver acetate as a terminal oxidant to regenerate the active species.

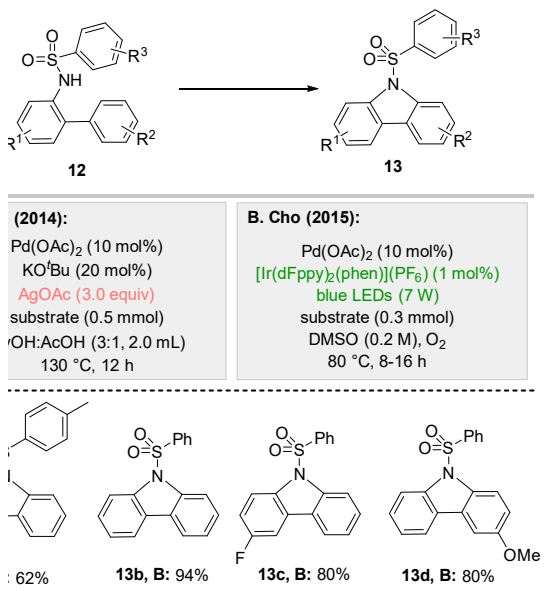
Substituents on the olefin and arene are well tolerated giving the respective products (**11a-c**) with very high efficiency. The abovementioned protocol can be compared with a silver-free version by Rueping and coworkers (reported in 2014), where the authors used $[Ir(bpy)(ppy)_2]PF_6$ as photocatalyst together with a light source (**Scheme 4B**).[31] The authors examined the behavior of the photocatalyst in a variety of solvents and only observed conversion in DMF. The presence of electron-deficient ligands on the photocatalyst led to decreased yields, whereas with electron-rich ligands, the product was obtained in slightly improved yields. Since the reduction potential of the excited state of the photocatalyst is +0.66 V_{SCE},[16] the Pd(0) can easily be oxidized to Pd(II). Under the optimized conditions, the product **11d** formed in 95% yield. Methoxy (**11e**) and chloro (**11f**) substituents are tolerated in the arene part. Similarly, a phenyl substituted olefin gave product **11g** in 91% yield.

In 2014, Laha and coworkers reported a Pd-catalyzed intramolecular oxidative coupling for the synthesis of annulated biaryl sultams. In this report, the authors reported a single example for the synthesis of carbazole (**13a**, **Scheme 5A**).[32]

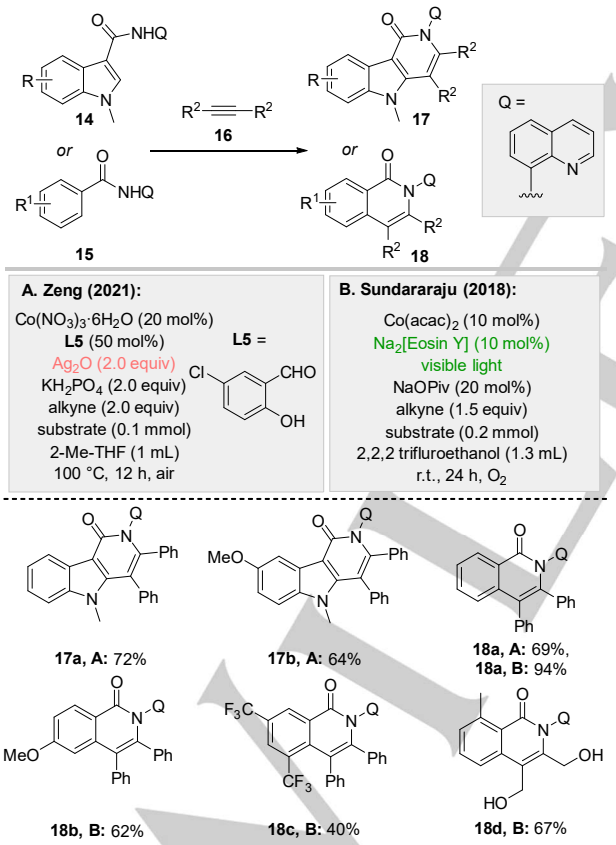


Scheme 4. A: Formation of indole derivatives.[30] **B:** Ag-free synthesis of indoles.[31]

10.1002/anie.202210825



Scheme 5. A: Synthesis of carbazole with Ag.[29] **B:** Ag-free synthesis of carbazoles.[30]



Scheme 6. A: Co-catalyzed C–H/N–H annulation of indolyl amides with alkynes.[31] **B:** Ag-free C–H/N–H annulation.[32]

The authors employed three equivalents of silver acetate to achieve the optimal yield.

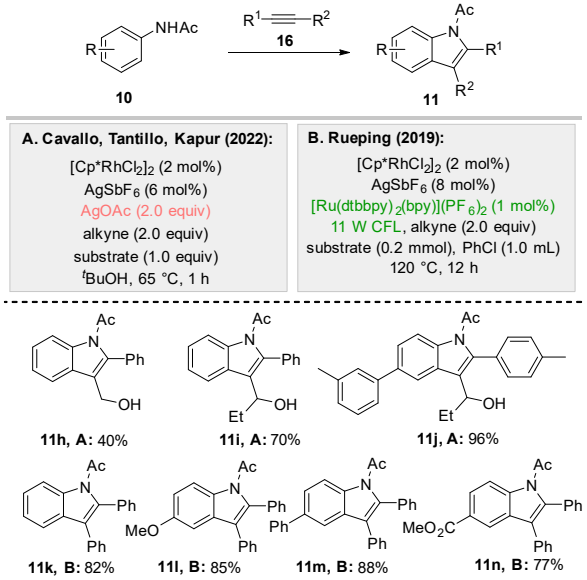
Cho et. al., in 2015, replaced the silver acetate with $[Ir(dFppy)_2(phen)]PF_6$ as the photocatalyst together with blue LEDs and O_2 (**Scheme 5B**).[30]

The protocol formed product **13b** in 94% yield. Similarly, a fluoro and methoxy substituent were tolerated under the reaction conditions giving access to products **13c** and **13d** respectively. Interestingly, photocatalysts with large excited state oxidation potentials were required for an efficient reaction, presumably in order to achieve a sufficiently effective re-oxidation of the palladium catalyst.

In 2021, Zeng and coworkers documented a salicylaldehyde promoted Co-catalyzed C–H/N–H annulation of indolyl amides with alkynes (**Scheme 6A**).[31] The protocol employed stoichiometric silver oxide as additive for the re-oxidation step. The authors showed the use of an indole motif in the heteroarene part and formed product **17a** and **17b** with 72% and 64% yield respectively. Product **18a** derived from arene formed in 69% yield. This protocol can be compared with a silver-free method by Sundararaju and coworkers (reported in 2018), where the authors used Na_2[Eosin Y] as the photocatalyst together with a visible light source (**Scheme 6B**).[35] In this case, household LED bulbs suffice as the source of energy to drive the desired reactions. Both a Ru-based and an organic dye as the photoredox mediator formed products efficiently. Under the reaction conditions, the product **18a** formed in 94% yield. An electron-donating methoxy and electron-withdrawing trifluoromethyl substituent on arene gave products **18b** and **18c** respectively. Product **18d**, derived from an alcohol containing olefin formed in 67% yield.

Since the initial report by Fagnou in 2008, the Rh-catalyzed oxidative coupling of acetanilides and internal alkynes to give indoles with stoichiometric Cu-salts as oxidants has become a widely used method in organic synthesis.[36]

Based on this approach, Cavallo, Tantillo, Kapur and coworkers reported a Rh-catalyzed *ortho*-C–H activation of arenes with acetyl protected amine as the DG specifically tuned to propargyl alcohols as alkyne reaction partners (**Scheme 7A**).[37] Two equivalents of silver acetate were employed to regenerate the active species after product release. Products **11h**, **11i**, and **11j** formed in good to excellent yields.



Scheme 7. A: Rh-catalyzed synthesis of indoles with alkynes.[37] **B:** Stoichiometric Ag-free synthesis of indoles.[38]

This protocol can be compared with a stoichiometric silver-free version by Rueping and coworkers that also closely resembles the original studies using Cu-oxidants (reported in 2019). The authors employed $[Ru(dtbbpy)_2(bpy)](PF_6)_2$ as the photocatalyst in combination with a suitable light source for the re-oxidation step (**Scheme 7B**).[38] Notably, the donor groups on the photocatalyst were essential for good yields.

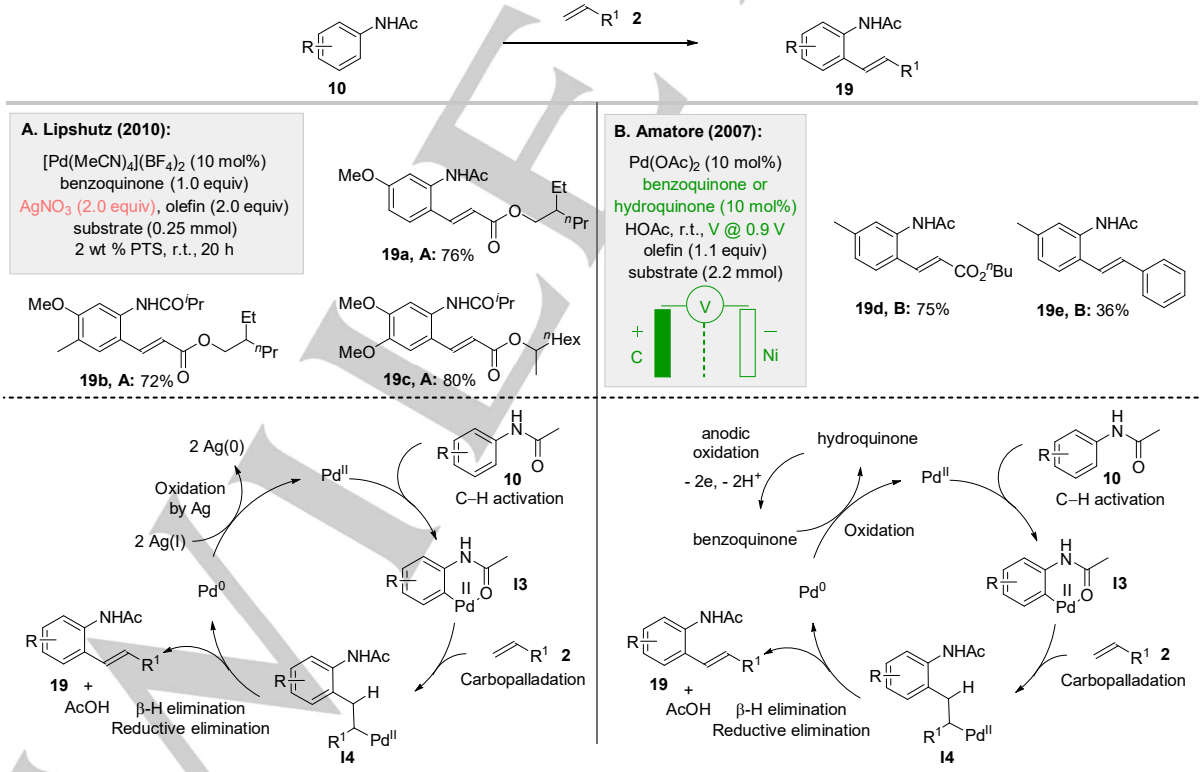
In both studies, $AgSbF_6$ is required in catalytic amounts for the initial generation of active Rh-catalyst from the chloride containing precursor. The product **11k** was obtained in 82% yield. An electron-donating methoxy or phenyl, as well as an electron-withdrawing ester group were tolerated giving access to products **11l**, **11m**, and **11n** in excellent yields. Notably, many further studies that employ photochemistry for the re-oxidation step are reported in literature without an immediate analog based on Ag-additives.[12,13,39]

2.2. Approaches employing electrochemistry

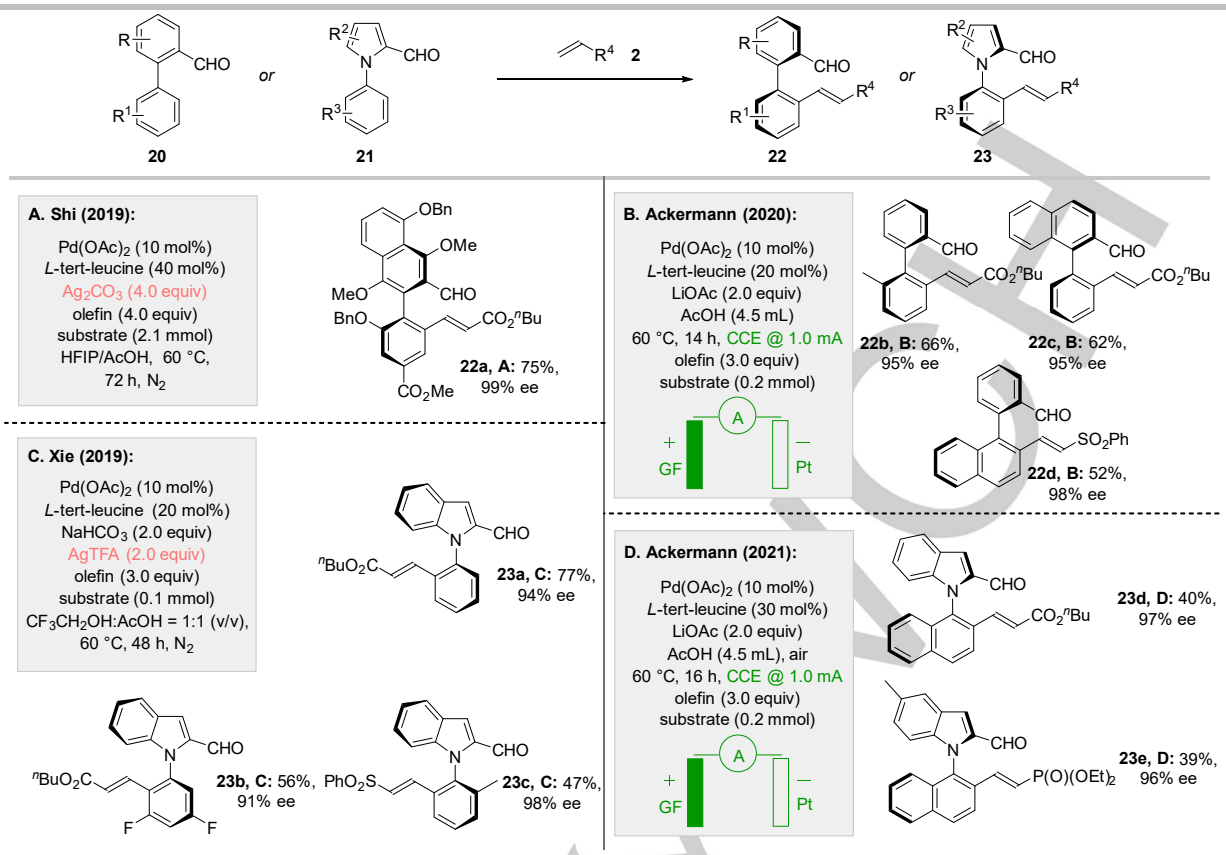
One of the most fundamental processes in chemistry is the change of redox-states. Arguably, the electrochemical addition or removal of electrons through the direct application of an electrical potential represents the conceptually simplest means of adjusting redox states, since it does not require any chemical agents to achieve this goal. Over the past decades, this technique has received renewed attention and has been applied to organic chemistry extensively.[40-43] In this sub-chapter, we will discuss examples where the use of silver is avoided by using electrochemical techniques for the regeneration of active species.

In order to enable a simple comparison of the different catalytic systems discussed, a standardized cell notation introduced by Mei is utilized, which differentiates the cell type (divided and undivided) and form of regulation (constant current or constant potential).[42] Furthermore, the electrode materials and further details are added to the respective examples. The most practical mode of electrolysis is to begin with constant current, because it benefits from a simpler setup and higher conversions. Here, the potential gradually increases until all redox-active species are consumed. Sometimes undesired redox-processes can be encountered at higher conversion. When a lack of selectivity leading to low isolated yield is found to be a disadvantage, switching to constant potential mode can become useful. However, this would require a reference electrode and the full conversion is often not achieved due to the decreasing concentration of redox active species, which lowers the current over time.[44]

In 2010, Lipshutz and coworkers documented a DG-assisted *ortho*-C–H olefination of arenes with activated olefins as the coupling partner (**Scheme 8A**).[45] After the initial DG-assisted *ortho*-C–H activation, the resulting intermediate **I3** undergoes carbopalladation and β-hydride elimination to generate the product. Subsequently, a reductive elimination generates Pd(0), which is re-oxidized to Pd(II) by a combination of benzoquinone and two equivalents of silver nitrate. The protocol was shown to tolerate electron-donating methyl and methoxy groups in the arene moiety and formed the corresponding products with excellent efficiency (**19a-c**). This protocol can be compared with a silver-free version by Amatore and coworkers (reported in 2007), where the authors employed an electrolysis in acetic acid at a carbon woven anode under constant voltage of 0.9 V (**Scheme 8B**).[46]



Scheme 8. A: Pd-catalyzed *ortho*-C–H olefination of aniline-derivatives.[45] **B:** Electrochemical *ortho*-C–H olefination of aniline-derivatives.[46]



Scheme 9. A: Pd-catalyzed atroposelective C–H olefination.[47] **B:** Ag-free atroposelective C–H olefination.[48] **C:** atroposelective C–H olefination of *N*-arylindoles.[49] **D:** Electrochemical atroposelective C–H olefination of *N*-arylindoles.[50]

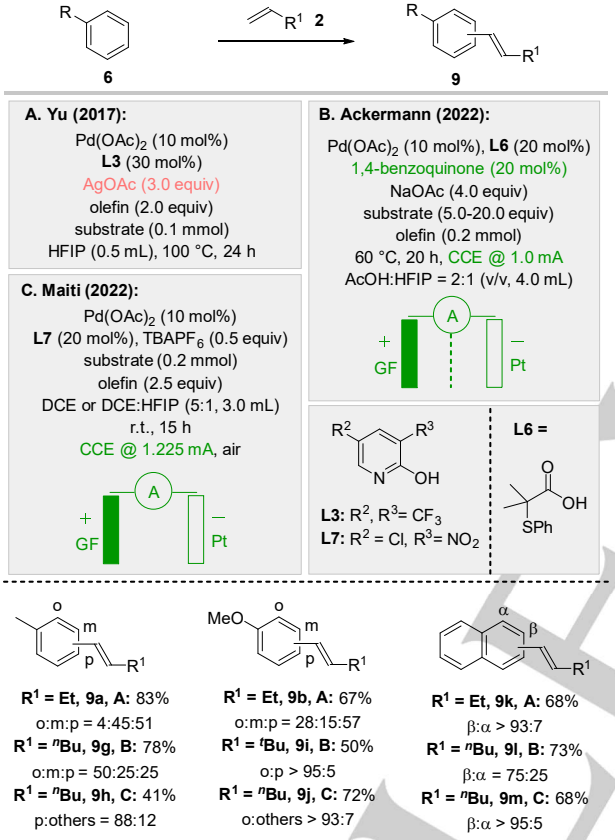
The electrochemical recycling of benzoquinone was performed in a divided cell. And the products **19d** and **19e** were obtained in 75% and 36% yield respectively. Electrolysis at constant potential or constant current provided similar yields. However, the use of an undivided cell would require that the quinone is not reduced at the cathode. From the reduction peak potentials of quinones determined in acetic acid at a gold disk electrode, it was deduced that quinones were reduced before the protons of the medium, whose reduction started at *ca* –0.6 V_{SCE}. This led to the need of using a divided-cell setup.

In 2019, Shi and coworkers reported asymmetric total synthesis of TAN-1085, with a Pd-catalyzed atroposelective C–H olefination as key step.[47]

The authors employed four equivalents of silver carbonate to achieve optimal yield. The corresponding product **22a** formed in 75% yield and with 99% enantiomeric excess (ee) (**Scheme 9A**). Ackermann and coworkers replaced the silver by an electrolysis in acetic acid at a graphite felt anode under constant current of 1 mA (**Scheme 9B**).[48] The electrochemical recycling of the catalyst was achieved in an undivided cell. The optimization studies showed that the redox mediator benzoquinone did not improve the performance in this case, indicating that under these conditions the direct electrochemical re-oxidation of the catalyst can take place efficiently. The products **22b-d** formed with a synthetically useful yield and excellent ee. An analogous atroposelective C–H olefination of *N*-arylindoles was reported by Xie and coworkers where the authors employed Pd/amino acid cooperative catalysis anlongside two equivalents of silver-TFA to close the catalytic cycle (**Scheme 9C**).[49] The product **23a** formed with 47% yield and 94% ee. The difluoro substituted starting material produced the product **23b** in 56% yield and 91% ee and a sulfone substituted olefin could be coupled with excellent selectivity. In 2021, Ackermann and coworkers avoided the use of silver in an analogous electrochemical atroposelective C–H olefination of biaryls employing a graphite felt anode under constant current of 1 mA in an undivided cell (**Scheme 9D**).[50] The corresponding products formed with a synthetically useful yield and an excellent enantioselectivity.

In 2017, Yu and coworkers reported an arene limited non-directed C–H olefination of arenes, in which the authors employed a pyridone ligand (**L3**) and three equivalents of silver acetate to induce the target reaction (**Scheme 10A**, *cf.* **Scheme 3C**).[25] The products **9a**, **9b**, and **9k** formed under the combination of steric and electronic control exerted by the substituents present in the starting material. In 2022, Ackermann and coworkers reported an olefination protocol where the authors replaced the silver by using benzoquinone and electrolysis in acetic acid at a graphite felt anode under a constant current of 1 mA (**Scheme 10B**).[51]The electrochemical recycling of benzoquinone was performed in a divided cell to avoid the quinone reduction at the cathode. The authors employed thiol containing carboxylic acid as ligand (**L6**) and formed products preferentially under electronic control. For example, toluene could be olefinated to deliver the product **9g** in 78% yield and with an o:m:p ratio of 50:25:25. Similarly, the product **9i** from anisole and **9l** from naphthalene could be formed with synthetically useful yields, although it should be mentioned that the method reported by Ackermann and coworkers uses the olefin rather than the arene as limiting reagent. The onset

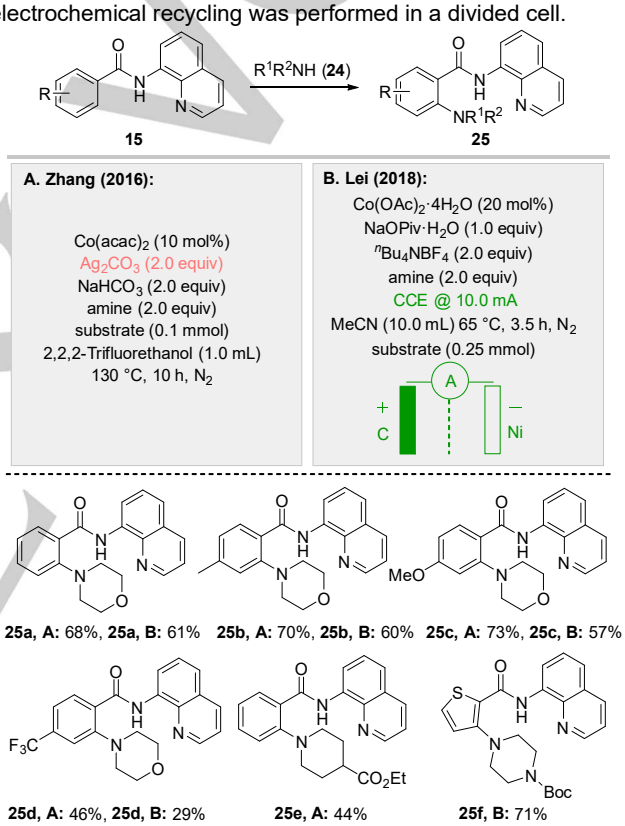
oxidation potential for the *in situ* generated palladium catalyst in the presence of **L6** was observed at 1.35 V_{SCE}, which is 200 mV lower than the one of the complexes derived from pyridone ligand **L4**, which directly correlates with the observed higher reactivity. In a contemporary study, Dutta, Werz, Paul, Maiti, and coworkers reported an electrochemistry-based protocol employing a graphite felt anode in an undivided cell under a constant current (**Scheme 10C**).[52] Addition of catalytic amounts of benzoquinone as a redox mediator or pivalic acid as an additive were proven to have minimal influence on the reaction outcome. Analogous to the method by Ackermann, the protocol also showed substantially increased electronic control compared to the parent system by Yu et al. Toluene could be coupled to give product **9h** in 41% yield with a p:others ratio of 88:12. Similarly the products **9j** and **9m** could be obtained in 72% and 68% yield respectively.



Scheme 10. A Non-directed C–H olefination of arenes with Ag.[25] **B:** Electrochemical C–H olefination of arenes.[51] **C:** Electrochemical C–H olefination of arenes.[52]

In 2016, Zhang and coworkers reported a Co-catalyzed *ortho*-C–H amination of arenes with an 8-aminoquinoline as the DG (**Scheme 11A**).[53] The authors employed two equivalents of silver carbonate as a terminal oxidant to regenerate the active catalyst after product formation. Under the reaction conditions, the product **25a** was formed in 68% yield. Arenes bearing electron-donating methyl- and methoxy- as well as an electron-withdrawing trifluoromethyl-substituent can be coupled to deliver the respective products **25b-d** in good yields. In a subsequent study, Lei and coworkers reported an electrochemical protocol employing a carbon woven anode in a divided cell under a constant current of 10 mA (**Scheme 11B**).[54] The products **25a-d** were formed in good yields. Furthermore, product **25f**, derived from a Boc-protected amine, could be produced in 71% yield. The reaction failed when undivided cell was employed.

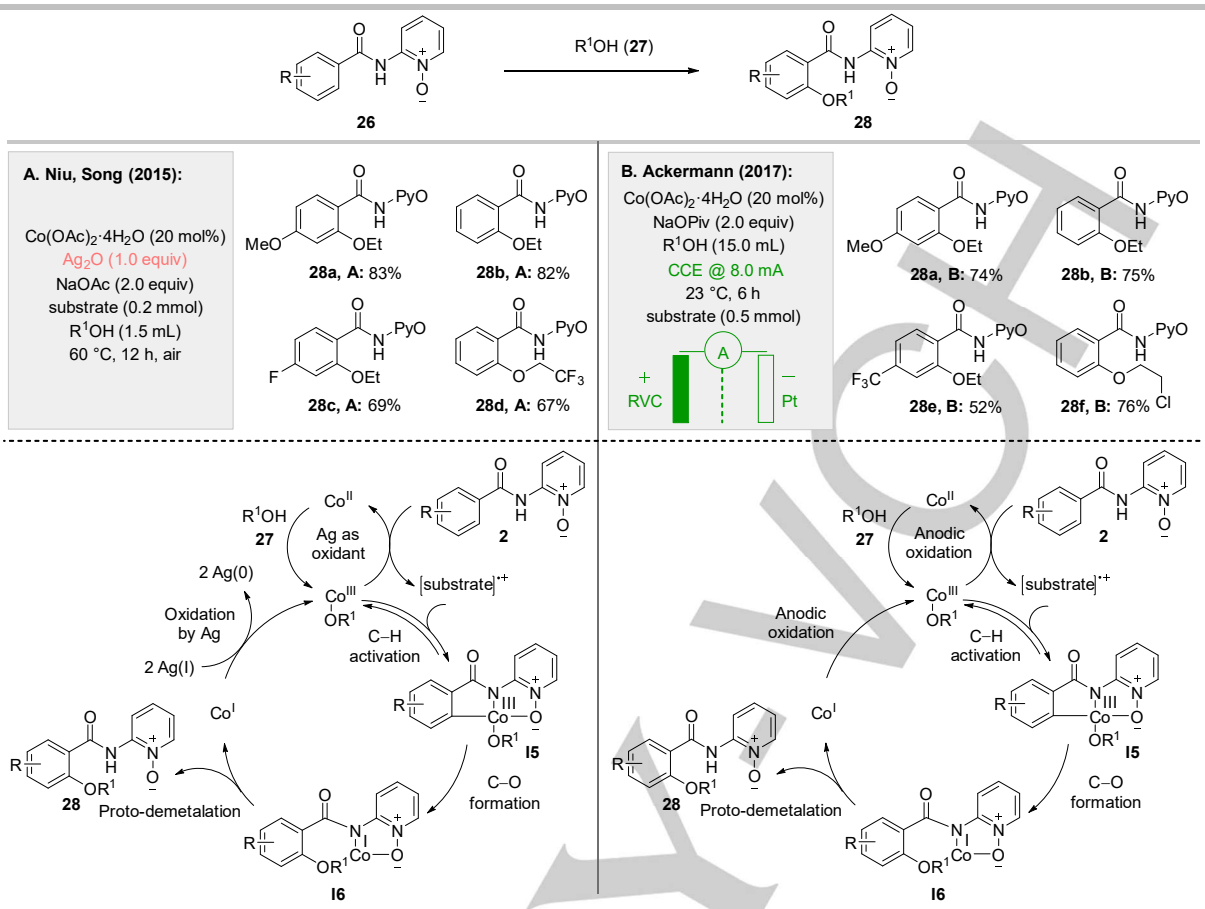
In 2015, Niu, Song and coworkers reported a Co-catalyzed *ortho*-C–H oxygenation of arenes (**Scheme 12A**).[55] The employed silver oxide was involved to produce Co(III) from the catalyst precursor Co(II) *via* a single electron oxidation. First, this Co(III)-species oxidizes the substrate to a radical cation, returning to the Co(II)-state. After re-oxidation to the Co(III)-state, the catalyst reacts with the oxidized substrate to generate the C–H activated complex **I5**. This intermediate then forms the C–O bond giving **I6**, followed by a proto-demetallation to produce the product. The resulting Co(I) is then re-oxidized to active Co(III) by the silver additive to close the catalytic cycle. The products **28a-d** could be formed in good to excellent yields showing a broad functional group tolerance. Ackermann and coworkers enabled a silver-free protocol by using an electrochemical setup with an RVC anode under a constant current of 8 mA (**Scheme 12B**).[56] The electrochemical recycling was performed in a divided cell.



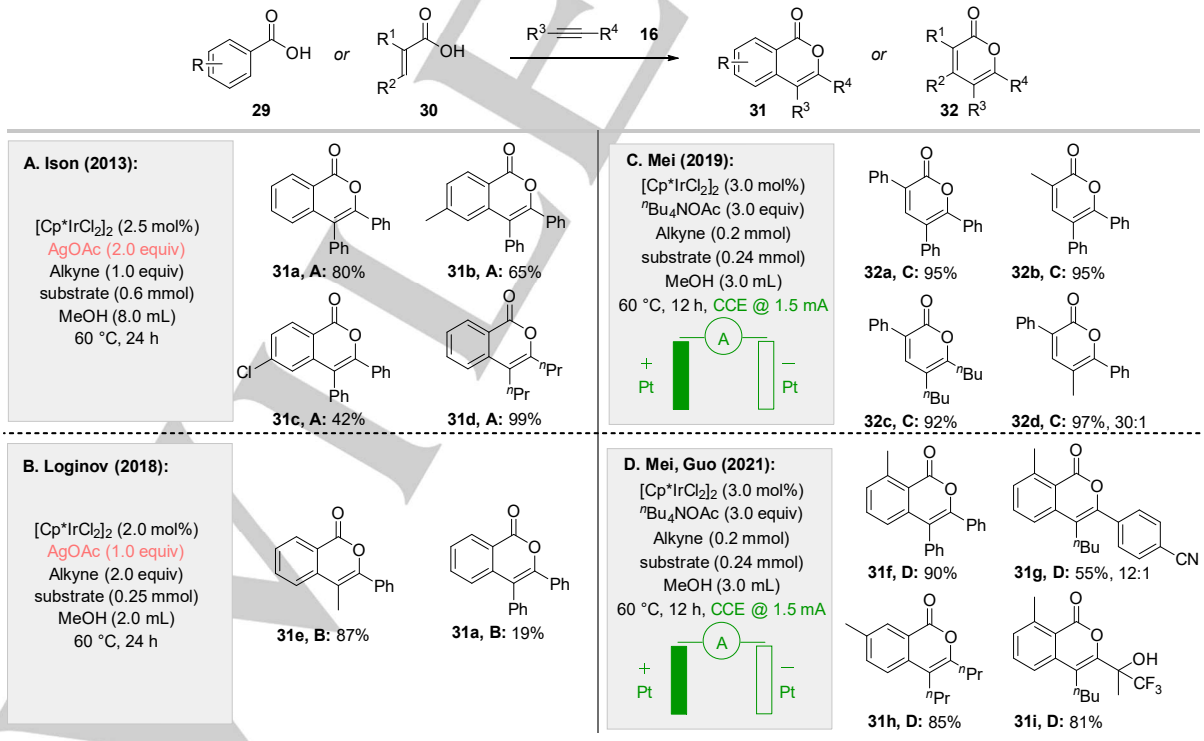
Scheme 11. A Co-catalyzed *ortho*-C–H amination of benzoic acid-derivatives with Ag.[53] **B:** Electrochemical *ortho*-C–H amination of benzoic acid-derivatives.[54]

Control experiments showed that an undivided cell setup led to slightly diminished yields. Detailed cyclovoltammetric studies indicated the formation of a Co(III) species by anodic oxidation. Specifically, the mixture of $Co(OAc)_2$ and NaOPiv in MeOH displayed an oxidation potential of 1.19 V_{SCE} for the oxidation of Co(II) to Co(III), whereas the oxidation potential of the substrate was found to be significantly higher (1.51 V_{SCE}). Thus, the anodic oxidation helps both the initial generation of the Co (III) catalyst *via* single electron transfer and the oxidation of Co(I) to Co(III) for the subsequent catalytic cycle.

10.1002/anie.202210825



Scheme 12. A Co-catalyzed C–H oxygenation of benzoic acid-derivatives with Ag.[55] **B:** Electrochemical C–H oxygenation of benzoic acid-derivatives.[56]



Scheme 13. A and **B:** Ir-catalyzed C–H activation of benzoic acids with Ag. [57,58] **C** and **D:** Electrochemical C–H activation of benzoic acids.[59,60]

Electron-donating methoxy and electron-withdrawing trifluoromethyl groups were well-tolerated under the reaction conditions giving the corresponding oxygenated products **28a** and **28e** respectively. A chloro-substituent in the reagent part is tolerated leading to the product **28f** in 76% yield.

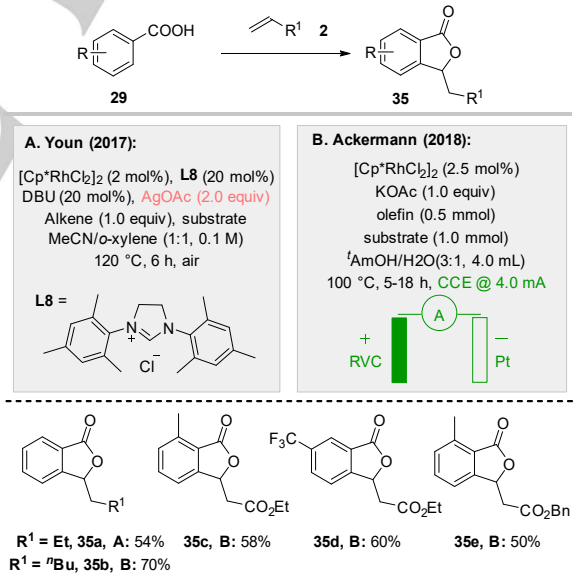
In 2013, Ison and coworkers reported an Ir-catalyzed *ortho*-C–H activation of carboxylic acids, which were then coupled with an alkyne to produce cyclized products (**Scheme 13A**).[57] A methyl and a chloro group on the arene, as well as phenyl- and alkyl-substituted alkynes are well-tolerated under the reaction conditions, delivering products **31a-d** in good to excellent yields.

Two equivalents of silver acetate were employed as a terminal oxidant. In a contemporary study, Loginov et. al. reported the same transformation employing similar reaction conditions (**Scheme 13B**).[58] Mei et. al., in 2019, employed an electrochemical approach to replace the silver additive. The authors reported a Pt anode under constant current of 1.5 mA and addressed a related olefinic C–H activation with carboxylic acid as DG (**Scheme 13C**).[59] The electrochemical recycling was performed in an undivided cell and the corresponding products **32a-d** were obtained with an outstanding efficiency. In 2021, Mei and Guo expanded the electrochemical method to benzoic acid-derivatives with the same reaction conditions (**Scheme 13D**).[60] Carboxylate additives proved critical for the transformation. Switching $^{n}Bu_4NOAc$ to NaOAc or KOPiv provided similar results. In contrast, alternative electrolytes including $^{n}Bu_4NX$ (X = BF_4, PF_6 and ClO_4) were entirely ineffective. The oxidation potentials of 2-methylbenzoic acid (**29f**), diphenylacetylene (**16a**), and isocoumarin **31f** were found at 2.69, 1.88, and 1.74 V_{SCE} respectively, while the intermediately generated Ir(I)-complex showed a significantly lower oxidation potential of 0.79 V_{SCE}, indicating an anodic Ir(I/III) oxidation with a concomitant release of **31f**. The authors observed a broad functional group tolerance and successfully coupled phenyl- and alkyl-substituted alkynes containing cyano, free hydroxyl and trifluoromethyl groups. The respective products **31f-i** were obtained in good yields.

Scheme 14. A Rh-catalyzed C–H activation of amides with Ag.[61] **B:** Electrochemical C–H activation of amides.[62]

In 2010, Song, Li and coworkers reported a Rh-catalyzed C–H activation of olefins with an amide DG and coupled these substrates with suitable alkynes (**Scheme 14A**).[61] The protocol employed a copper-based oxidant, but the authors describe one example in which silver carbonate is used as the terminal oxidant giving product **34a** in 92% yield. In 2021, Hong, Mei et al. employed electrochemistry to avoid the stoichiometric oxidant (**Scheme 14B**).[62] The authors reported a Pt anode under constant current of 1.5 mA and the electrochemical recycling was performed in an undivided cell. The protocol tolerates alkyl substituents, ester and ether groups in the olefinic part as well as phenyl- and alkyl-substituted alkynes as the coupling partners, giving access to products such as **34a-e**.

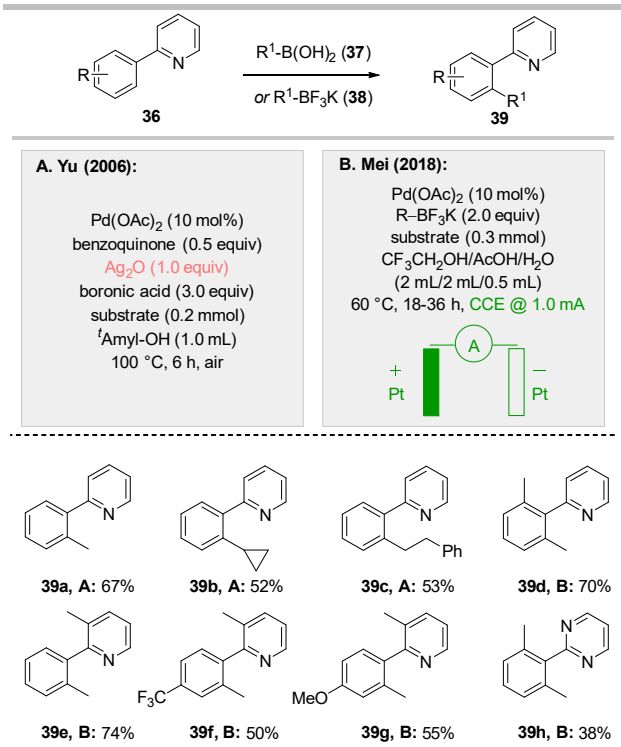
In 2017, the group of Youn reported *N*-heterocyclic carbene/Rh-catalyzed C–H alkenylation/cyclization reactions, employing benzaldehydes as substrates (**Scheme 15A**).[63] In this report, the authors documented a single example of using a carboxylic acid as the substrate and obtained product **35a** in 54% yield. Two equivalents of silver acetate were used to assist the re-oxidation step. Ackermann et. al., in 2018, employed electrochemistry to replace the silver additive (**Scheme 15B**).[64] The authors reported an RVC anode under constant current of 4 mA and the electrochemical recycling was performed in an undivided cell. Carboxylate additives were found to be essential for the C–H alkenylation. In contrast, simple electrolytes such as KPF_6 and NaBr were completely ineffective. This observation supports the hypothesis that a carboxylate-assisted C–H activation is operative. The product **35b** could be obtained in 70% yield. Electron-donating methyl as well as electron-withdrawing trifluoromethyl substituents on arene are well-tolerated yielding products **35c** and **35d** respectively. Similarly, a benzyl group was shown to be tolerated in the olefin part, delivering product **35e** in 50% yield.



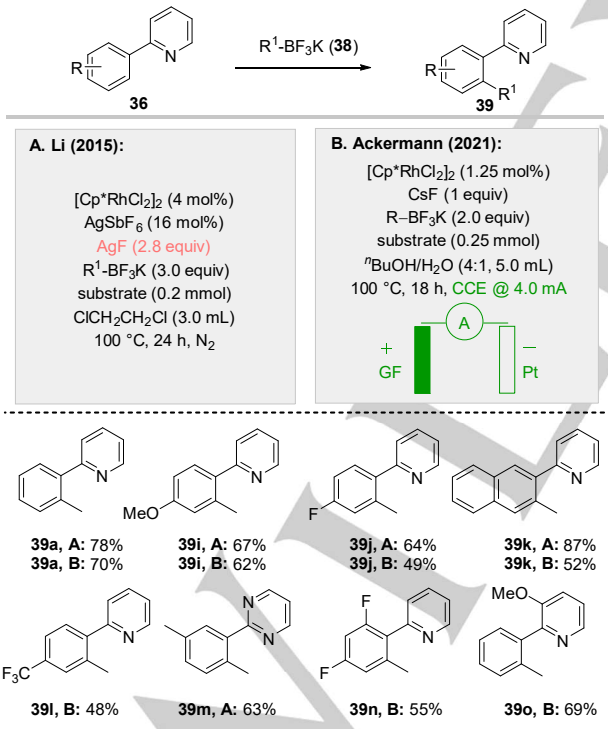
Scheme 15. A Rh-catalyzed coupling of carboxylic acid and olefin with Ag.[63] **B:** Electrochemical coupling of carboxylic acid and olefins.[64]

In 2006, Yu and coworkers reported a Pd-catalyzed alkylation of sp^2 and sp^3 C–H bonds with methylboroxine and alkylboronic acids. In the case of alkylboronic acids, the authors demonstrated the use of stoichiometric silver oxide as oxidant to regenerate the active catalyst. Varied alkylboronic acids delivered products **39a-d** in synthetically useful yields (**Scheme 16A**).[65]

10.1002/anie.202210825



Scheme 16. A Pd-catalyzed alkylation of 2-phenyl pyridines with Ag.[65] **B:** Electrochemical alkylation of 2-phenyl pyridines.[66]



Scheme 17. A Rh-catalyzed alkylation of 2-phenyl pyridines with Ag.[67] **B:** Rh-catalyzed electrochemical alkylation of 2-phenyl pyridines.[68]

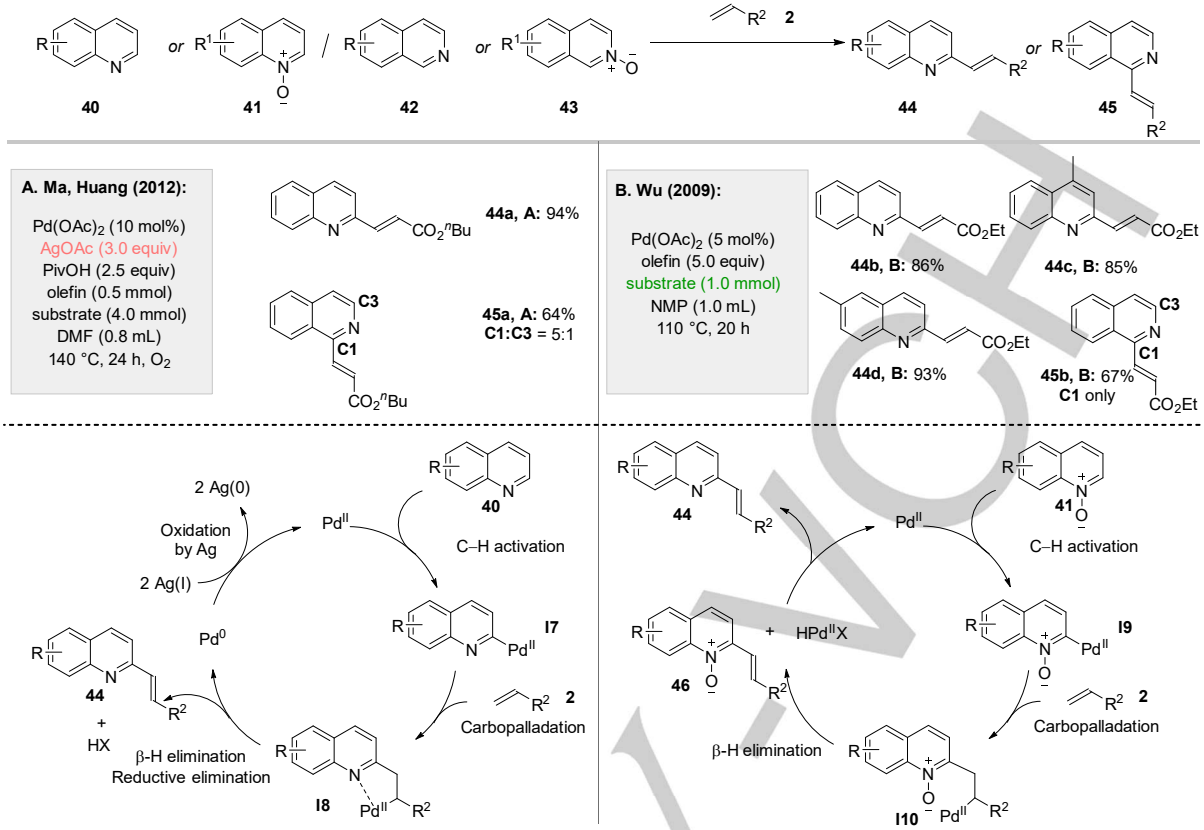
Mei and coworkers replaced the silver with an electrochemical oxidation. The authors employed an Pt anode under a constant current of 1 mA and the electrochemical recycling was performed in an undivided cell (**Scheme 16B**).[66] A variety of substituents including methyl, trifluoromethyl, and methoxy groups was tolerated and delivered the products **39e-g** in good to moderate yields. A pyrazine-based DG gave product **39h** in 38% yield. In 2015, The group of Li reported a Rh-catalyzed protocol for the *ortho*-C–H alkylation of arenes with a pyridine-based DG (**Scheme 17A**).[67] Substrates with a wide range of substituents including methoxy and fluoro groups as well as extended π-systems can be methylated producing products **39a** and **39i-k** in good to excellent yields with exclusive selectivity. The authors used 2.8 equivalents of silver fluoride for the regeneration of the active catalyst. In 2021, Ackermann et. al. replaced the silver additive using electrochemistry. In particular, they employed a graphite felt anode under a constant current of 4 mA and the electrochemical recycling was performed in an undivided cell (**Scheme 17B**).[68] Similar to the method by Li, this protocol delivered products **39a** and **39i-k** in good yields. Trifluoromethyl-substituted, as well as trisubstituted arenes delivered products **39l-n** in 48-63% yield. A methoxy substituent on the pyridine DG delivered product **39o** in 69% yield. Beyond these examples, many further studies using electrochemical re-oxidation but without a directly analogous silver-based method have been reported in literature.[41,43,69]

2.3. Replacement of silver with redox-active directing groups

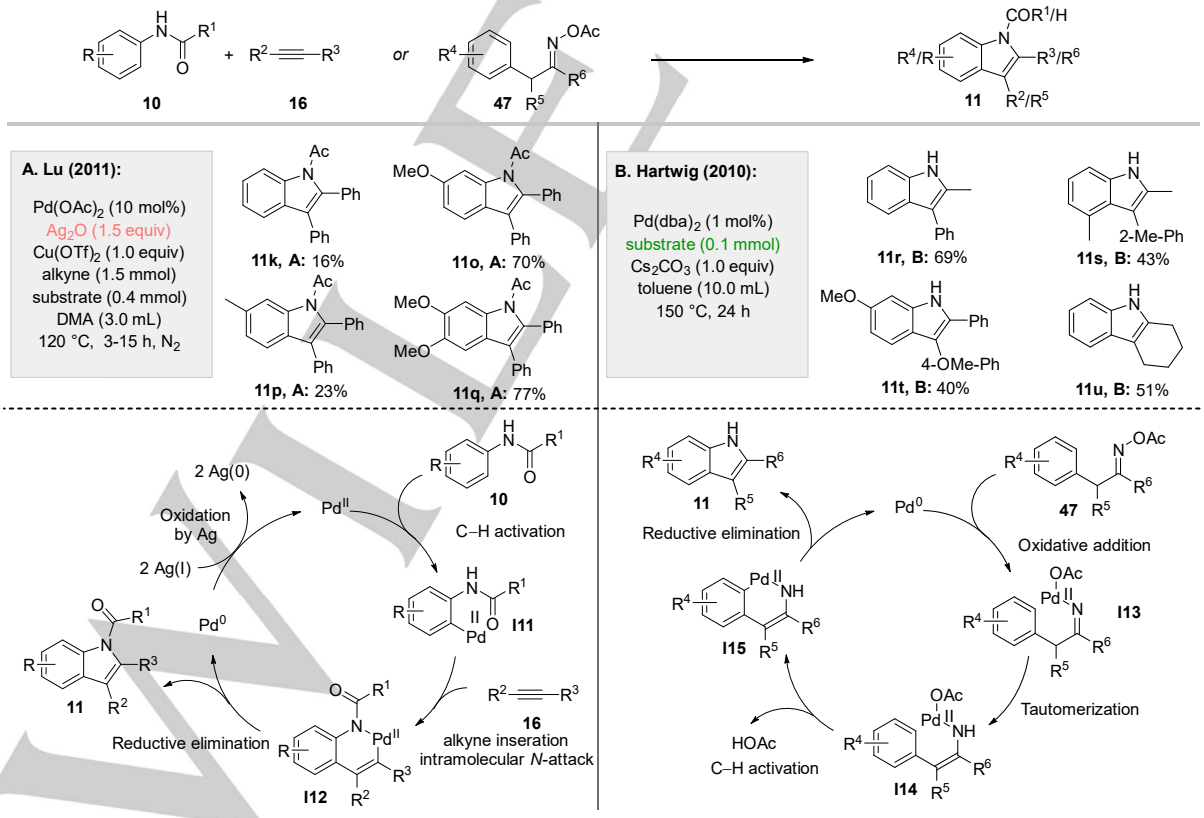
The use of DGs is arguably the most reliable means of inducing the regioselective C–H activation/functionalization of organic molecules. When the C–H activation proceeds through a redox-neutral mechanism, the metal catalyst typically exits the product forming steps in an oxidation state two below the one upon entering the catalytic cycle, leading to the need for a terminal oxidant. From this combination of circumstances, the general concept of redox-active DGs has been developed.[70-72] Generally, such DG contain bonds that can engage in an oxidative addition elementary step and thereby serve both as DG and as terminal oxidant, leaving a non-redox-active functional group in the product molecule at the point of attachment. Typically, redox-active DGs contain easily cleavable N–O and N–N bonds. In this section, we will discuss examples where synthetic methods using stoichiometric silver additives or redox-active DGs achieve the same synthetic result. In contrast to the previous sections, the presence of redox-active DGs implies that the starting materials in the methods being compared differ. As such, the comparisons drawn here highlight the general approach that developing silver-free C–H activations may also be achieved by choosing a strategically more suitable starting material rather than tuning of the reaction conditions.

In 2012, Ma, Huang and coworkers reported a Pd-catalyzed olefination of heterocycles, where the authors achieved the selective C2-activation of quinolines and C1-activation of isoquinolines in excellent yields (**Scheme 18A**).[73] After the initial C–H activation of the substrate, the intermediate **I7** undergoes carbopalladation to produce **I8**. A subsequent β-hydride elimination releases the product and finally a reductive elimination generates Pd(0). The authors employed three equivalents of silver acetate for the re-oxidation step to achieve the optimal yield. A complementary study by Wu and coworkers employed the analogous *N*-oxides as starting materials and could thereby avoid the use of stoichiometric silver (**Scheme 18B**).[74]

10.1002/anie.202210825



Scheme 18. A Pd-catalyzed olefination of heterocycles with Ag.[73] **B:** Pd-catalyzed olefination with a redox-active DG.[74]



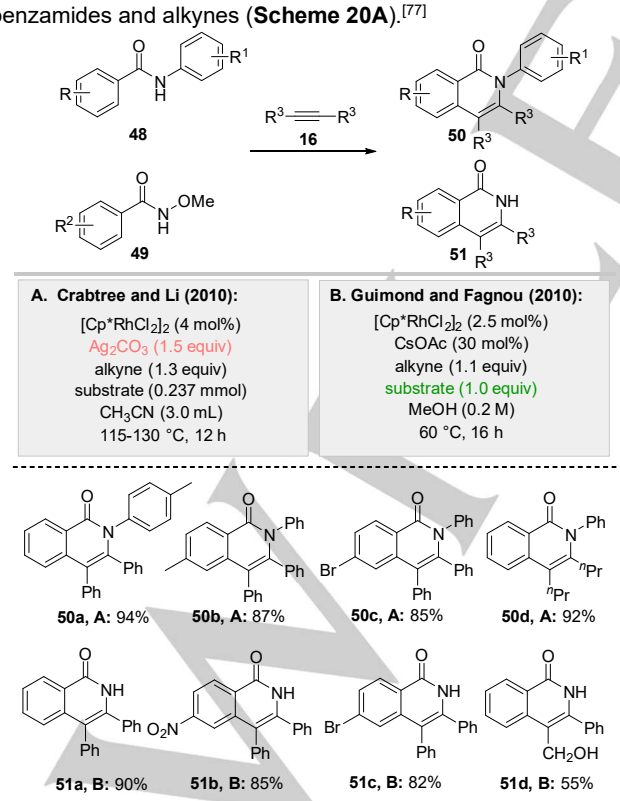
Scheme 19. A Pd-catalyzed coupling of *N*-aryl amides and alkynes.[75] **B:** Pd-catalyzed amination of aromatic C–H bonds with oxime esters.[76]

After the C–H activation, carbopalladation and β-hydride elimination, the primary product **46**, an olefinated heterocycle-*N*-oxide, is formed alongside Pd(II). The authors propose that instead of undergoing a reductive elimination, the Pd(II)-hydride species reacts with the *N*-oxide, leading to its reduction to product **44** and a concomitant regeneration of the $Pd(OAc)_2$-catalyst. The products **44b-d** were synthesized in excellent yields. Also, the product **45b** from isoquinoline can be formed in good yields with exclusive C1-selectivity.

In 2011, Lu and coworkers reported the synthesis of indoles *via* the Pd-catalyzed C–H activation of *N*-aryl amides followed by coupling with alkynes (**Scheme 19A**).[75] After the C–H activation, the intermediate **I11** couples with the alkyne to generate **I12**. After a reductive elimination, **I12** releases the product **11** and forms Pd(0). The silver oxide oxidizes Pd(0) to Pd(II) and thereby closes the catalytic cycle. Using this protocol, the product **11k** was formed in 16% yield, whereas electron-donating methoxy substituents on the heterocycle led to much improved yields of the corresponding products (**11o** and **11q**).

Hartwig and coworkers reported a complementary study (in 2010) employing oxime esters as the redox-active DG (**Scheme 19B**).[76] In the first step, the Pd(0) is oxidized to Pd(II) *via* an oxidative addition of the N-O bond giving intermediate **I13**. The carbon-nitrogen double bond tautomerizes to a carbon-carbon double bond and the resulting intermediate **I14** undergoes an *ortho*-C–H activation to generate **I15**. Subsequently, a reductive elimination releases the product **11** and delivers Pd(0), which can re-enter the catalytic cycle. The product **11r** formed in 69% yield. Electron-donating methyl and methoxy substituents are tolerated on the arene part, producing the corresponding products **11s** and **11t** in 43% and 40% yield.

In 2010, Crabtree and Li developed a Rh-catalyzed coupling of benzamides and alkynes (**Scheme 20A**).[77]

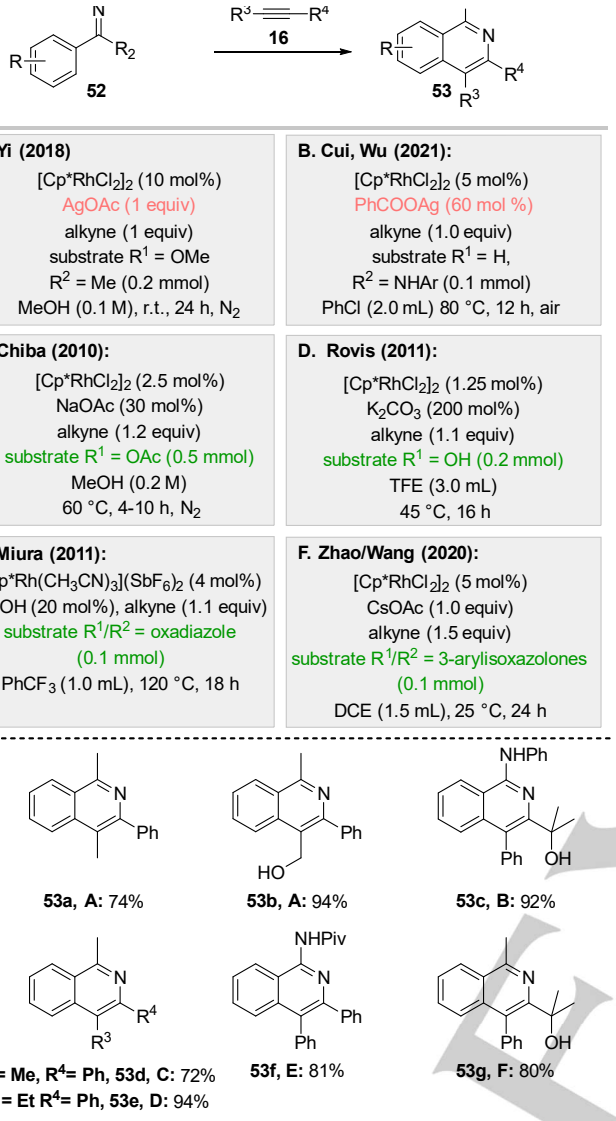


Scheme 20. A Rh-catalyzed coupling of benzamides and alkynes.[77] **B:** Rh-catalyzed isoquinolone synthesis with redox-active DG.[79]

The authors employed one and a half equivalents of silver carbonate to achieve an optimal yield during the re-oxidation step of Rh(I) to Rh(III). The product **50a** was formed in 94% yield. Methyl and bromo-substituted arenes coupled successfully to generate the products **50b** and **50c** in 87% and 85% yields respectively. Alkyl containing alkynes are tolerated for example to provide the product **50d**. Contemporaneously, the groups of Rovis and Ackermann developed analogous methods using $Cu(OAc)_2$ as the stoichiometric oxidant.[78]

In the same year, Guimond and Fagnou reported the use of a redox-active DG containing an N–O bond (**Scheme 20B**).[79] After the initial *ortho*-C–H activation directed by nitrogen, the alkyne insertion occurs. Until this point, the Rh maintains the oxidation state of +3. Subsequently, a reductive elimination produces Rh(I), which is then oxidized by oxidative addition of the N–O bond leading to the regeneration of Rh(III) and concomitant product release. The product **51a** formed in 90% yield. An electron-withdrawing nitro substituent and a bromo substituent produced the products **51b** and **51c** in 85% and 82% yield respectively. Free alcohol was tolerated in the alkyne part, thereby generating **51d** in synthetically useful yield.

In analogy to the Rh-catalyzed synthesis of indoles from acetanilides and alkynes, the reaction of substrates containing a benzimine-substructure can be used to access isoquinolines. Seminal reports by the groups of Fagnou and Miura used Cu(II)-salts as oxidants towards this end, which have since been widely employed.[80] In 2018, Yi reported several examples of isoquinoline syntheses using an O-methyl oxime as starting material alongside silver as stoichiometric additive (**Scheme 21A**).[81] Both regular alkynes (**53a**) and propargyl alcohols (**53b**) could be used as reaction partners. In the latter case, the alcohol functionality was incorporated in the 4-position. In 2021, Cui, Wu and coworkers reported a Rh-catalyzed [4 + 2] annulation of *N*-arylbenzamidines with propargyl alcohols to produce isoquinolines with a complementary regioselectivity placing the alcohol functionality in the 3-position (**53c**, **Scheme 21B**).[82] The authors proposed a combined action of silver benzoate and air for the oxidation of Rh(I) to Rh(III) to achieve catalyst turnover. The product **53c** was formed in 92% yield. In a previous study, Chiba and coworkers showed that a silver-free transformation is possible when an internal O-acyloxime is used as the DG (**Scheme 21C**).[83] Contemporarily, Rovis et. al. showed that an oxime as a DG can also form the isoquinolines without an external oxidant (**Scheme 21D**).[84] The latter two studies delivered products with alkyl substituents in the 1-position (**53e-f**), analogous to the ones obtained by Yi. Later, Zhu and coworkers showed that analogous transformations are possiible starting from an N–Cl bond as an internal oxidant.[85] Complementarily, in 2011 Miura reported that using oxadiazoles as starting materials products with an *N*-acyl group in the 1-position can be generated (**53g**, **Scheme 21E**).[86] Finally, Zhao, Wang and coworkers used 3-arylisooxazolones as substrates together with propargyl alcohols as reaction partners, complementing the silver-based studies by Yi et al as well as Cu, Wang and coworkers (**Scheme 21F**).[87] Products such as **53g** were obtained with the hydroxy group on the 3-position. The systems described in **Scheme 21C-F** all rely on an internal bond that oxidizes the Rh(I) to Rh(III) to close the catalytic cycle.



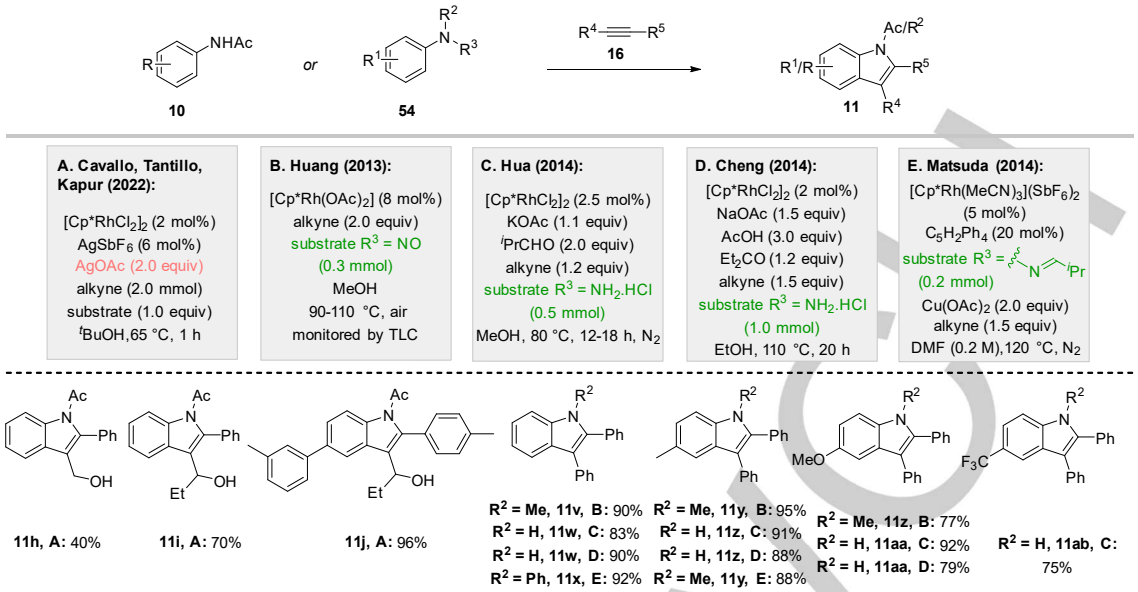
Scheme 21. A: Rh-catalyzed [4 + 2] annulation of O-methyl oxime and alkynes.[81] **B:** Rh-catalyzed [4 + 2] annulation of *N*-arylbenzamidines with propargyl alcohols.[82] **C:** Rh-catalyzed synthesis of isoquinolines from aryl ketone O-acyloxime derivatives and internal alkynes.[83] **D:** Rh-catalyzed coupling of oximes and alkynes.[84] **E:** Rh-catalyzed synthesis of isoquinolines from oxadiazoles.[86] **F:** Rh-catalyzed synthesis of isoquinolines from 3-arylisoxazolones.[87]

As mentioned above, the Rh-catalyzed oxidative coupling of acetanilides and internal alkynes to give indoles with stoichiometric Cu-salts as oxidants is well established and applicable to alkynes with diverse substitution patterns.[36]

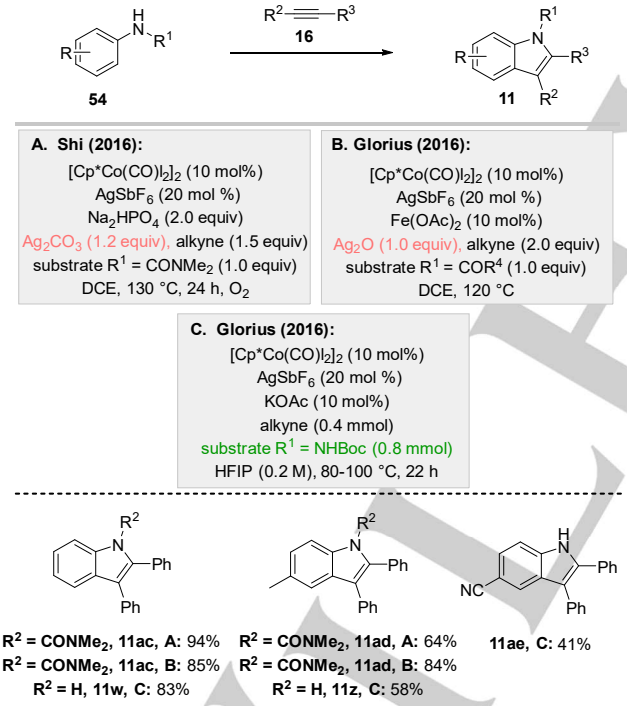
Based on this approach, Cavallo, Tantillo, Kapur and coworkers reported a Rh-catalyzed *ortho*-C–H activation of acetanilides specifically tuned to propargyl alcohols as alkyne reaction partners (**Scheme 22A**).[37] The authors coupled the resulting organometallic intermediate with an alkyne to form indole derivatives. Two equivalents of silver acetate were employed to regenerate the active species after product release. Products **11h**, **11i**, and **11j** formed in good to excellent yields. This protocol can be compared with four contemporary studies that employed redox-active directing groups in place of the silver additives. The first one, from Huang and coworkers, used directed *ortho*-C–H activation followed by coupling with alkyne and subsequent generation of the indole derivative as product (**Scheme 22B**).[88] The Rh(III) oxidation sate is restored by the N–N bond present in the DG. The second and third studies, by Hua et al. and Cheng et al., employed arylhydrazines as starting material, *in situ* generating a hydrazone DG, which likewise contains a N–N bond (**Scheme 22C**[89] and **Scheme 22D**[90]). Finally, Matsuda and coworkers directly employed an hydrazone-based DG (**Scheme 22E**).[91] The mechanisms of the last three studies strongly resembles the one described by Huang and coworkers. The products **11v-x** derived from mono-substituted arenes were formed in excellent yields employing all four protocols. Similarly, a methyl group was tolerated, producing products **11y-z**. Furthermore, a methoxy substituent was tolerated using conditions B, C, and D. Under the reaction conditions C, an electron-withdrawing trifluoromethyl substituent was tolerated giving the product **11ab** in 75% yield.

In 2016, Shi and coworkers employed a Co-based catalyst for the synthesis of indole derivatives (**Scheme 23A**).[92] Similar to the protocols from Cavallo, Tantillo, Kapur and coworkers, the authors used an alkyne source to couple with substrate after the C–H activation step. The authors used 1.2 equivalents of silver carbonate for the optimal outcome in the oxidation step. In a contemporary study, Glorius et. al. documented the use of silver oxide as an oxidant (**Scheme 23B**).[93] The product **11ac** was formed in 94% and 85% yield using conditions A and B respectively. A methyl substituent on the arene part was tolerated producing the product **11ad** in good yield. Importantly, in both studies, the authors employed 20 mol% of $AgSbF_6$ for the initial generation of active catalyst from a commercially available precatalyst. In 2016, Glorius and coworkers reported a Co-catalyzed redox-neutral reaction system with an oxidizable DG on the substrate (**Scheme 23C**).[94] The authors used an N–N bond as the oxidant and a Boc protected nitrogen DG for *ortho*-C–H activation. Under the reaction conditions, the product **11w** from mono-substituted arene was formed in 83% yield. An electron-donating methyl and electron-withdrawing cyano substituent were tolerated, producing the products **11z** and **11ae** in 58% and 41% yield respectively. It should be pointed out that, while the discussion of the methods shown in **Scheme 22** highlights the possibility to develop silver-free methods, the products obtained in **Scheme 22 B-E** closely resemble the ones that can be obtained from Cu(II)-based methods.[36] This highlights that the approaches discussed herein can often also be useful to avoid the use of other commonly employed stoichiometric metal salts.

It should be noted that the use of redox-active DGs has been established as a highly valuable tool in C–H activation with many more applications described in literature, to which no immediate analogs based on the use of silver as terminal oxidant exist.[71,72,95]



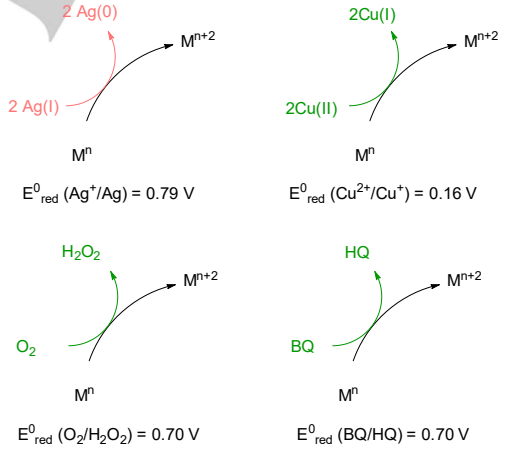
Scheme 22. A: Rh-catalyzed formation of indoles from aniline-derivatives with alkynes.[37] **B:** Rh-catalyzed synthesis of *N*-alkyl indoles *via* redox neutral C–H activation.[86] **C:** Rh-catalyzed C–H activation and indole synthesis with hydrazone as redox-active DG.[89] **D:** Rh-catalyzed C–H activation directed by an *in situ* generated redox-active DG.[90] **E:** Rh-catalyzed synthesis of indoles from 1-alkylidene-2-arylhydrazines and alkynes.[91]



Scheme 23. A: Co-catalyzed oxidative coupling of *N*-arylureas and internal alkynes.[92] **B:** Co-catalyzed synthesis of indols *N*-acyl anilines and alkynes.[93] **C:** Co-catalyzed C–H activation and redox-neutral indole synthesis from arylhydrazine-derivatives.[94]

2.4. Approaches employing other oxidants

A simple strategic approach towards avoiding stoichiometric silver additives is the use of more sustainable chemical oxidants. The standard reduction potential of Ag(I)/Ag(0) is +0.79 V_{SHE},[96] which is very close to the O_2/H_2O_2 and BQ/HQ systems (both +0.70 V_{SHE}).[96] Considering these values, it seems reasonable that if the role of silver is exclusively that of an oxidant in a given reaction, it can potentially be replaced with O_2 and/or BQ as ecologically and economically more attractive oxidants (**Scheme 24**).



Scheme 24. Comparison between alternative oxidants.

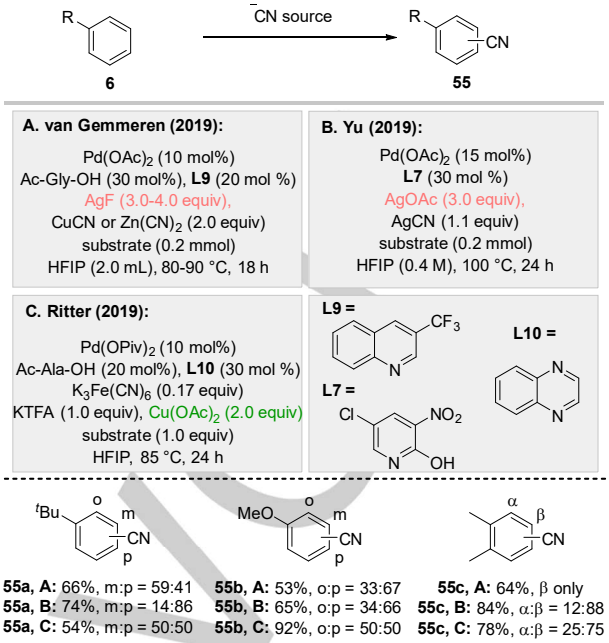
In contrast, the Cu(II)/Cu(I) couple displays a much lower reduction potential of 0.16 V_{SHE},[97] rendering it a much weaker oxidant than silver. Nevertheless, the existence of such important precedent as the Wacker process proves that the Cu(II)/Cu(I) couple can be used effectively to re-oxidize palladium from Pd(0) to Pd(II), which implies that similar redox reactions should also be possible in the context of C–H activation methods.[98] Note that the existence of analogous methods using Cu(II)-salts was already highlighted in the sections above. When planning such replacements, further strategic considerations include that the oxidation power should not be too high for the catalytically active metal employed, such that the catalyst might be oxidized beyond the desired oxidation state that closes the catalytic cycle.

Furthermore, the kinetics of the redox-processes should be considered. Besides the thermodynamic ability of a given oxidant to restore the active catalyst, the pathway for the re-oxidation must be able to outcompete potential catalyst decomposition in the reduced state. In this section, we will discuss the examples where the silver is replaced with these oxidants in the case of C–H activation.

As discussed above, Cavallo, Tantillo, Kapur and coworkers reported a Rh-catalyzed *ortho*-C–H activation of arenes with acetyl protected amine as the DG that was specifically developed for propargylic alcohols as reaction partners (**Scheme 25A**, *cf.* **Scheme 7A**).[37] The authors coupled the resulting organometallic intermediate with an alkyne to form indole derivatives. Two equivalents of silver acetate were employed to regenerate the active species after the release of the product. The Cu-salts commonly used for non-propargylic substrates gave poor results in this case, such that the silver-additive became necessary for this substrate class. Products **11h**, **11i**, and **11j** could be formed in good to excellent yields. This protocol can be compared with the seminal studies by Stuart, Fagnou and coworkers reported in 2010. In this study, the authors employed a stoichiometric Cu(II)-salt as additive for the oxidation step, which enabled the use of various internal alkynes as reaction partners and established Cu(II)-salts as widely used stoichiometric oxidants in C–H activation (**Scheme 25B**).[99] The product **11af** from mono-substituted arene was formed in 86% yield. Methoxy and a chloro substituents were tolerated under the reaction conditions, producing products **11ag-ai** in good to excellent yields.

Scheme 25. A: Rh-catalyzed formation of indoles from *N*-acyl anilines and alkynes.[37] **B:** Ag-free Rh-catalyzed synthesis of indoles from *N*-acyl anilines and alkynes.[99]

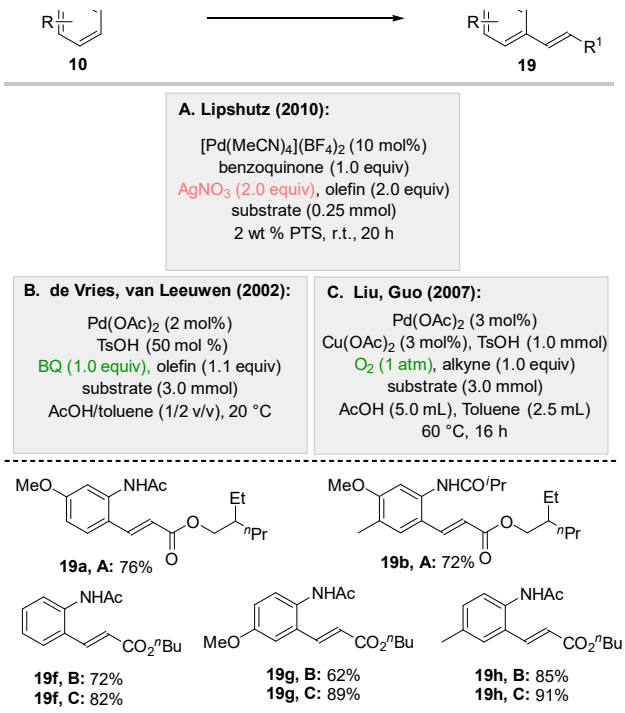
The replacement of silver with copper can also be used for Pd-catalysts. In 2019, van Gemmeren and coworkers reported a C–H cyanation of arenes[100] employing a dual-ligand based catalyst[26,101] system based on a catalyst design previously introduced by this group (**Scheme 26A**). The authors employed three or four equivalents of silver fluoride for the oxidation step to obtain an optimal yield.



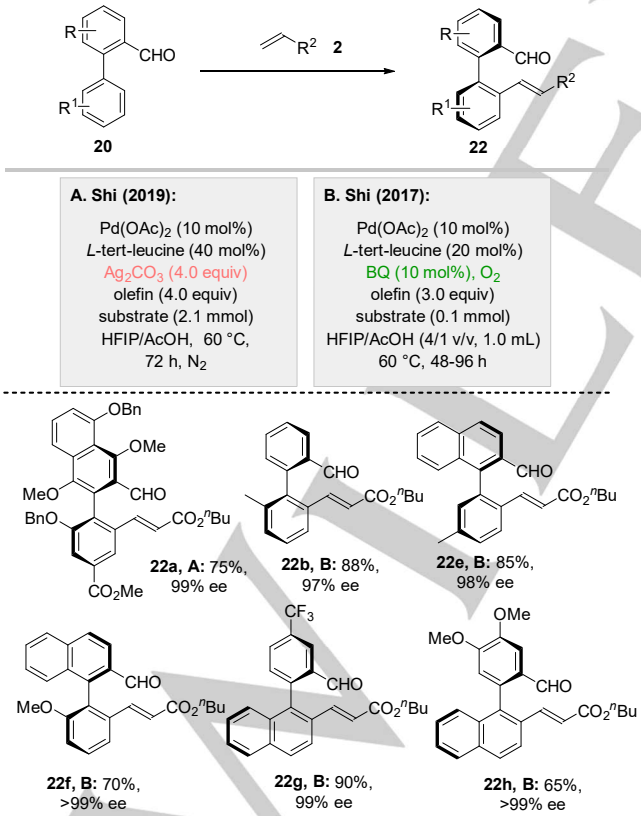
Scheme 26. A and **B:** Silver-based nondirected Pd-catalyzed C–H cyanation of arenes.[100, 102] **C:** Pd-catalyzed C–H cyanation of arenes with Cu additives.[103]

In a contemporary study, Yu and coworkers reported a Pd-pyridone catalyst system-based C–H cyanation of arenes, where the authors employed three equivalents of silver acetate for the re-oxidation step (**Scheme 26B**).[102] In a third contemporary study, Ritter and coworkers, likewise using a dual-ligand based catalyst system showed that in some cases copper(II) acetate instead of silver additive can be used to affect the re-oxidation step (**Scheme 26C**).[103] All three systems formed cyanated alkyl benzenes in good to excellent yields. The dual-ligand catalyst systems by van Gemmeren and Ritter show lower electronic control with increased steric sensitivity compared to the Pd-pyridone system described by Yu. However, with strongly electron-donating methoxy substituents all the three systems formed product under electronic control. Di-alkyl substituted arene formed product **55c**, maintain steric control for the dual-ligand systems and electronic control in case of Pd-pyridone system.

In 2010, Lipshutz and coworkers documented a DG-assisted *ortho*-C–H olefination of arenes with activated olefins as the coupling partner (**Scheme 27A**, *cf.* **Scheme 2A**).[45] The authors employed two equivalents of silver nitrate to achieve optimal results. The protocol was shown to tolerate electron-donating methyl and methoxy groups in the arene moiety and formed the corresponding products with excellent efficiency (**19a-b**). In a previous study, de Vries, van Leeuwen and coworkers showed that benzoquinone can alternatively be used as organic oxidant (**Scheme 27B**),[104] giving product **19f** with 72% yield.



Scheme 27. A: Pd-catalyzed *ortho*-C–H olefination of *N*-acyl anilines with silver additive.[45] **B:** Pd-catalyzed *ortho*-C–H olefination of *N*-acyl anilines using BQ.[104] **C:** Pd-catalyzed *ortho*-C–H olefination of *N*-acyl anilines using O_2.[105]



Scheme 28. A: Pd-catalyzed atroposelective C–H olefination with silver additive.[47] **B:** Pd-catalyzed atroposelective C–H olefination using BQ and O_2.[106]

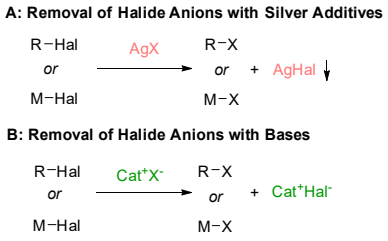
Electron-donating methoxy and methyl substituents on the arene were tolerated delivering the products **19g** and **19h** respectively. In 2007, Liu, Guo et. al. reported a similar system employing elemental oxygen as the terminal oxidant, which renders the method highly attractive from a green chemistry perspective (**Scheme 27C**)[105], allowing the products **19f-h** to be produced in excellent yields.

In 2019, Shi and coworkers reported an asymmetric total synthesis of TAN-1085, with a Pd-catalyzed atroposelective C–H olefination as key step (**Scheme 28A**, *cf.* **Scheme 9A**).[47] The authors employed four equivalents of silver carbonate to achieve optimal yield. The corresponding product **22a** was formed in 75% yield and with 99% enantiomeric excess (ee). In a subsequent study, the authors replaced the silver additive with a catalytic amount of benzoquinone and O_2 (**Scheme 28B**)[106]. The reduced metal gets oxidized by BQ, the latter being reduced to HQ. Since the reduction potential of BQ/HQ and O_2/H_2O_2 are similar, the HQ then gets oxidized back by O_2 present, allowing use of the benzoquinone in a catalytic quantity. Electron-donating methyl, methoxy and electron-withdrawing trifluoromethyl groups were well-tolerated, producing **22b** and **22e-h** with excellent yield and ee. It should be noted that the use other oxidants has been established as a highly valuable tool in C–H activation with many more applications described in literature, to which no immediate analogs based on the use of silver as terminal oxidant exist.[107]

3. Silver as Halide Scavenger

Silver additives are well known to act as a halide scavenger due to their ability to form silver halides, which often precipitate from the reaction mixture due to their insolubility in commonly employed solvents. Replacing silver in its role as a halide scavenger requires an alternative strategy to remove halide anions from the metal/pre-reactive reagent to regenerate the active species and close the catalytic cycle. This has been achieved using alternative bases (to induce counteranion metathesis), phosphine ligands (to achieve reactivity in the presence of halide anions), and by changing the reagent in such a way that the formation of halide anions is avoided and silver becomes unnecessary.

3.1 Replacement of silver with suitable base

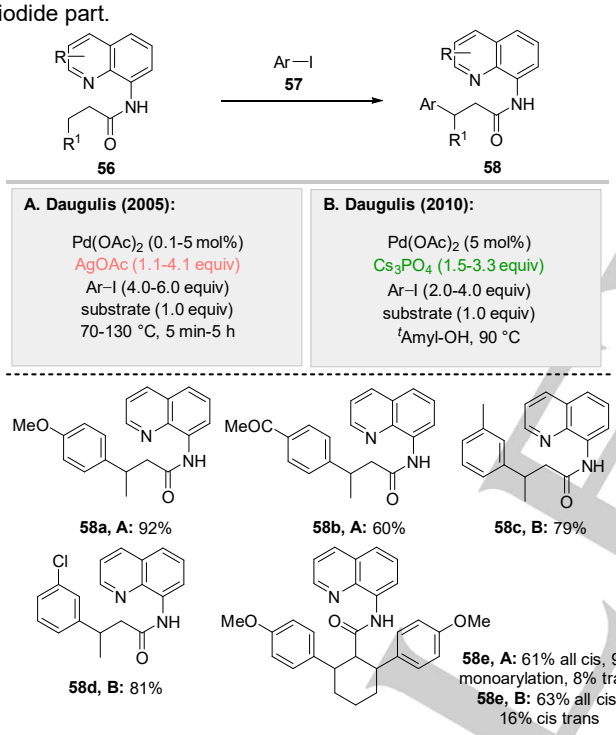


Scheme 29: Scavenging of halide anions with **A.** silver additives and **B.** base.

Conceptually, in metal catalyzed reactions the halide ion can be abstracted from the reagent to form a reactive intermediate or from the metal after the reagent activation step (**Scheme 29**). In case of C–H activation reactions, it is often the case that after the key C–H activation step, the metal undergoes an oxidative addition with the halide containing reagent and further steps

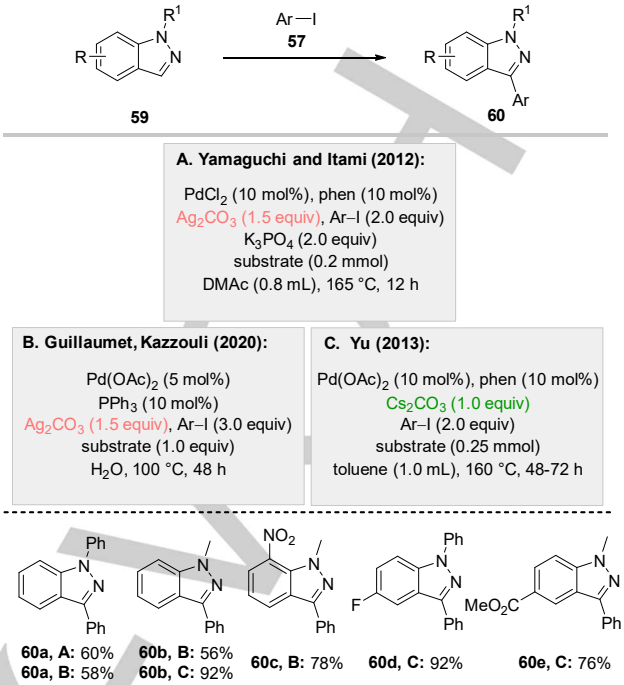
towards product formation. At the end of such a sequence, the metal remains in the correct oxidation state for re-entering the catalytic cycle, but the catalytic activity is diminished or suppressed by the halide ligands. Thus, a removal of the halide is required for turnover, which can be achieved through either silver additives or base.

In 2005, Daugulis and coworkers reported an 8-amino quinoline assisted Pd-catalyzed *β*-C–H arylation of carboxylic acid derivatives (**Scheme 30A**).[108] The authors employed aryl iodide as the coupling partner and stoichiometric silver acetate as iodine scavenger. Electron-donating methoxy and electron-withdrawing ketone substituents were tolerated on the coupling partner, producing products **58a** and **58b** in 92% and 60% yields respectively. The substrate derived from cyclohexane carboxylic acid produced all cis isomer of di-arylated product **58e** in 61% yield. In 2010, the same group replaced the silver additive with cesium phosphate for the iodine scavenger step (**Scheme 30B**).[109] A slight modification of the reaction conditions resulted in the formation of products **58c-e** with excellent yield and selectivity. Alkyl and chloro groups were tolerated on the aryl iodide part.



Scheme 30 A: Pd-catalyzed *β*-C–H arylation with 8-amino quinoline DG.[108] **B:** Pd-catalyzed *β*-C–H arylation with 8-amino quinoline DG employing base as iodine scavenger.[109]

A sp^2-C–H activation/arylation with indazoles as substrates employing aryl iodide as the coupling partner and stoichiometric silver carbonate as halide scavenger was reported by Yamaguchi, Itami, and coworkers (**Scheme 31A**).[110] The product **60a** derived from phenyl iodide was produced in 60% yield. Recently, a modified version of this reaction was documented by Guillaumet, Kazzouli and coworkers employing water as the reaction solvent (**Scheme 31B**).[111] The products **60a** and **60b** were formed in synthetically useful yields. An electron-withdrawing nitro group was tolerated on the arene part delivering product **60c** in 78% yield. A complementary silver free version of this reaction was reported by Yu et. al. in 2013 (**Scheme 31C**).[112] The authors employed one equivalent of cesium carbonate, which served a similar role than the silver additives in the other protocols.



Scheme 31 A: Pd-catalyzed C–H arylation of indazoles.[110] **B:** "On water" Pd-catalyzed direct arylation of *1H*-indazole.[111] **C:** Pd-catalyzed C–H arylation of indazoles with base as iodide scavenger.[112]

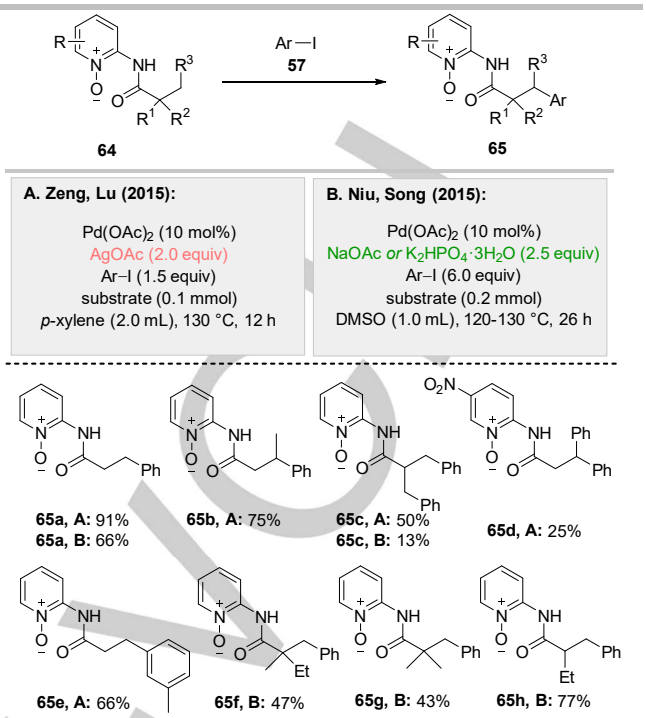
Product **60b** was formed in 92% yield and an excellent selectivity for the 3-position. Electron-withdrawing fluoro and ester substituents on arene produced products **60d** and **60e** respectively.

Similar to the report from Daugulis and coworkers, the group of Babu reported an 8-aminoquinoline aided Pd-catalyzed diastereoselective β-arylation of the secondary sp^3 C–H bonds of 2-phenylbutanamides and related aliphatic carboxamides (**Scheme 32A**).[113] The authors employed more than two equivalents of silver acetate for optimal halide removal. The product **58f** was formed in 91% yield and a syn:anti ratio of 20:80. Electron-donating methoxy and electron-withdrawing nitro substituents on the arene part are tolerated, generating products **58g** and **58h** respectively.

In 2014, Shi and coworkers employed a PIP-amine based DG for the Pd-catalyzed arylation of unactivated methylene C(sp^3)–H bonds with aryl bromides (**Scheme 32B**).[114] The product **63a** derived from butanoic acid derivative and aryl halide was formed in 74% yield and excellent β-selectivity. Electron donating methoxy and electron-withdrawing trifluoromethyl substituents were tolerated producing products **63b** and **63c** respectively in synthetically useful yields. The authors employed two and a half equivalents of potassium carbonate for halide scavenging. It should be noted, that in the same study, Shi and coworkers also described the use of aryl iodides as arylating agents in conjunction with silver acetate as halide scavenger. Another interesting report from Wu, Zeng and coworkers also employed potassium carbonate as the base, however employing 8-amino quinoline as the DG (**Scheme 32C**).[115] With this protocol, the authors formed products **58i-k** in good to excellent yields. Finally, in 2017, Chen, Qin and coworkers reported a cesium acetate mediated Pd-catalyzed C(sp^3)–H arylation of carboxylic acid

10.1002/anie.202210825

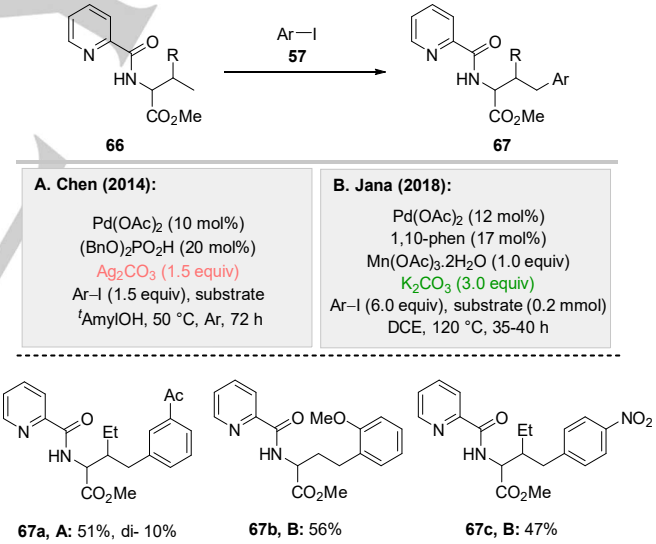
derivatives (**Scheme 32D**).[116] The product **58i** was prepared in 97% yield. Similarly, methoxy, ester, ketone and $-OCF_3$ substituents on the aryl iodide part produced products **58l**, **58m**, **58b** and **58n** respectively.



Scheme 33 A: Pd-catalyzed pyridine-*N*-oxide directed C–H arylation of C(sp^3)–H bonds with silver additive.[117] **B:** Pyridine-*N*-oxide directed Pd-catalyzed C(sp^3)–H arylation with base.[118]

Scheme 32 A: Pd-catalyzed diastereoselective C–H arylation of 2-phenylbutanamides with silver additive.[113] **B:** PIP-amine based DG for Pd-catalyzed arylation of unactivated methylene C(sp^3)–H bonds.[114] **C:** Pd-catalyzed C–H arylation of C(sp^3)–H bonds.[115] **D:** Pd-catalyzed base-promoted C–H arylation of C(sp^3)–H bonds.[116]

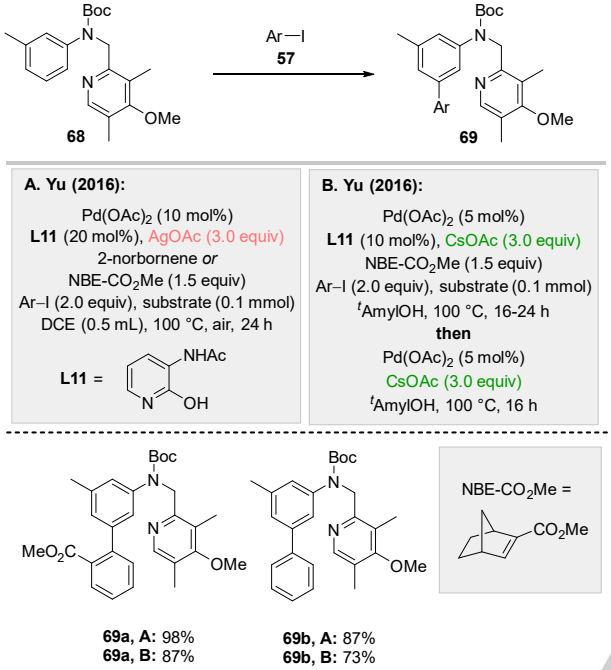
In 2015, Zeng, Lu and coworkers employed a pyridine-*N*-oxide directed C–H arylation of β-C(sp^3)–H bonds and used two equivalents of silver acetate for halide scavenging (**Scheme 33A**).[117] A series of products **65a-d** was produced from propionic acid derivatives with synthetically useful to excellent yields. A nitro group was tolerated in the directing group as well as a methyl substituent on the aryl iodide. Shortly after, the group of Niu and Song replaced the silver additives with sodium acetate or di potassium hydrogen phosphate as base (**Scheme 33B**).[118] The products **65f-h** were documented in the scope studies with synthetically useful yields.



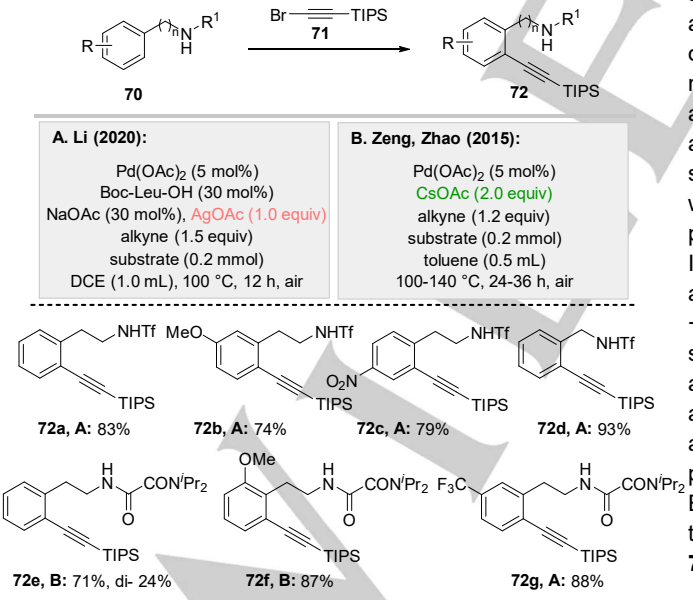
Scheme 34 A: Pd-catalyzed γ- C(sp^3)–H arylation with silver.[119] **B:** Ligand promoted γ- C(sp^3)–H arylation to access unnatural amino acid derivatives.[120]

In 2014, Chen and coworkers reported the total synthesis of Hibispeptin A *via* a Pd-catalyzed γ-C(sp^3)–H arylation employing silver carbonate as halide scavenger (**Scheme 34A**).[119] The monomeric product **67a** was produced in 51% yield along with 10% dimer. Jana and coworkers replaced the silver additive with potassium carbonate (**Scheme 34B**).[120] Electron-donating methoxy as well as electron-withdrawing nitro groups were tolerated, producing products **67b** and **67c** in synthetically useful yields.

In 2016, Yu and co-workers reported a *meta*-C–H activation/arylation of arenes by merging *ortho*-C–H activation with a transient mediator norbornene, followed by coupling with a suitable aryl iodine source. Inside the same publication, the authors described the use of silver acetate and a silver-free variant using cesium acetate as base (**Scheme 35A** and **B**).[121]



Scheme 35 A: Pd-catalyzed ligand promoted *meta*-C–H arylation with silver additive.[121] **B:** Pd-catalyzed ligand promoted *meta*-C–H arylation without silver additive.[121]



Scheme 36 A: Pd-catalyzed *ortho*-C–H alkynylation with silver additive.[122] **B:** Silver-free Pd-catalyzed *ortho*-C–H alkynylation.[123]

The products **69a** and **69b** were formed with excellent yield and selectivity using both sets of reaction conditions.

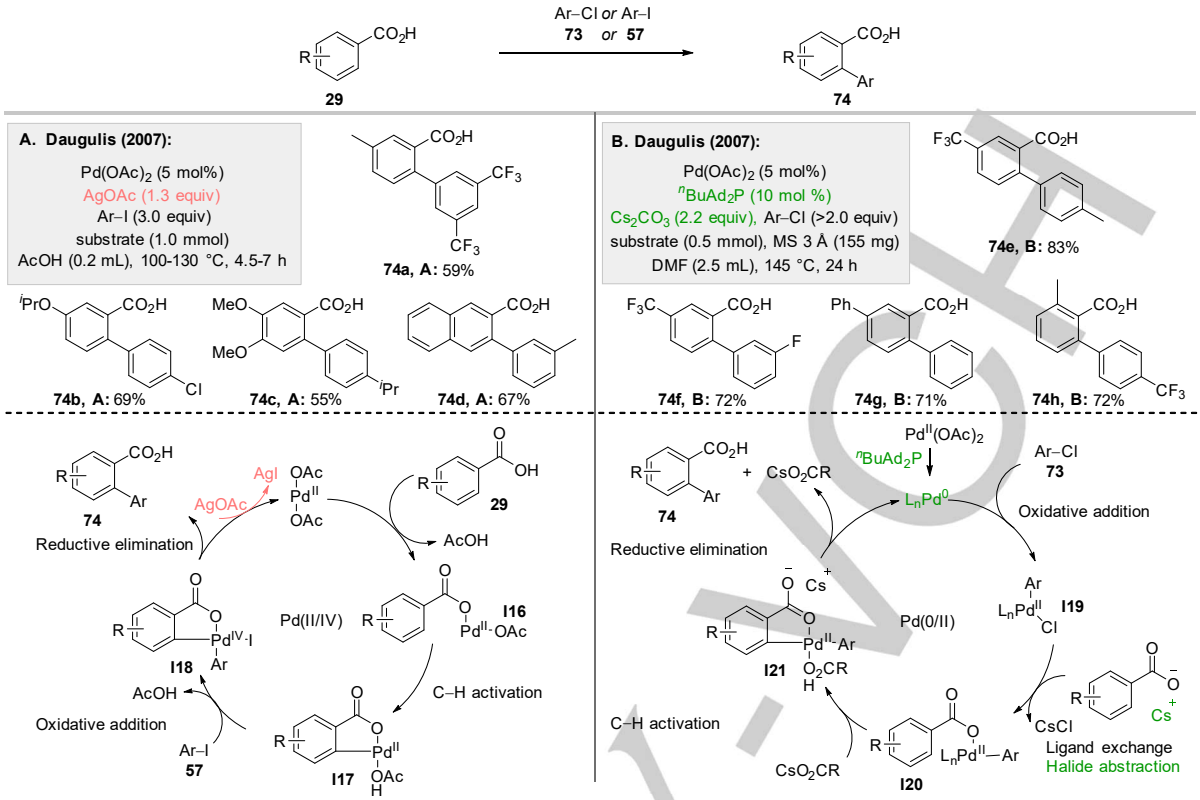
Li and coworkers reported a Pd-catalyzed *ortho*-C–H alkynylation of arenes employing a nitrogen-based DG (**Scheme 36A**).[122] The authors used an amino-acid derived bidentate ligand together with Pd for the optimal catalyst system. One equivalent of silver acetate was used for bromide scavenging. The product **72a** from a mono-substituted starting material was formed in 83% yield with exclusive *ortho* selectivity. Electron-donating methoxy and electron-withdrawing nitro groups were tolerated producing products **72b** and **72c** respectively. A shorter chain length between the arene and DG could also deliver product **72d** in 93% yield. In 2015, Zeng and Zhao documented an *ortho*-C–H alkynylation protocol that is complementary with the method from Li. The authors employed cesium acetate for halide scavenging (**Scheme 36B**).[123] Mono-substituted arene as well as methoxy and trifluoromethyl substituents were tolerated under the reaction conditions, delivering products **72e-g** with excellent efficiency. Importantly, many further studies have employed bases for halide scavenging, which are not discussed here since no immediate silver-based method is described in literature.[124]

3.2 Changing the redox manifold within the catalytic cycle

Some cases have been described, specifically in Pd-catalyzed C–H arylation, where by changing the ligand and thereby the redox manifold of the catalytic cycle eliminated the need for stoichiometric silver additives. In 2007, Daugulis and coworkers described two complementary methods for the direct *ortho*-arylation of benzoic acids. In the first method, the authors employed aryl iodide along with a silver additive for iodide scavenging (**Scheme 37A**).[125] First, the substrate coordinates to a Pd^{II} center, forming **I16**, which subsequently undergoes C–H activation to generate **I17**. Afterwards an oxidative addition with aryl iodide results in intermediate **I18**, in which Pd is in +4 oxidation state. From this intermediate, a reductive elimination releases the product and Pd returns to the +2-oxidation state with an iodide ligand. The silver additive then scavenges the iodide and regenerates the active species. Only electron-donating substituents on the arene and both electron-donating and withdrawing substituents on the aryl iodide reagent were tolerated, producing products **74a-d** in synthetically useful yields.

In the second protocol, the authors propose that Pd(0) undergoes an oxidative addition with the aryl chloride to generate **I19** with a +2 oxidation state of Pd. Subsequently, a cesium salt of the substrate enters the catalytic cycle and the chloride gets abstracted by cesium to generate **I20**, which undergoes C–H activation to give **I21**. A reductive elimination releases the product and also regenerates the active metal. The electron-rich phosphine ligand is responsible to maintain the Pd(0/II) cycle. Electron-donating and electron-withdrawing substituents were tolerated in both arene and the aryl chloride, producing products **74e-h** in excellent yields.

10.1002/anie.202210825

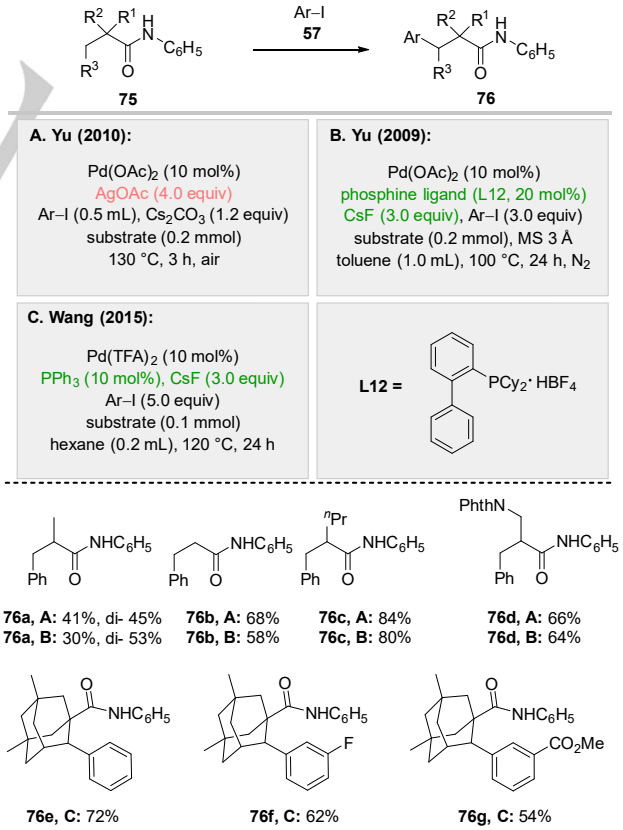


Scheme 37 A: Pd-catalyzed *ortho*-C–H arylation of benzoic acids with silver additive in a Pd (II/IV) cycle.[125] **B:** Pd-catalyzed *ortho*-C–H arylation of benzoic acids without silver additive in a Pd (0/II) cycle.[125]

The concept was further extended to C–H functionalization of carboxylic acid derivatives. In 2010, the group of Yu reported a Pd-catalyzed C(sp^3)–H arylation of amides employing –$CONHC_6H_5$ as the DG (**Scheme 38A**).[126] They used four equivalents of silver acetate to scavenge the iodide within a Pd(II/IV) catalytic cycle. Shortly before, the authors also showed a complementary protocol using a phosphine ligand **L12** to induce a Pd(0/II) catalytic cycle with cesium fluoride to eliminate the iodine (**Scheme 38B**).[127] With both protocols, the product **76a** was formed alongside substantial amounts of di product. Also, products **76b-d** were formed with good to excellent yield employing both the Pd(II/IV) and Pd(0/II)catalytic cycle. In 2015, Wang and coworkers applied the same strategy of using phosphine ligand and –$CONHC_6H_5$ as the DG for the arylation of the adamantly scaffold (**Scheme 38C**).[128] The products **76e-g** formed in good yields, showing the tolerance for electron-withdrawing fluoro and ester substituents.

3.3 The choice of reagent eliminates the need of silver

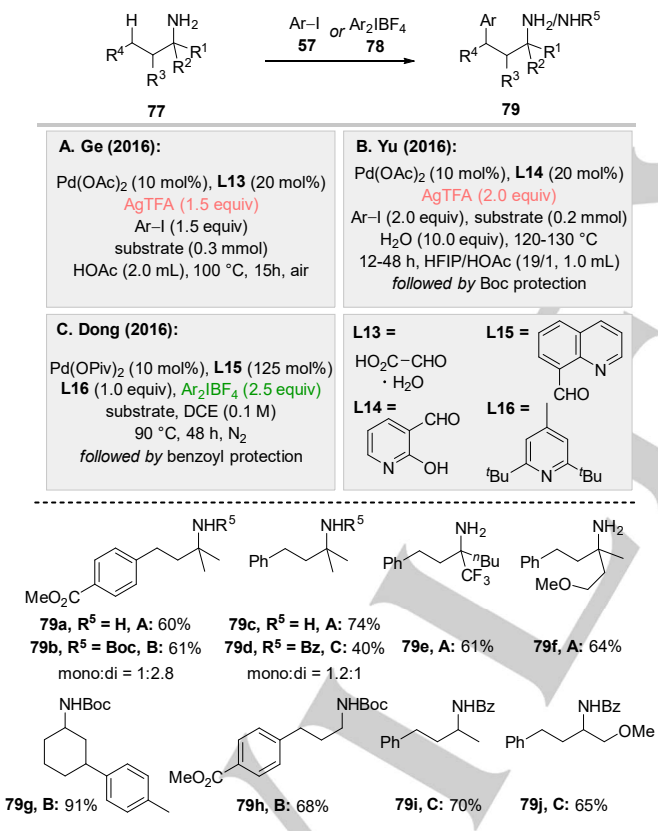
If the role of the silver is solely that of a halide scavenger in a given transformation, it is possible to develop silver-free transformations by changing the reagent to a species that avoids the concomitant generation of halide anions. In 2016, Ge and co-workers reported a Pd-catalyzed C–H arylation of primary aliphatic amines enabled by a transient directing group (TDG) (**Scheme 39A**).[129] The authors employed stoichiometric AgTFA to remove the iodide for catalyst re-generation. The TDG reacts with the free amine to generate an imine-based DG in situ, which then directs a selective γ-C–H activation.



Scheme 38 A: Pd-catalyzed C(sp^3)–H arylation of amides with silver additive in a Pd (II/IV) cycle.[126] **B:** Pd-catalyzed C(sp^3)–H arylation of amides without silver additive.[127] **C:** Pd-catalyzed methylene C(sp^3)–H arylation of the adamantyl scaffold.[128]

10.1002/anie.202210825

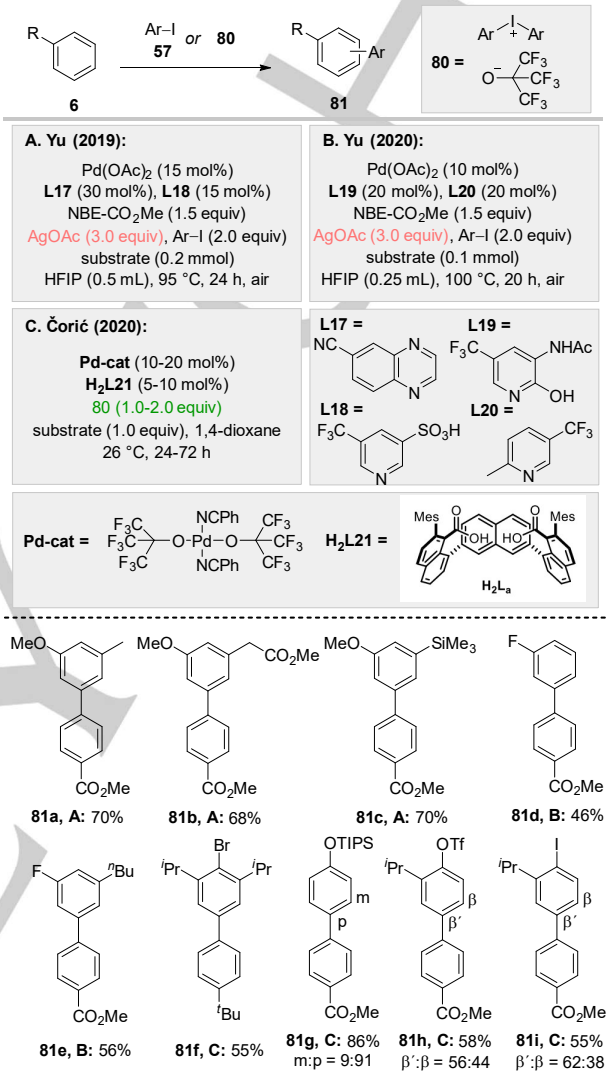
The products **79a** and **79c** were formed in 60% and 74% yield respectively. Trifluoromethyl and methoxy containing substrates produced products **79e** and **79f** in good yields. Notably, a tertiary center at the α-position is required to obtain sufficient reactivity. In a contemporary study, Yu et al. realized the same transformation and collected the final products as Boc protected amines (**Scheme 39B**).[130] The authors employed two equivalents of AgTFA to remove the iodide for catalyst re-generation. Product **79b** was formed in 61% yield with a mono:di ratio of 1:2.8. When the α-position is a tertiary center, the formation of di product dominates under the reaction conditions developed by Yu. However, if the α-position is not a tertiary center, the reaction can be stopped at mono arylation stage, as evidenced by the formation of **79g-h**. Shortly before these studies, the group of Dong reported an arylation protocol where the authors used Ar_2IBF_4 as the arylating reagents (**Scheme 39C**).[131] The choice of the reagent made the use of silver unnecessary, because no halide ion is generated as by-product. Similar to the study by Yu, the authors observed a significant amount of di product formation when the α-position is tertiary. The products **79i-j**, derived from an α-non-tertiary amine, were formed with good to excellent efficiency.



Scheme 39 A: Pd-catalyzed C–H arylation of primary aliphatic amines enabled by a TDG.[129] **B:** Pd-catalyzed γ-C(sp^3)–H arylation of free amines using a TDG.[130] **C:** Silver-free Pd-catalyzed γ-C(sp^3)–H arylation of free amines using a TDG.[131]

In 2019, Yu and coworkers reported a Pd-catalyzed *meta*-C–H arylation of electron-rich arenes employing NBE-CO_2Me (modified norbornene) as the mediator (**Scheme 40A**).[132] The authors used three equivalents of silver acetate for iodide removal. The methoxy-substituted substrates formed products **81a-c** in good to excellent yields at the most electron-deficient position.

The same group also reported a related protocol and addressed fluoroarenes and simple arenes as substrates (**Scheme 40B**).[133] The products **81d** and **81e** were formed in 46% and 56% yield respectively. Čorić and coworkers replaced the silver additive by employing a modified reagent **80**, which does not contain halide ions (**Scheme 40C**).[134]



Scheme 40 A: Pd-catalyzed *meta*-C–H arylation of electron-rich arenes.[132] **B:** Pd-catalyzed *meta*-C–H arylation of fluoro arenes.[133] **C:** Spatial anion control on Pd for the mild C–H arylation of arenes.[134]

The authors used the novel concept of spatial anion control to design catalytic sites for C–H bond activation, and achieved nondirected C–H arylation of arenes at ambient temperature. The products **81f-i** were formed with good to excellent efficiency with a combination of steric and electron control of the regioselectivity, the latter being the dominating factor.

It should be noted that the use of halide-free reagents has been established as a highly valuable tool in silver-free C–H activation/functionalization with many more applications described in literature, to which no immediate analogs based on the use of silver as halide scavenger exist.[135]

4. Summary and outlook

During the past decades the activation and functionalization of C–H bonds has been recognized as a powerful tool for method development, which bears the potential to enable shorter, more sustainable syntheses compared to traditional cross-couplings. However, the use silver salts as additives together with the catalytically active transition metal was often found indispensable for those reactions, which has limited the ability to reach the full potential of C–H activation in the context of sustainability and from an economic perspective. Substantial efforts have been directed towards avoiding the use of such stoichiometric silver salts and several general strategies have emerged. The comparisons between silver-based and silver-free methods drawn in this review highlight, that the development of silver-free protocols intimately relies on the knowledge which role or roles silver plays in the respective reactions. Even more generally, it can be observed that the fast pace with which the field of C–H activation has developed over the past years has led to a situation where synthetic methodology is further developed than the underlying mechanistic understanding. The latter, however, will be key for a sustainable future development of the field, as evidenced here for the design of silver-free methods. The rapid developments witnessed over the last years raise the expectation that general approaches such as the combination of C–H activation with photocatalysis or electrochemistry will find widespread application and become common techniques in laboratories far beyond the ones who have pioneered these strategies. Towards this goal, the discussions presented herein equip the reader with the knowledge required to systematically implement silver-free C–H activation starting from silver-based protocols described in literature or discovered by the reader.

Acknowledgements

We acknowledge generous financial support by the DFG (Emmy Noether Programme), WWU Münster and CAU Kiel.

Keywords: C–H activation • silver-additives • electrosynthesis • sustainability • catalysis

[1] a) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529; b) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879; c) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826; d) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077; e) A. S. Goldman, K. I. Goldberg in *ACS Symposium Series* (Eds.: K. I. Goldberg, A. S. Goldman), American Chemical Society, Washington, DC, **2004**, pp. 1–43; f) K. Godula, D. Sames, *Science* **2006**, *312*, 67; g) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890; h) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; i) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362; j) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; k) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588; l) J. F. Hartwig, *J. Am. Chem. Soc.* **2016**, *138*, 2; m) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset et al., *Chem. Soc. Rev.* **2018**, *47*, 6603; n) G. Liao, T. Zhang, Z.-K. Lin, B.-F. Shi, *Angew. Chem. Int. Ed.* **2020**, *59*, 19773; o) N. Y. S. Lam, K. Wu, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2021**, *60*, 15767.

[2] a) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885; b) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; c) J. Wencel-Delord, F. Glorius, *Nature Chem* **2013**, *5*, 369; d) J. F. Hartwig, M. A. Larsen, *ACS Cent. Sci.* **2016**, *2*, 281; e) P. Wedi, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2018**, *57*, 13016; f) J. Boström, D. G. Brown, R. J. Young, G. M. Keserü, *Nat. Rev. Drug Discov.* **2018**, *17*, 709; g) R. Jana, H. M. Begam, E. Dinda, *Chem. Commun.* **2021**, *57*, 10842; h) D. Maiti, S. Guin (Eds.) *Remote C-H bond functionalizations. Methods and strategies in organic synthesis*, Wiley-VCH, Weinheim, Germany, **2021**.

[3] a) J.-M. Weibel, A. Blanc, P. Pale, *Chem. Rev.* **2008**, *108*, 3149; b) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; c) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147.

[4] D. Whitaker, J. Burés, I. Larrosa, *J. Am. Chem. Soc.* **2016**, *138*, 8384.

[5] M. D. Lotz, N. M. Camasso, A. J. Canty, M. S. Sanford, *Organometallics* **2017**, *36*, 165.

[6] a) K. L. Bay, Y.-F. Yang, K. N. Houk, *J. Organomet. Chem.* **2018**, *864*, 19; b) T. Bhattacharya, S. Dutta, D. Maiti, *ACS Catal.* **2021**, *11*, 9702.

[7] a) S. Radhika, C. M. A. Abdulla, T. Aneeja, G. Anilkumar, *New J. Chem.* **2021**, *45*, 15718; b) G. Athavan, T. F. N. Tanner, A. C. Whitwood, I. J. S. Fairlamb, R. N. Perutz, *Organometallics* **2022**, *asap*.

[8] a) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566; b) B. Sahoo, M. N. Hopkinson, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 5505; c) L. Chu, J. M. Lipshultz, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2015**, *54*, 7929; d) J. J. Murphy, P. Melchiorre, *Nature* **2015**, *524*, 297; e) A. Tlahuext-Aca, M. N. Hopkinson, R. A. Garza-Sanchez, F. Glorius, *Chem. Eur. J.* **2016**, *22*, 5909.

[9] a) R. H. Crabtree in *Catalysis by Metal Complexes* (Eds.: R. Ugo, B. R. James, K. Kalyanasundaram, M. Grätzel), Springer Netherlands, Dordrecht, **1993**, pp. 391–405; b) W.-J. Zhou, Y.-H. Zhang, Y.-Y. Gui, L. Sun, D.-G. Yu, *Synthesis* **2018**, *50*, 3359.

[10] K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035.

[11] L. Guillemard, J. Wencel-Delord, *Beilstein J. Org. Chem.* **2020**, *16*, 1754.

[12] F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem. Int. Ed.* **2010**, *50*, 1064.

13] Y. Wang, C. Li, Y. Li, F. Yin, X.-S. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1724.

[14] S. Ochiai, R. Yoshimoto, Y. Usuki, T. Satoh, *Asian J. Org. Chem.* **2022**, *11*, e202100774.

[15] D. C. Fabry, J. Zoller, S. Raja, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 10228.

[16] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322.

[17] D. C. Fabry, M. A. Ronge, J. Zoller, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, *54*, 2801.

[18] a) Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166; b) Y. Fujiwara, R. Asano, I. Moritani, S. Teranishi, *J. Org. Chem.* **1976**, *41*, 1681; c) C. Jia, W. Lu, T. Kitamura, Y. Fujiwara, *Org. Lett.* **1999**, *1*, 2097; d) L. Zhou, W. Lu, *Chem. Eur. J.* **2014**, *20*, 634.

[19] D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518.

[20] M. Bera, A. Modak, T. Patra, A. Maji, D. Maiti, *Org. Lett.* **2014**, *16*, 5760.

[21] G. Meng, N. Y. S. Lam, E. L. Lucas, T. G. Saint-Denis, P. Verma, N. Chekshin, J.-Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 10571.

[22] A. Saha, S. Guin, W. Ali, T. Bhattacharya, S. Sasmal, N. Goswami, G. Prakash, S. K. Sinha, H. B. Chandrashekar, S. Panda, S. S. Anjana, D. Maiti., *J. Am. Chem. Soc.* **2022**, *144*, 1929.

[23] S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra et al., *J. Am. Chem. Soc.* **2015**, *137*, 11888.

[24] A. Maji, S. Guin, S. Feng, A. Dahiya, V. K. Singh, P. Liu, D. Maiti, *Angew. Chem. Int. Ed.* **2017**, *56*, 14903.

[25] P. Wang, P. Verma, G. Xia, J. Shi, J. X. Qiao, S. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K.-S. Yeung et al., *Nature* **2017**, *551*, 489.

[26] H. Chen, P. Wedi, T. Meyer, G. Tavakoli, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2018**, *57*, 2497.

[27] Y. Budnikova, Y. Dudkina, M. Khrizanforov, *Inorganics* **2017**, *5*, 70.

[28] a) G. W. Gribble, *J. Chem. Soc., Perkin Trans.* **2000**, 1045; b) W. Gul, M. T. Hamann, *Life Sci.* **2005**, *78*, 442; c) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195.

[29] a) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, F. Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 7230; b) J. J. Neumann, S. Rakshit, T. Dröge, S. Würtz, F. Glorius, *Chem. Eur. J.* **2011**, *17,* 7298.

[30] C. Cheng, W.-W. Chen, B. Xu, M.-H. Xu, *J. Org. Chem.* **2016**, *81*, 11501.

[31] J. Zoller, D. C. Fabry, M. A. Ronge, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 13264.
[32] J. K. Laha, K. P. Jethava, N. Dayal, *J. Org. Chem.* **2014**, *79*, 8010.
[33] S. Choi, T. Chatterjee, W. J. Choi, Y. You, E. J. Cho, *ACS Catal.* **2015**, *5*, 4796.
[34] M.-G. Huang, S. Shi, M. Li, Y.-J. Liu, M.-H. Zeng, *Org. Lett.* **2021**, *23*, 7094.
[35] D. Kalsi, S. Dutta, N. Barsu, M. Rueping, B. Sundararaju, *ACS Catal.* **2018**, *8*, 8115.
[36] a) D. R. Stuart, M. Bertrand-Laperle, K. M .N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474; b) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326; J. Chen. G. Song, C.-L. Pan, X. Li, *Org. Lett.* **2010**, *12*, 5426; d) Y. Hoshino, Y. Shibata, K. Tanaka, *Adv. Synth. Catal.* **2014**, *356*, 1577; e) G. N. Hermann, C. L. Jung, C. Bolm, *Green Chem.* **2017**, *19*, 2520; f) J. Terasawa, Y. Shibata, Y. Kimura, K. Tanaka, *Chem. Asian J.* **2018**, *13*, 505.
[37] P. Nagtilak, M. Mane, S. Prasad, L. Cavallo, D. Tantillo, M. Kapur, ChemRxiv, **2022**, 10.26434/chemrxiv-2022-24zf4-v2.
[38] H. J. Kim, D. C. Fabry, S. Mader, M. Rueping, *Org. Chem. Front.* **2019**, *6*, 2319.
[39] a) D. C. Fabry, M. Rueping, *Acc. Chem. Res.* **2016**, *49*, 1969; b) K. Liu, M. Zou, A. Lei, *J. Org. Chem.* **2016**, *81*, 7088.
[40] a) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230; b) K.-J. Jiao, Y.-K. Xing, Q.-L. Yang, H. Qiu, T.-S. Mei, *Acc. Chem. Res.* **2020**, *53*, 300.
[41] X. Wang, X. Xu, Z. Wang, P. Fang, T. Mei, *Chin. J. Org. Chem.* **2020**, *40*, 3738.
[42] C. Ma, P. Fang, T.-S. Mei, *ACS Catal.* **2018**, *8*, 7179.
[43] J. E. Erchinger, M. Gemmeren, *Asian J. Org. Chem.* **2021**, *10*, 50.
[44] C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantourout, B. K. Peters, Y. Kawamata, P. S. Baran, *Acc. Chem. Res.* **2020**, *53*, 72.
[45] T. Nishikata, B. H. Lipshutz, *Org. Lett.* **2010**, *12*, 1972.
[46] C. Amatore, C. Cammoun, A. Jutand, *Adv. Synth. Catal.* **2007**, *349*, 292.
[47] J. Fan, Q.-J. Yao, Y.-H. Liu, G. Liao, S. Zhang, B.-F. Shi, *Org. Lett.* **2019**, *21*, 3352.
[48] U. Dhawa, C. Tian, T. Wdowik, J. C. A. Oliveira, J. Hao, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 13451.
[49] J. Zhang, Q. Xu, J. Wu, J. Fan, M. Xie, *Org. Lett.* **2019**, *21*, 6361.
[50] U. Dhawa, T. Wdowik, X. Hou, B. Yuan, J. C. A. Oliveira, L. Ackermann, *Chem. Sci.* **2021**, *12*, 14182.
[51] L. Ackermann, Z. Lin, U. Dhawa, B. Yuan, Y.-C. Liou, M. Johansson, Research Square, **2022,** 10.21203/rs.3.rs-1607467/v1.
[52] S. Panja, S. Ahsan, T. Pal, S. Kolb, W. Ali, S. Sharma, C. Das, J. Grover, A. Dutta, D. B. Werz, A. Paul, D. Maiti, *Chem. Sci.* **2022**, *13*, 9432.
[53] Q. Yan, T. Xiao, Z. Liu, Y. Zhang, *Adv. Synth. Catal.* **2016**, *358*, 2707.
[54] X. Gao, P. Wang, L. Zeng, S. Tang, A. Lei, *J. Am. Chem. Soc.* **2018**, *140*, 4195.
[55] L.-B. Zhang, X.-Q. Hao, S.-K. Zhang, Z.-J. Liu, X.-X. Zheng, J.-F. Gong, J.-L. Niu, M.-P. Song, *Angew. Chem. Int. Ed.* **2015**, *54*, 272.
[56] N. Sauermann, T. H. Meyer, C. Tian, L. Ackermann, *J. Am. Chem. Soc.* **2017**, *139*, 18452.
[57] D. A. Frasco, C. P. Lilly, P. D. Boyle, E. A. Ison, *ACS Catal.* **2013**, *3*, 2421.
[58] V. P. Datsenko, Y. V. Nelyubina, A. F. Smol'yakov, D. A. Loginov, *J. Organomet. Chem.* **2018**, *874*, 7.
[59] Q.-L. Yang, Y.-K. Xing, X.-Y. Wang, H.-X. Ma, X.-J. Weng, X. Yang, H.-M. Guo, T.-S. Mei, *J. Am. Chem. Soc.* **2019**, *141*, 18970.
[60] Q.-L. Yang, H.-W. Jia, Y. Liu, Y.-K. Xing, R.-C. Ma, M.-M. Wang, G.-R. Qu, T.-S. Mei, H.-M. Guo, *Org. Lett.* **2021**, *23*, 1209.
[61] a) Y. Su, M. Zhao, K. Han, G. Song, X. Li, *Org. Lett.* **2010**, *12*, 5462. For further Cu-based methods, see: b) L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153; c) Q. Jiang, C. Zhu, H. Zhao, W. Su, *Chem. Asian. J.* **2016**, *11*, 356.
[62] Y.-K. Xing, X.-R. Chen, Q.-L. Yang, S.-Q. Zhang, H.-M. Guo, X. Hong, T.-S. Mei, *Nat. Commun.* **2021**, *12*, 930.
[63] S. W. Youn, H. J. Yoo, *Adv. Synth. Catal.* **2017**, *359*, 2176.
[65] Y. Qiu, W.-J. Kong, J. Struwe, N. Sauermann, T. Rogge, A. Scheremetjew, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5828.
[65] X. Chen, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 12634.
[66] Q.-L. Yang, C.-Z. Li, L.-W. Zhang, Y.-Y. Li, X. Tong, X.-Y. Wu, T.-S. Mei, *Organometallics* **2019**, *38*, 1208.
[67] H. Wang, S. Yu, Z. Qi, X. Li, *Org. Lett.* **2015**, *17*, 2812.
[68] K. Kuciński, H. Simon, L. Ackermann, *Chem. Eur. J.* **2022**, *28*, e202103837.
[69] a) Y. B. Dudkina, D. Y. Mikhaylov, T. V. Gryaznova, O. G. Sinyashin, D. A. Vicic, Y. H. Budnikova, *Eur. J. Org. Chem.* **2012**, *2012*, 2114; b) F. Saito, H. Aiso, T. Kochi, F. Kakiuchi, *Organometallics* **2014**, *33*, 6704; c) C. Tian, L. Massignan, T. H. Meyer, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 2383; d) S. Tang, D. Wang, Y. Liu, L. Zeng, A. Lei, *Nat. Commun.* **2018**, *9*, 798; e) F. Xu, Y.-J. Li, C. Huang, H.-C. Xu, *ACS Catal.* **2018**, *8*, 3820; f) Q.-L. Yang, X.-Y. Wang, J.-Y. Lu, L.-P. Zhang, P. Fang, T.-S. Mei, *J. Am. Chem. Soc.* **2018**, *140*, 11487; g) Y. Qiu, M. Stangier, T. H. Meyer, J. C. A. Oliveira, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14179; h) R. Mei, J. Koeller, L. Ackermann, *Chem. Commun.* **2018**, *54*, 12879; i) M.-J. Luo, M. Hu, R.-J. Song, D.-L. He, J.-H. Li, *Chem. Commun.* **2019**, *55*, 1124; j) M.-J. Luo, T.-T. Zhang, F.-J. Cai, J.-H. Li, D.-L. He, *Chem. Commun.* **2019**, *55*, 7251; k) W.-J. Kong, L. H. Finger, A. M. Messinis, R. Kuniyil, J. C. A. Oliveira, L. Ackermann, *J. Am. Chem. Soc.* **2019**, *141*, 17198; l) Z.-Q. Wang, C. Hou, Y.-F. Zhong, Y.-X. Lu, Z.-Y. Mo, Y.-M. Pan, H.-T. Tang, *Org. Lett.* **2019**, *21*, 9841; m) L. Yang, R. Steinbock, A. Scheremetjew, R. Kuniyil, L. H. Finger, A. M. Messinis, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 11130; n) P.-S. Gao, X.-J. Weng, Z.-H. Wang, C. Zheng, B. Sun, Z.-H. Chen, S.-L. You, T.-S. Mei, *Angew. Chem. Int. Ed.* **2020**, *59*, 15254; o) X. Tan, X. Hou, T. Rogge, L. Ackermann, *Angew. Chem. Int. Ed.* **2021**, *60*, 4619; p) L. Massignan, C. Zhu, X. Hou, J. C. A. Oliveira, A. Salamé, L. Ackermann, *ACS Catal.* **2021**, *11*, 11639; q) Y. Wang, J. C. A. Oliveira, Z. Lin, L. Ackermann, *Angew. Chem. Int. Ed.* **2021**, *60*, 6419; r) M. Stangier, A. M. Messinis, J. C. A. Oliveira, H. Yu, L. Ackermann, *Nat. Commun.* **2021**, *12*, 4736; s) I. Choi, A. M. Messinis, X. Hou, L. Ackermann, *Angew. Chem. Int. Ed.* **2021**, *60*, 27005; t) W. Wei, A. Scheremetjew, L. Ackermann, *Chem. Sci.* **2022**, *13*, 2783.
[70] a) F. W. Patureau, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 1977; b) H. Huang, X. Ji, W. Wu, H. Jiang, *Chem. Soc. Rev.* **2015**, *44*, 1155; c) J. Mo, L. Wang, Y. Liu, X. Cui, *Synthesis* **2015**, *47*, 439.
[71] H. Sun, Y. Huang, *Synlett* **2015**, *26*, 2751.
[72] G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651.
[73] P. Wen, Y. Li, K. Zhou, C. Ma, X. Lan, C. Ma, G. Huang, *Adv. Synth. Catal.* **2012**, *354*, 2135.
[74] J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888.
[75] F. Zhou, X. Han, X. Lu, *Tetrahedron Lett.* **2011**, *52*, 4681.
[76] Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676.
[77] G. Song, D. Chen, C.-L. Pan, R. H. Crabtree, X. Li, *J. Org. Chem.* **2010**, *75*, 7487.
[78] a) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565; b) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 6379; c) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744; d) B. Su, J.-b. Wei, W.-i. Wu, Z.-j. Shi, *ChemCatChem*, **2015**, *7*, 2986.
[79] a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; b) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449.
[80] a) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050; b) T. Fukatani, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Commun.* **2009**, 5141; c) X. Wei, M. Zhao, Z. Du, X. Li, *Org. Lett.* **2011**, *13*, 4636; d) J. Li, M. John, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 5403; e) J. Jayakumar, K. Parthasarathy, Y.-H. chen, T.-H. Lee, S.-C. Chuang, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2014**, *53*, 9889; f) X.-G. Liu, H. Gao, S.-S. Zhang, Q. Li, H. Wang, *ACS Catal.* **2017**, *7*, 5078; g) S. Yugandar, H. Nakamura, *Chem. Commun.* **2019**, *55*, 8382.
[81] W. Gong, Z. Zhou, J. Shi, B. Wu. B. Huang, W. Yi, *Org. Lett.* **2018**, *20*, 182.
[82] J. Ren, C. Pi, X. Cui, Y. Wu, *Org. Lett.* **2021**, *23*, 6628.
[83] P. C. Too, Y.-F. Wang, S. Chiba, *Org. Lett.* **2010**, *12*, 5688.
[84] T. K. Hyster, T. Rovis, *Chem. Commun.* **2011**, *47*, 11846.
[85] B. Qi, L. Fang, Q. Wang, S. Guo, P. Shi, B. Chu, J. Zhu, *Tetrahedron Lett.* **2020**, *61*, 151771.

[86] Y. Nishii, A.-K. Bachon, S. Moon, C. Bolm, M. Miura, *Chem. Lett.* **2017**, *46*, 1347

[87] T.-T. Wang, H.-S. Jin, M.-M. Cao, R.-B. Wang, L.-M. Zhao, *Org. Lett.* **2021**, *23*, 5952.

[88] C. Wang, Y. Huang, *Org. Lett.* **2013**, *15*, 5294.

[89] L. Zheng, R. Hua, *Chem. Eur. J.* **2014**, *20*, 2352.

[90] K. Muralirajan, C.-H. Cheng, *Adv. Synth. Catal.* **2014**, *356*, 1571.

[91] T. Matsuda, Y. Tomaru, *Tetrahedron Lett.* **2014**, *55*, 3302.

[92] Z.-Z. Zhang, B. Liu, J.-W. Xu, S.-Y. Yan, B.-F. Shi, *Org. Lett.* **2016**, *18*, 1776.

[93] Q. Lu, S. Vásquez-Céspedes, T. Gensch, F. Glorius, *ACS Catal.* **2016**, *6*, 2352.

[94] A. Lerchen, S. Vásquez-Céspedes, F. Glorius, *Angew. Chem. Int. Ed.* **2016**, *55*, 3208.

[95] a) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350; b) L. Ackermann, S. Fenner, *Org. Lett.* **2011**, *13*, 6548; c) C. Kornhaaß, J. Li, L. Ackermann, *J. Org. Chem.* **2012**, *77*, 9190; d) B. Ye, N. Cramer, *Science* **2012**, *338*, 504; e) T. K. Hyster, K. E. Ruhl, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 5364; f) J. M. Neely, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 66; g) S. Cui, Y. Zhang, D. Wang, Q. Wu, *Chem. Sci.* **2013**, *4*, 3912; h) D. Zhao, F. Lied, F. Glorius, *Chem. Sci.* **2014**, *5*, 2869; i) J. R. Huckins, E. A. Bercot, O. R. Thiel, T.-L. Hwang, M. M. Bio, *J. Am. Chem. Soc.* **2013**, *135*, 14492; j) Z. Zhang, H. Jiang, Y. Huang, *Org. Lett.* **2014**, *16*, 5976; k) T. Piou, T. Rovis, *Nature* **2015**, *527*, 86; l) A. Lerchen, T. Knecht, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2016**, *55*, 15166; m) X. Wang, A. Lerchen, T. Gensch, T. Knecht, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 1381; n) X. Wang, T. Gensch, A. Lerchen, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **2017**, *139*, 6506.

[96] *CRC handbook of chemistry and physics. A ready-reference book of chemical and physical data*, CRC Press, Boca Raton, FL, **1915-**.

[97] A. J. Bard, *Standard potentials in aqueous solution*, Internat. Union of Pure and Applied Chemistry, Oxford, **1985**.

[98] C. Elschenbroich, *Organometallics*, Wiley-VCH; [John Wiley, distributor], Weinheim, [Chichester], **2006**.

[99] D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326.

[100] H. Chen, A. Mondal, P. Wedi, M. van Gemmeren, *ACS Catal.* **2019**, *9*, 1979.

[101] a) A. Mondal, H. Chen, L. Flämig, P. Wedi, M. van Gemmeren, *J. Am. Chem. Soc.* **2019**, *141*, 18662; b) A. Mondal, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2021**, *60*, 742; c) P. Wedi, M. Farizyan, K. Bergander, C. Mück-Lichtenfeld, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2021**, *60*, 15641; d) M. Farizyan, A. Mondal, S. Mal, F. Deufel, M. van Gemmeren, *J. Am. Chem. Soc.* **2021**, *143*, 16370.

[102] L.-Y. Liu, K.-S. Yeung, J.-Q. Yu, *Chem. Eur. J.* **2019**, *25*, 2199.

[103] Da Zhao, P. Xu, T. Ritter, *Chem* **2019**, *5*, 97.

[104] M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586.

[105] J.-R. Wang, C.-T. Yang, L. Liu, Q.-X. Guo, *Tetrahedron Lett.* **2007**, *48*, 5449.

[106] Q.-J. Yao, S. Zhang, B.-B. Zhan, B.-F. Shi, *Angew. Chem. Int. Ed.* **2017**, *56*, 6617.

[107] a) M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art, M. Nomura, *J. Org. Chem.* **1998**, *63*, 5211; b) G. Cai, Y. Fu, Y. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 7666; c) G. Brasche, J. García-Fortanet, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 2207; d) C. E. Houlden, C. D. Bailey, J. G. Ford, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2008**, *130*, 10066; e) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072; f) T.-S. Mei, X. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806; g) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci.* **2010**, *1*, 331; h) M. J. Tredwell, M. Gulias, N. G. Bremeyer, C. C. C. Johansson, B. S. L. Collins, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2011**, *50*, 1076; i) T. W. Lyons, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 4455; j) X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 13864; k) X.-G. Zhang, H.-X. Dai, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 11948; l) A. Deb, S. Bag, R. Kancherla, D. Maiti, *J. Am. Chem. Soc.* **2014**, *136*, 13602; m) H.-J. Xu, Y. Lu, M. E. Farmer, H.-W. Wang, D. Zhao, Y.-S. Kang, W.-Y. Sun, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 2200; n) A. Bechtoldt, M. E. Baumert, L. Vaccaro, L. Ackermann, *Green Chem.* **2018**, *20*, 398; o) G. Liao, B. Li, H.-M. Chen, Q.-J. Yao, Y.-N. Xia, J. Luo, B.-F. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 17151; p) H. Song, Y. Li, Q.-J. Yao, L. Jin, L. Liu, Y.-H. Liu, B.-F. Shi, *Angew. Chem. Int. Ed.* **2020**, *59*, 6576.

[108] V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154.

[109] D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965.

[110] K. Hattori, K. Yamaguchi, J. Yamaguchi, K. Itami, *Tetrahedron* **2012**, *68*, 7605.

[111] K. Gambouz, A. El Abbouchi, S. Nassiri, F. Suzenet, M. Bousmina, M. Akssira, G. Guillaumet, S. El Kazzouli, *Molecules* **2020**, *25*, 2820.

[112] M. Ye, A. J. F. Edmunds, J. A. Morris, D. Sale, Y. Zhang, J.-Q. Yu, *Chem. Sci.* **2013**, *4*, 2374.

[113] B. Gopalakrishnan, S. A. Babu, R. Padmavathi, *Tetrahedron* **2015**, *71*, 8333.

[114] Q. Zhang, X.-S. Yin, S. Zhao, S.-L. Fang, B.-F. Shi, *Chem. Commun.* **2014**, *50*, 8353.

[115] Y. Wei, H. Tang, X. Cong, B. Rao, C. Wu, X. Zeng, *Org. Lett.* **2014**, *16*, 2248.

[116] Q. Gou, G. Liu, L. Zhou, S. Chen, J. Qin, *Eur. J. Org. Chem.* **2017**, 6314.

[117] J. Liu, Y. Xie, W. Zeng, D. Lin, Y. Deng, X. Lu, *J. Org. Chem.* **2015**, *80*, 4618.

[118] S.-K. Zhang, X.-Y. Yang, X.-M. Zhao, P.-X. Li, J.-L. Niu, M.-P. Song, *Organometallics* **2015**, *34*, 4331.

[119] G. He, S.-Y. Zhang, W. A. Nack, R. Pearson, J. Rabb-Lynch, G. Chen, *Org. Lett.* **2014**, *16*, 6488.

[120] S. Das, G. Bairy, R. Jana, *Org. Lett.* **2018**, *20*, 2667.

[121] P. Wang, M. E. Farmer, X. Huo, P. Jain, P.-X. Shen, M. Ishoey, J. E. Bradner, S. R. Wisniewski, M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 9269.

[122] B. Liu, W. Ouyang, J. Nie, Y. Gao, K. Feng, Y. Huo, Q. Chen, X. Li, *Chem. Commun.* **2020**, *56*, 11255.

[123] M. Guan, C. Chen, J. Zhang, R. Zeng, Y. Zhao, *Chem. Commun.* **2015**, *51*, 12103.

[124] a) M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496; b) Y. Zhao, G. Chen, *Org. Lett.* **2011**, *13*, 4850; c) M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19090; d) F. Pan, P.-X. Shen, L.-S. Zhang, X. Wang, Z.-J. Shi, *Org. Lett.* **2013**, *15*, 4758; e) C. Arroniz, J. G. Denis, A. Ironmonger, G. Rassias, I. Larrosa, *Chem. Sci.* **2014**, *5*, 3509; f) Q. Gou, Z.-F. Zhang, Z.-C. Liu, J. Qin, *J. Org. Chem.* **2015**, *80*, 3176; g) S.-B. Yan, S. Zhang, W.-L. Duan, *Org. Lett.* **2015**, *17*, 2458; h) M. D. Reddy, E. B. Watkins, *J. Org. Chem.* **2015**, *80*, 11447; i) X. Ye, C. Xu, L. Wojtas, N. G. Akhmedov, H. Chen, X. Shi, *Org. Lett.* **2016**, *18*, 2970; j) L. Huang, D. J. Weix, *Org. Lett.* **2016**, *18*, 5432; k) N. Hoshiya, M. Kondo, H. Fukuda, M. Arisawa, J. Uenishi, S. Shuto, *J. Org. Chem.* **2017**, *82*, 2535; l) J. Kim, S. H. Hong, *ACS Catal.* **2017**, *7*, 3336; m) C. E. Coomber, L. Benhamou, D.-K. Bučar, P. D. Smith, M. J. Porter, T. D. Sheppard, *J. Org. Chem.* **2018**, *83*, 2495; n) M. Chen, T. Doba, T. Sato, H. Razumkov, L. Ilies, R. Shang, E. Nakamura, *J. Am. Chem. Soc.* **2020**, *142*, 4883; o) J. Struwe, K. Korvorapun, A. Zangarelli, L. Ackermann, *Chem. Eur. J.* **2021**, *27*, 16237.

[125] H. A. Chiong, Q.-N. Pham, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879.

[126] M. Wasa, J.-Q. Yu, *Tetrahedron* **2010**, *66*, 4811.

[127] M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886.

[128] Y.-X. Lao, J.-Q. Wu, Y. Chen, S.-S. Zhang, Q. Li, H. Wang, *Org. Chem. Front.* **2015**, *2*, 1374.

[129] Y. Liu, H. Ge, *Nature Chem* **2017**, *9*, 26.

[130] Y. Wu, Y.-Q. Chen, T. Liu, M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14554.

[131] Y. Xu, M. C. Young, C. Wang, D. M. Magness, G. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 9084.

[132] L.-Y. Liu, J. X. Qiao, K.-S. Yeung, W. R. Ewing, J.-Q. Yu, *J. Am. Chem. Soc.* **2019**, *141*, 14870.

[133] L.-Y. Liu, J. X. Qiao, K.-S. Yeung, W. R. Ewing, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2020**, *59*, 13831.

[134] J. Dhankhar, E. González-Fernández, C.-C. Dong, T. K. Mukhopadhyay, A. Linden, I. Čorić, *J. Am. Chem. Soc.* **2020**, *142*, 19040.

10.1002/anie.202210825

[135] a) P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579; b) I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem.* **2007**, *119*, 768; c) R. Koller, K. Stanek, D. Stolz, R. Aardoom, K. Niedermann, A. Togni, *Angew. Chem.* **2009**, *121*, 4396; d) J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem. Int. Ed.* **2009**, *48*, 9346; e) M. S. Wiehn, E. V. Vinogradova, A. Togni, *J. Fluor. Chem.* **2010**, *131*, 951; f) J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2010**, *49*, 7304; g) Y. Li, J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 6743; h) J. Waser, *Top. Curr. Chem.* **2016**, *373*, 187.

10.1002/anie.202210825

Entry for the Table of Contents

The use of silver additives has enabled many highly valuable synthetic methods in the field of C–H activation. However, such additives are disadvantageous with respect to sustainability, scalability, and economic considerations. This review provides a systematic overview of strategic approaches towards developing silver-free protocols based on the mechanistic role of silver.

Institute and/or researcher Twitter usernames: @vangemmerenlab @kieluni @wwu_muenster @arup_mondal1995

Explanatory Text for Frontispiece:

Silver additives play a key role in the development of methods for C–H activaton/functionalization. However, they also limit the applicability of such methods due to ecologic and economic concerns. In this Review Mondal and van Gemmeren present systematic approaches that enable avoiding stoichiometric silver additives, such as electrochemistry, photocatalysis, or alternate additives depending on the mechanistic role silver plays in the reaction mechanism.