

C-H Activation

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

Arup Mondal and Manuel van Gemmeren*

*Dedicated to Professor Frank Glorius on the occasion of his 50th birthday.***Replacing Ag in C-H Activation****Ag-Additives**

- poor ecological footprint
- stoichiometric metal waste
- cost intensive
- not scalable



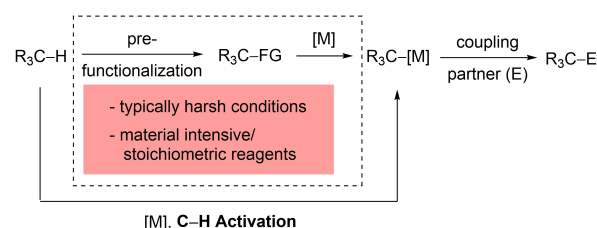
- sustainable synthesis
- electrochemistry
- photocatalysis
- alternate oxidants
- halide scavengers
- scalability

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 feed-stock 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.^[3–5] Despite their effectiveness, these protocols automatically fall far short of 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.

A: Potential of C–H activation



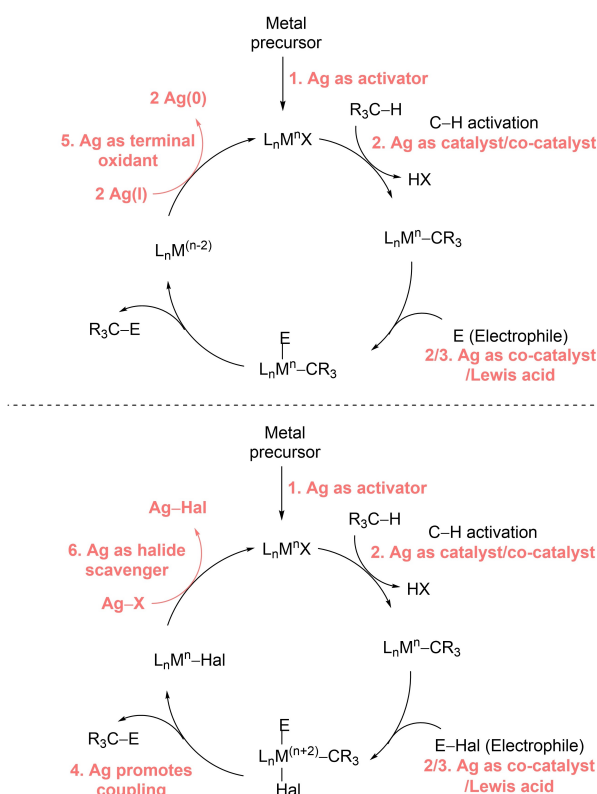
Potential:

- greener synthesis
- catalytic activation
- step economical benefits
- complementary product

Current methods often use stoichiometric silver additives:

- cost intensive
- poor ecological fingerprint
- not scalable
- excessive metal waste

B: Different 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.

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1.1. 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 groups (DGs). 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 catalyst's oxidation state.^[8] This concept has been extended to C–H activation/functionalization processes.^[9–11]

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 co-workers in 2013.^[13]

In 2021, Satoh and co-workers 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 **II**, 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 co-workers (Scheme 2B).^[15] The authors employed [Ru(bpy)₃](PF₆)₂ as a photocatalyst in combination with a suitable light source and achieved the same overall transformation. Importantly, the protocol employed 4 mol% AgSbF₆ 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 photo-



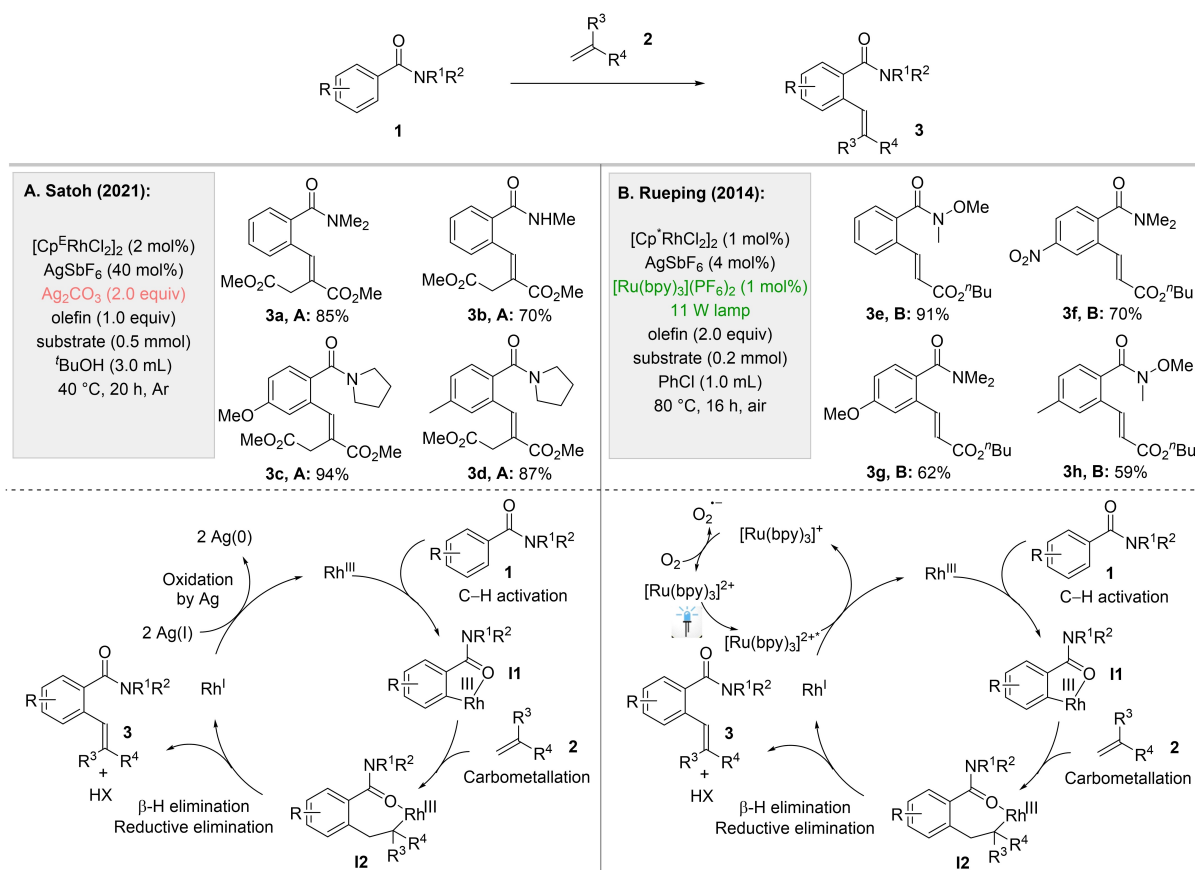
Arup Mondal was born in West Bengal, India (in 1995). After receiving the B.Sc. degree in Chemistry from University of Calcutta, he moved to Indian Institute of Technology Bombay, where he obtained the M.Sc. degree in Chemistry. He then joined the organic chemistry institute of Westfälische Wilhelms-Universität Münster to pursue his doctoral studies. As a part of the master and doctoral thesis, he worked in the area of ligand-controlled C–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. He 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 focuses on the development of novel synthetic methods that enable challeng-

ing transformations to proceed with catalyst-controlled reactivity and selectivity.

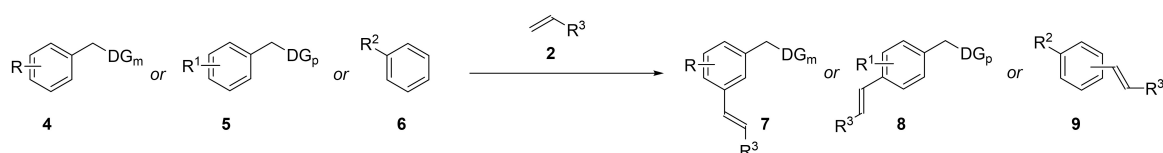


Scheme 2. A) Ortho-C-H olefination with Ag.^[14] B) Complementary stoichiometric Ag-free transformation.^[15]

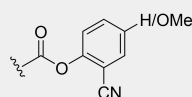
catalytic cycle. The authors did not observe a significant impact on the yield by changing the weakly coordinating PF₆ counter anion to the more strongly coordinating Cl presumably due to the presence of the AgSbF₆ activator. However, increasing the electron density through sequential introduction of ^tBu 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)/Mⁿ} 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 ions. In the present case, the reduction potential of Rh^{III/I} typically varies in the range from -0.1 to +0.1 V_{SCE}, whereas that of excited state 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 derivatives (with pyridine as the DG) reported by the Rueping group represents another case study of employing photocatalyst to regenerate the active catalyst.^[17]

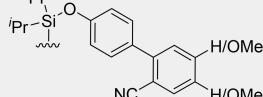
The Pd-catalyzed oxidative C-H olefination of arenes, known as Fujiwara-Moritani reaction, is known to often employ stoichiometric additives as terminal oxidant.^[18] In 2014, Maiti and co-workers (based on the original report by Yu^[19]) developed a nitrile-containing template with a carboxylate linker 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 co-workers 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 co-workers 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 deliver products with high *para*

**A. Maiti (2014):**

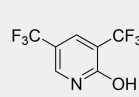
Pd(OAc)₂ (10 mol%)
Ac-Gly-OH (**L1**, 30 mol%)
Ag₂CO₃ (2.0 equiv)
olefin (2.0 equiv)
substrate (0.2 mmol)
HFIP (1.0 mL), 90 °C, 24 h

DG_m =**B. Maiti (2015):**

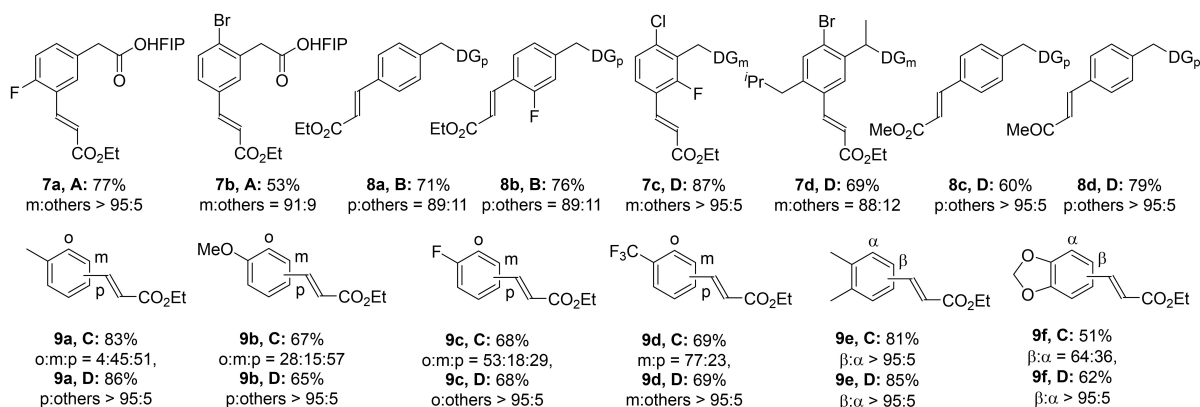
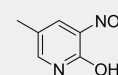
Pd(OAc)₂ (10 mol%)
Ac-Phe-OH (**L2**, 20 mol%)
AgOAc (3.0 equiv)
olefin (2.0 equiv)
substrate (0.2 mmol)
HFIP (2.0 mL), 90 °C, 36 h

DG_p =**C. Yu (2017):**

Pd(OAc)₂ (10 mol%)
L3 (30 mol%)
AgOAc (3.0 equiv)
olefin (2.0 equiv)
substrate (0.1 mmol)
HFIP (0.5 mL), 100 °C, 24 h

L3 =**D. Maiti (2022):**

Pd(OAc)₂ (10 mol%)
L4 or Ac-Phe-OH (**L2**, 20 mol%)
fluorescein or eosin-Y (3 mol%)
CFL (23W)
olefin (2.0-3.0 equiv)
substrate (0.1 mmol)
HFIP (1.0 mL), 30-35 °C, 28 h

L4 =

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]

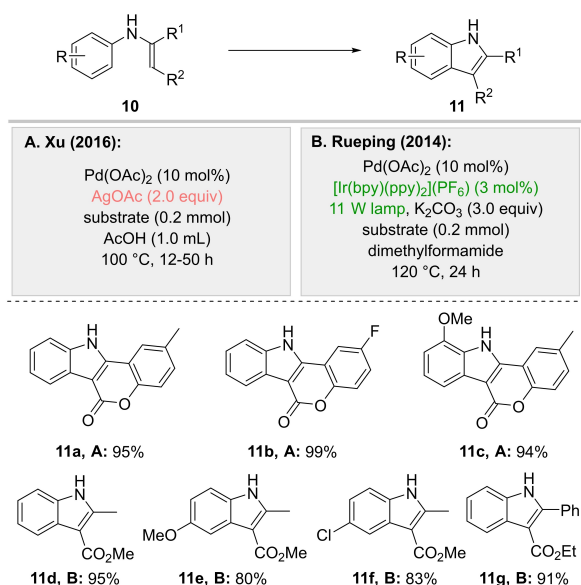
selectivity (**8a**, **8b**). The same group again replaced the silver in the same photocatalytic study mentioned above (**8c** and **8d**).^[22] In 2017, Yu and co-workers reported an arene-limited non-directed C–H olefination, where the authors employed a pyridine-based ligand (**L3**) on the palladium catalyst and three equivalents of silver acetate to induce the desired transformation (Scheme 3C).^[25] In a contemporary study, van Gemmeren and co-workers 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 Pd⁰ 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. Monosubstituted 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.

These effects were found to be consistent when disubstituted 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 co-workers 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 above-mentioned protocol can be compared with a silver-free version by Rueping and co-workers (reported in 2014), where the authors used [Ir(bpy)-(ppy)₂]PF₆ 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



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

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 Pd⁰ can easily be oxidized to Pd^{II}. Under the optimized conditions, the product **11d** was 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.

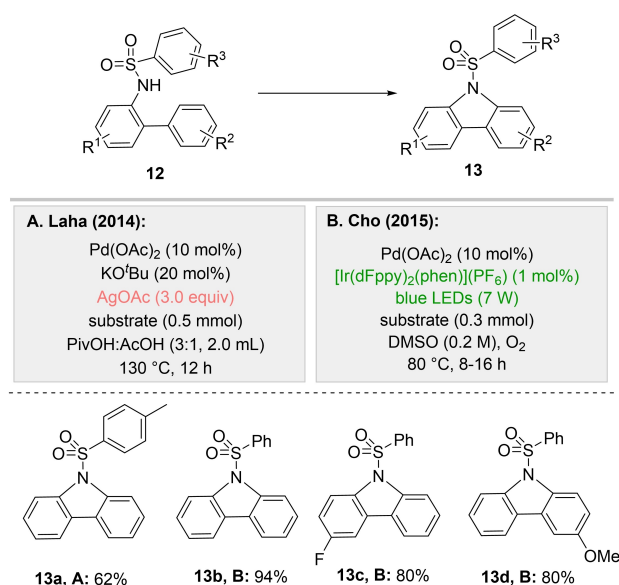
In 2014, Laha and co-workers reported a Pd-catalyzed intramolecular oxidative coupling for the synthesis of annulated biaryl sultams. In this report, the authors reported a single example for the synthesis of carbazole (**13a**, Scheme 5A).^[32]

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

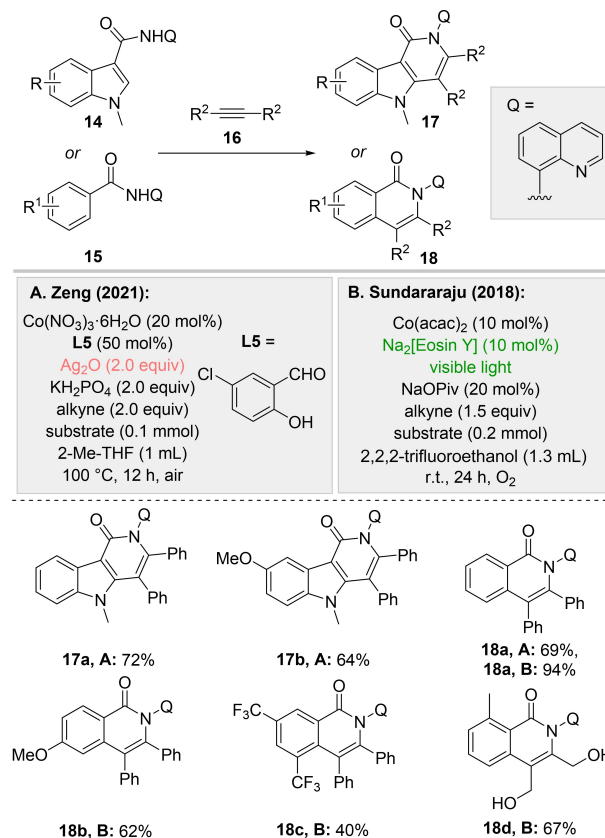
Cho et al., in 2015, replaced the silver acetate with [Ir(dFppy)₂(phen)]PF₆ as the photocatalyst together with blue LEDs and O₂ (Scheme 5B).^[30]

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 co-workers 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 was formed in 69 % yield. This protocol



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]

can be compared with a silver-free method by Sundararaju and co-workers (reported in 2018), where the authors used Na₂[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** was 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, was 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 co-workers 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** were formed in good to excellent yields.

This protocol can be compared with a stoichiometric silver-free version by Rueping and co-workers that also closely resembles the original studies using Cu-oxidants (reported in 2019). The authors employed [Ru(dtbbpy)₂](PF₆)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, AgSbF₆ 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

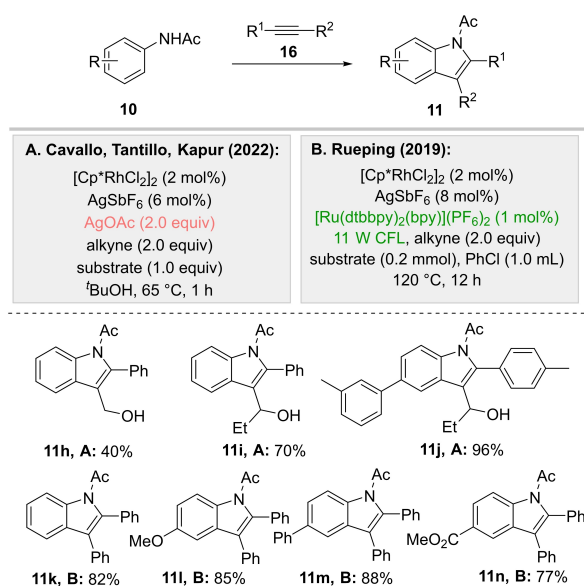
excellent yields. Notably, many further studies that employ photochemistry for the re-oxidation step are reported in literature without an immediate analogue based on Ag-additives.^[12,13,39]

2.2. Approaches Employing Electrochemistry

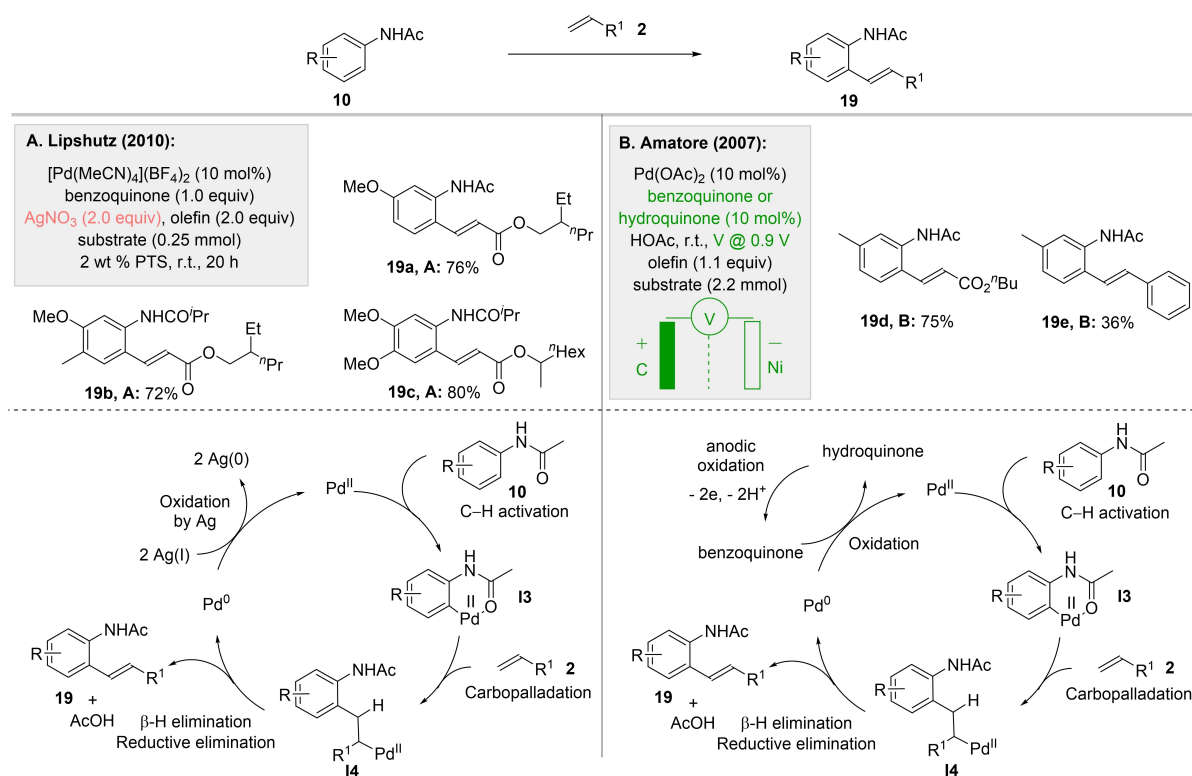
One of the most fundamental processes in chemistry is the change of redox-states. Arguably, the electrochemical addition or removal of electrons through the direct application of an electrical potential represents the conceptually simplest means of adjusting redox states, since it does not require any 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 co-workers 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 **13** undergoes carbopalladation and β -hydride elimination to generate the product. Subsequently, a reductive elimination generates Pd⁰, 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 co-workers (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]

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



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



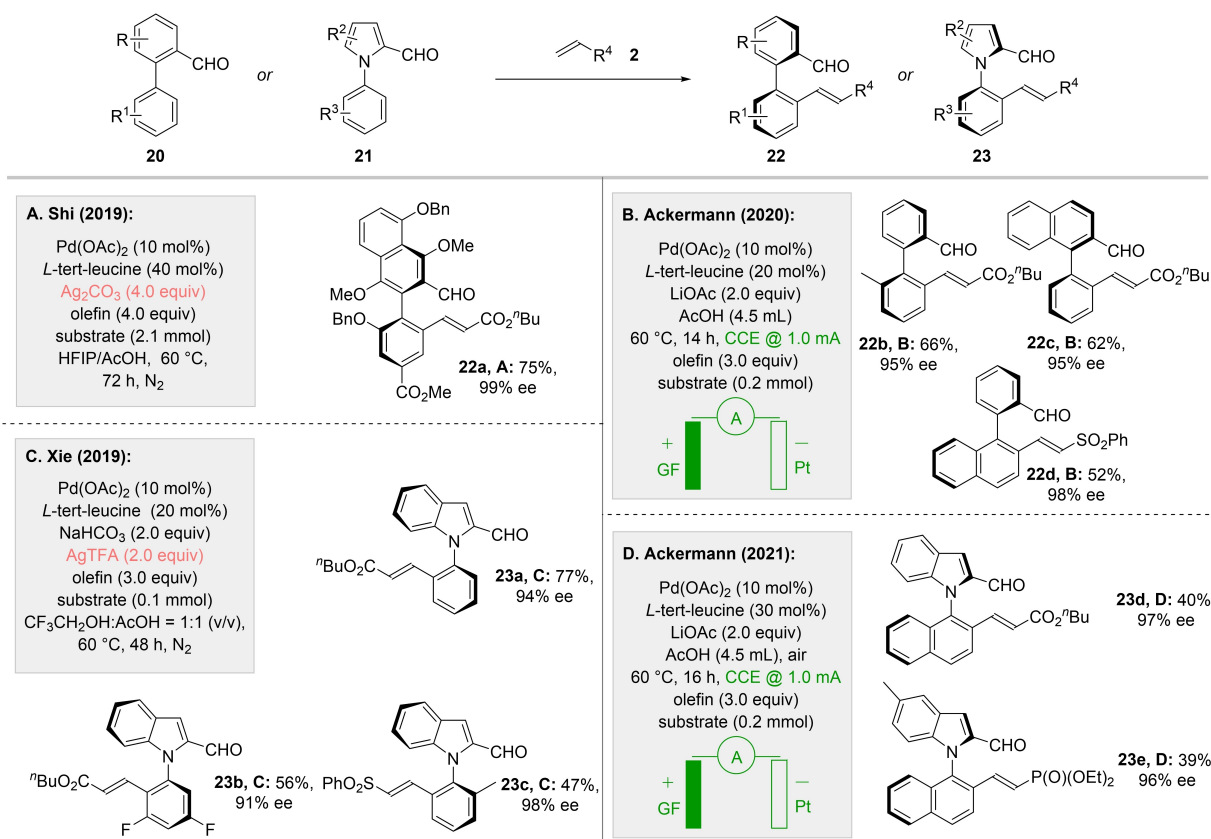
acetic acid at a gold disk electrode, it was deduced that quinones were reduced before the protons of the medium, whose reduction started at ca. $-0.6 \text{ V}_{\text{SCE}}$. This led to the need of using a divided-cell setup.

In 2019, Shi and co-workers reported the 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** was formed in 75 % yield and with 99 % enantiomeric excess (*ee*) (Scheme 9A). Ackermann and co-workers 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** were formed with a synthetically useful yield and excellent *ee*. An analogous atroposelective C–H olefination of *N*-aryllindoles was reported by Xie and co-workers where the authors employed Pd/amino acid cooperative catalysis alongside two equivalents of silver–TFA to close the catalytic cycle (Scheme 9C).^[49] The product **23a** was 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 co-workers 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 were formed with a synthetically useful yield and an excellent enantioselectivity.

In 2017, Yu and co-workers 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** were formed under the combination of steric and electronic control exerted by the substituents present in the starting material. In 2022, Ackermann and co-workers 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 co-workers 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 $1.35 \text{ V}_{\text{SCE}}$, which is 200 mV lower than the one



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]

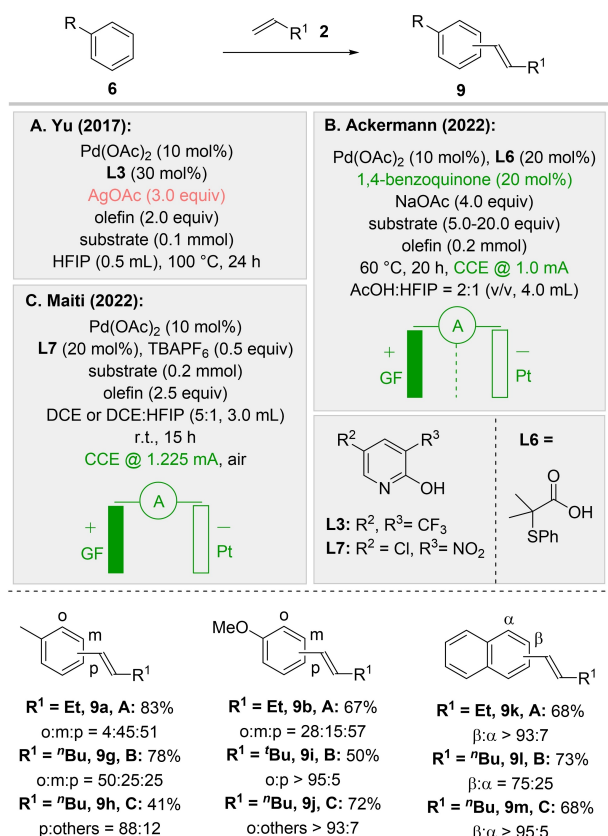
of the complexes derived from pyridone ligand **L4**, which directly correlates with the observed higher reactivity. In a contemporary study, Dutta, Werz, Paul, Maiti, and co-workers reported an electrochemistry-based protocol employing a graphite felt anode in an undivided cell under a constant current (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.

In 2016, Zhang and co-workers 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 co-workers 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 an undivided cell was employed.

In 2015, Niu, Song and co-workers 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 **15**. This intermediate then forms the C–O bond giving **16**, followed by a proto-demetalation 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 co-workers 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.

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



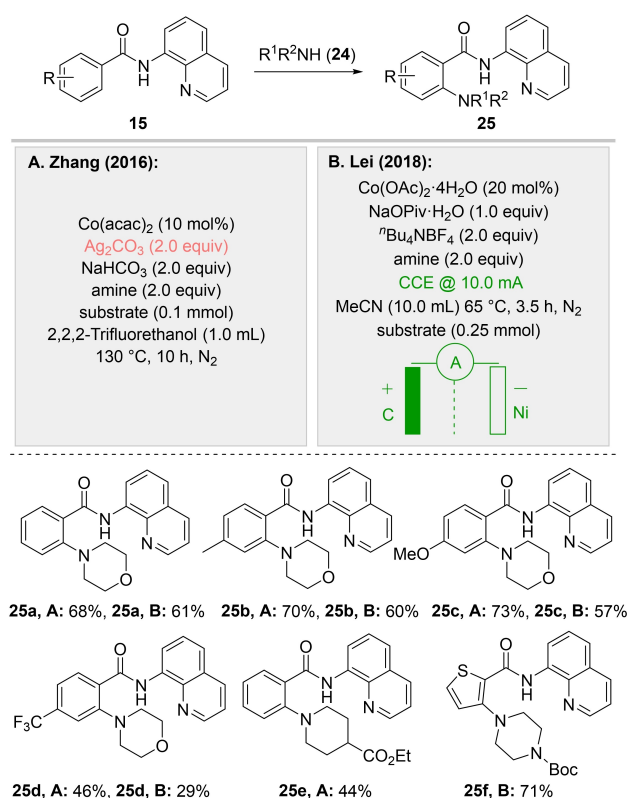
Scheme 10. A) Non-directed C–H olefination of arenes with Ag.^[25] B) Electrochemical C–H olefination of arenes.^[51] C) Electrochemical C–H olefination of arenes.^[52]

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.

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 co-workers 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.

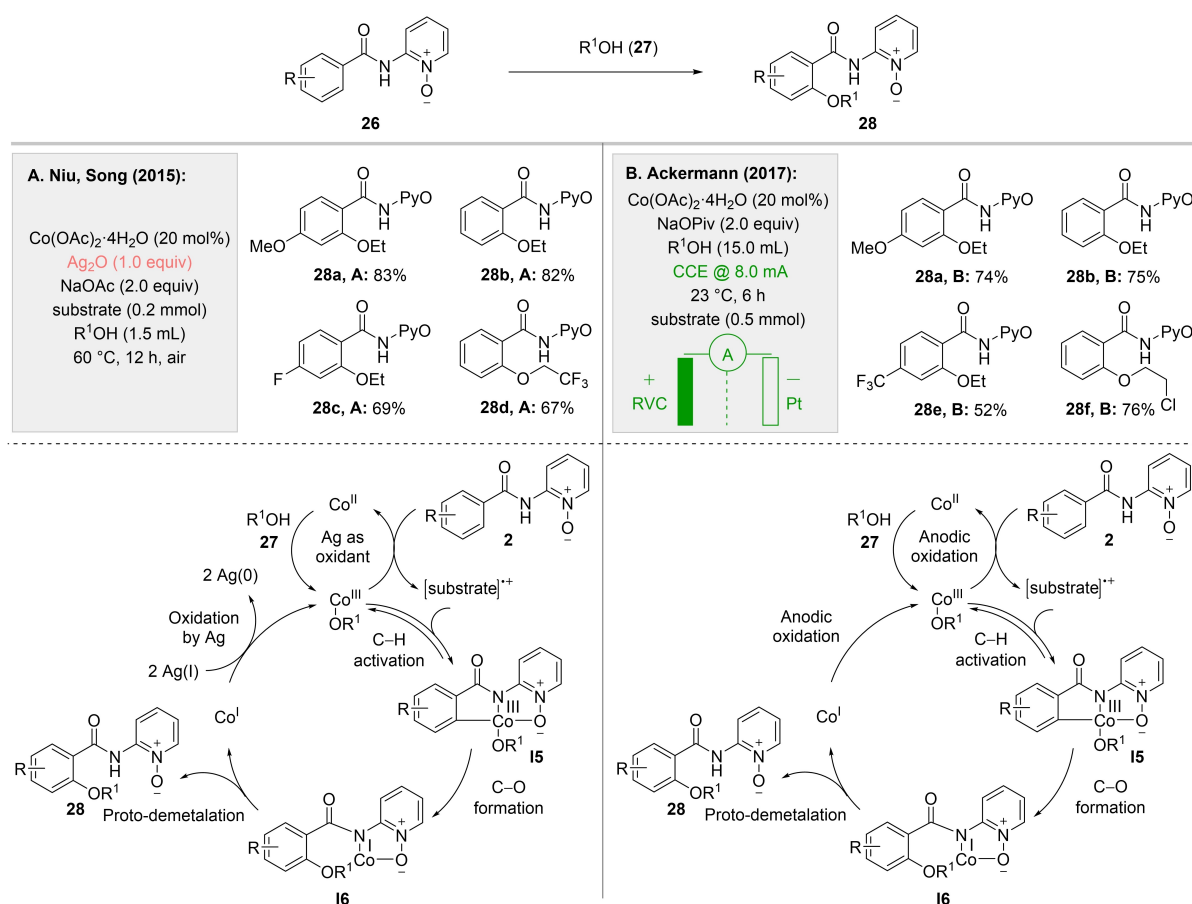
Two equivalents of silver acetate were employed as a terminal oxidant. In a contemporary study, Loginov et al. reported the same transformation employing similar reaction conditions (Scheme 13B).^[58] Mei et al., in 2019, employed an electrochemical approach to replace the silver additive. The authors reported a Pt anode under constant



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]

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 ^tBu₄NOAc to NaOAc or KOAc provided similar results. In contrast, alternative electrolytes including ^tBu₄NX (X = BF₄, PF₆, and ClO₄) 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 hydroxy and trifluoromethyl groups. The respective products **31f–i** were obtained in good yields.

In 2010, Song, Li and co-workers 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



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]

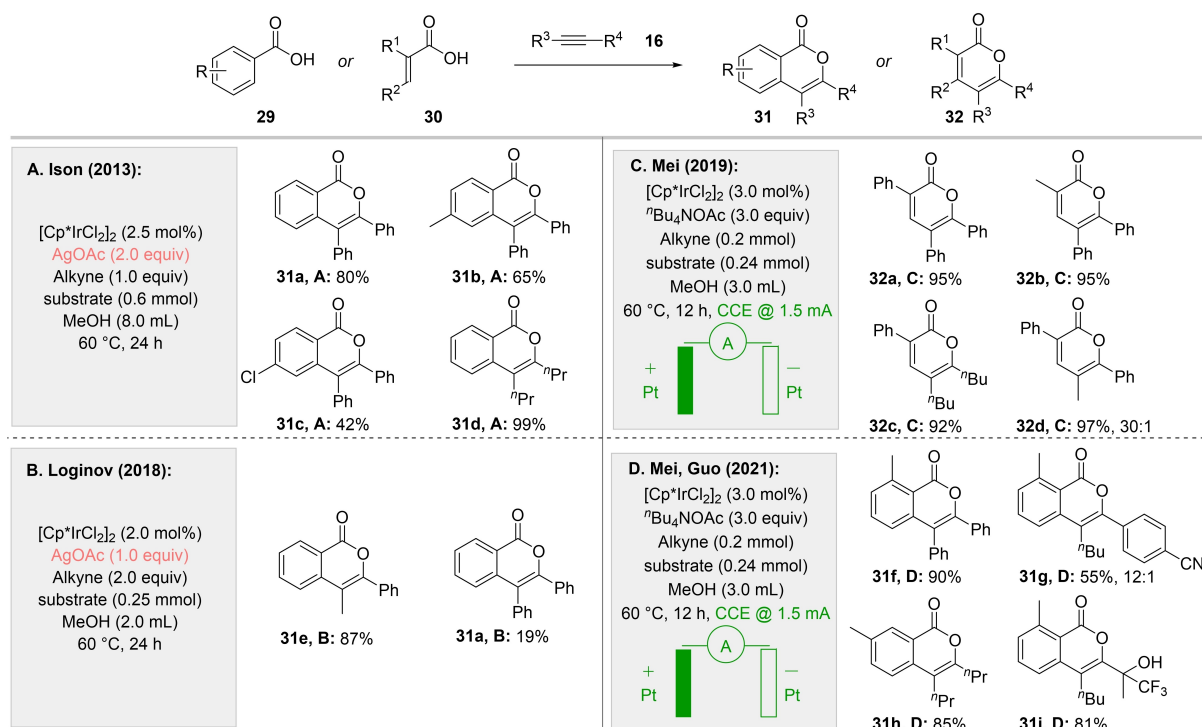
silver carbonate is used as the terminal oxidant giving product **34a** in 92 % yield. In 2021, Hong, Mei et al. employed electrochemistry to avoid the stoichiometric oxidant (Scheme 14B).^[62] The authors reported a Pt anode under constant current of 1.5 mA and the electrochemical recycling was performed 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 KPF₆ and NaBr were completely ineffective. This observation supports the hypothesis that a

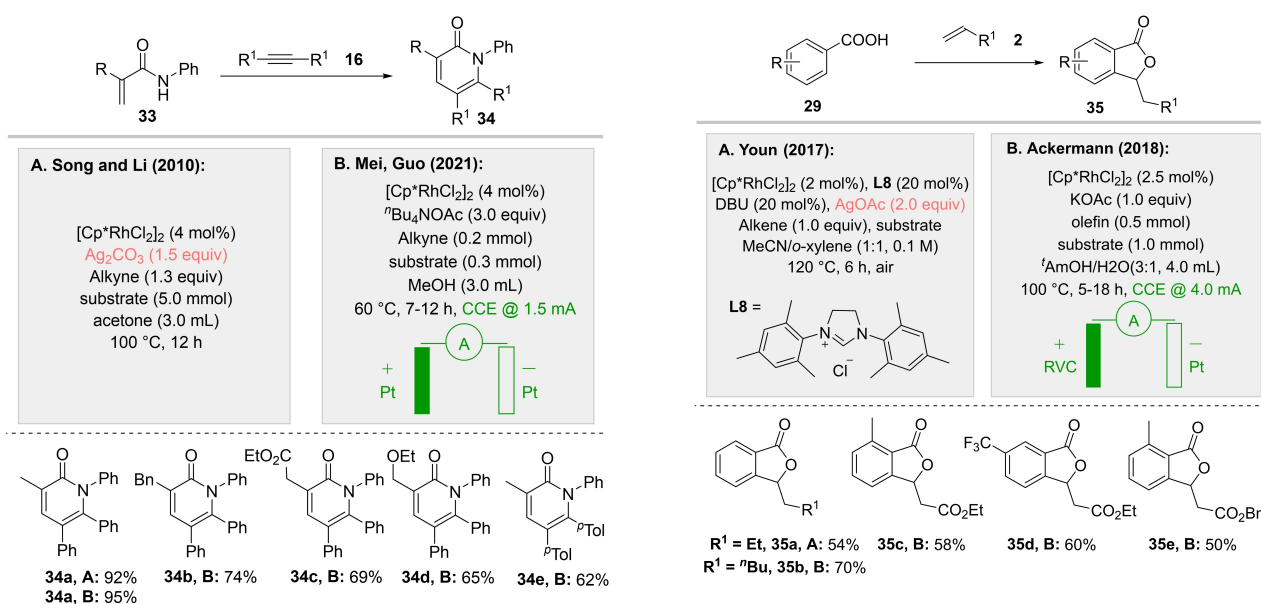
carboxylate-assisted C–H activation is operative. The product **35b** could be obtained in 70 % yield. Electron-donating methyl as well as electron-withdrawing trifluoromethyl substituents on arene are well-tolerated yielding products **35c** and **35d**, respectively. Similarly, a benzyl group was shown to be tolerated in the olefin part, delivering product **35e** in 50 % yield.

In 2006, Yu and co-workers reported a Pd-catalyzed alkylation of C(sp²)–H and C(sp³)–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]

Mei and co-workers replaced the silver with an electrochemical oxidation. The authors employed a 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 substitu-



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]

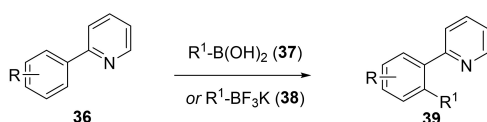


Scheme 14. A) Rh-catalyzed C–H activation of amides with Ag.^[61]
 B) Electrochemical C–H activation of amides.^[62]

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

ents 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

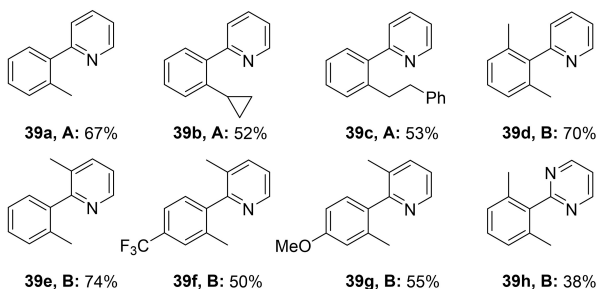
recycling was performed in an undivided cell (Scheme 17B).^[68] Similar to the method by Li, this protocol delivered products **39a** and **39i–k** in good yields. Trifluoromethyl-substituted, as well as trisubstituted arenes delivered products **39l–n** in 48–63 % yield. A methoxy substituent on the pyridine DG delivered product **39o** in 69 % yield. Beyond these examples, many further studies using electrochemical re-oxidation but without a directly

**A. Yu (2006):**

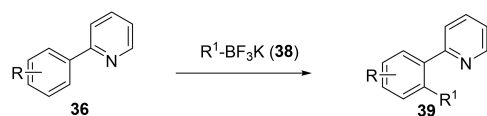
Pd(OAc)₂ (10 mol%)
benzoquinone (0.5 equiv)
Ag₂O (1.0 equiv)
boronic acid (3.0 equiv)
substrate (0.2 mmol)
tAmyl-OH (1.0 mL)
100 °C, 6 h, air

B. Mei (2018):

Pd(OAc)₂ (10 mol%)
R-BF₃K (2.0 equiv)
substrate (0.3 mmol)
CF₃CH₂OH/AcOH/H₂O
(2 mL/2 mL/0.5 mL)
60 °C, 18–36 h, CCE @ 1.0 mA



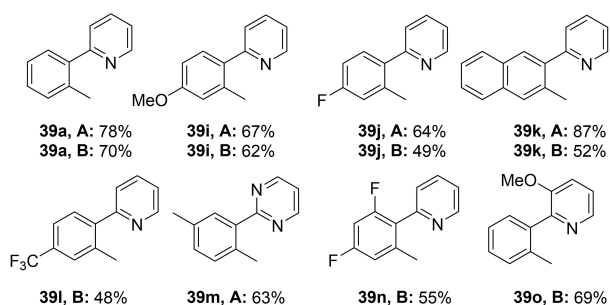
Scheme 16. A) Pd-catalyzed alkylation of 2-phenyl pyridines with Ag.^[65] B) Electrochemical alkylation of 2-phenyl pyridines.^[66]

**A. Li (2015):**

[Cp*RhCl₂]₂ (4 mol%)
AgSbF₆ (16 mol%)
AgF (2.8 equiv)
R¹-BF₃K (3.0 equiv)
substrate (0.2 mmol)
ClCH₂CH₂Cl (3.0 mL)
100 °C, 24 h, N₂

B. Ackermann (2021):

[Cp*RhCl₂]₂ (1.25 mol%)
CsF (1 equiv)
R-BF₃K (2.0 equiv)
substrate (0.25 mmol)
tBuOH/H₂O (4:1, 5.0 mL)
100 °C, 18 h, CCE @ 4.0 mA



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

analogous silver-based method have been reported in literature.^[41,43,69]

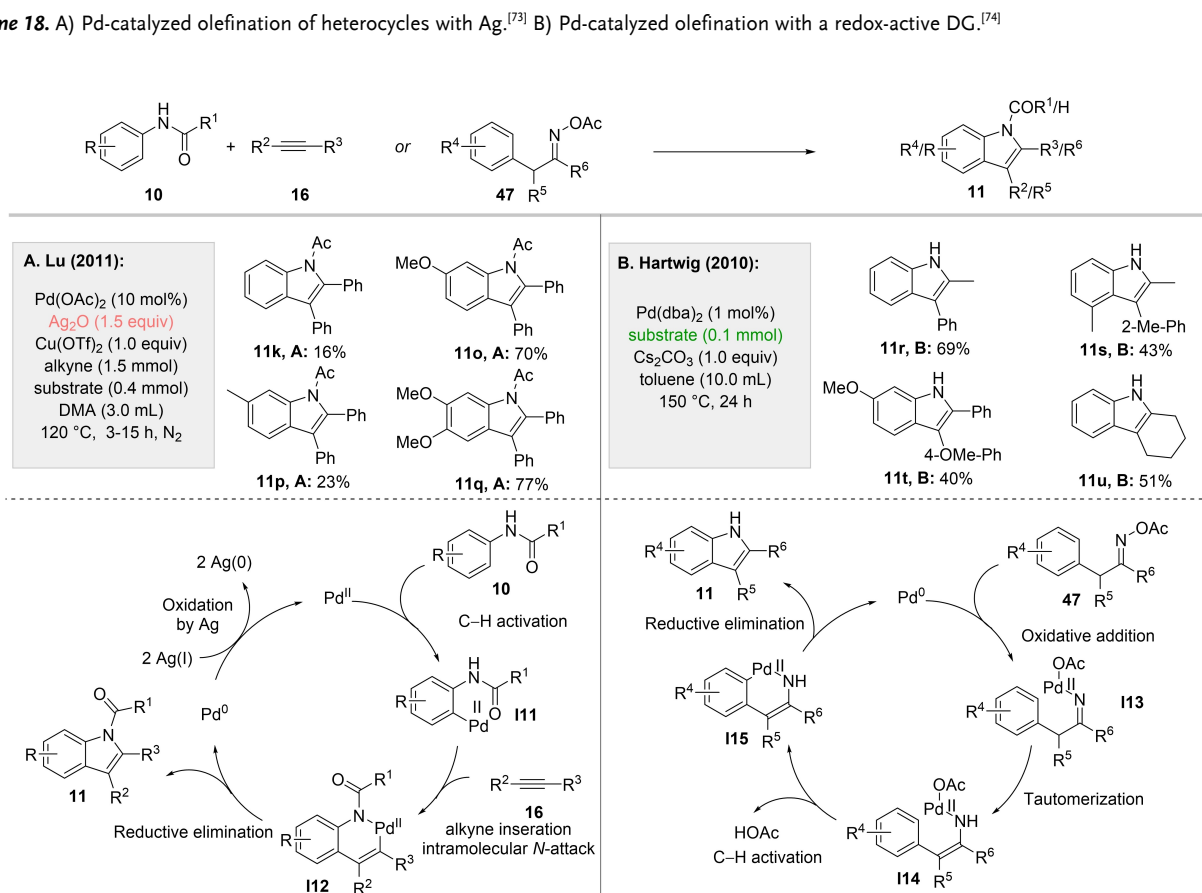
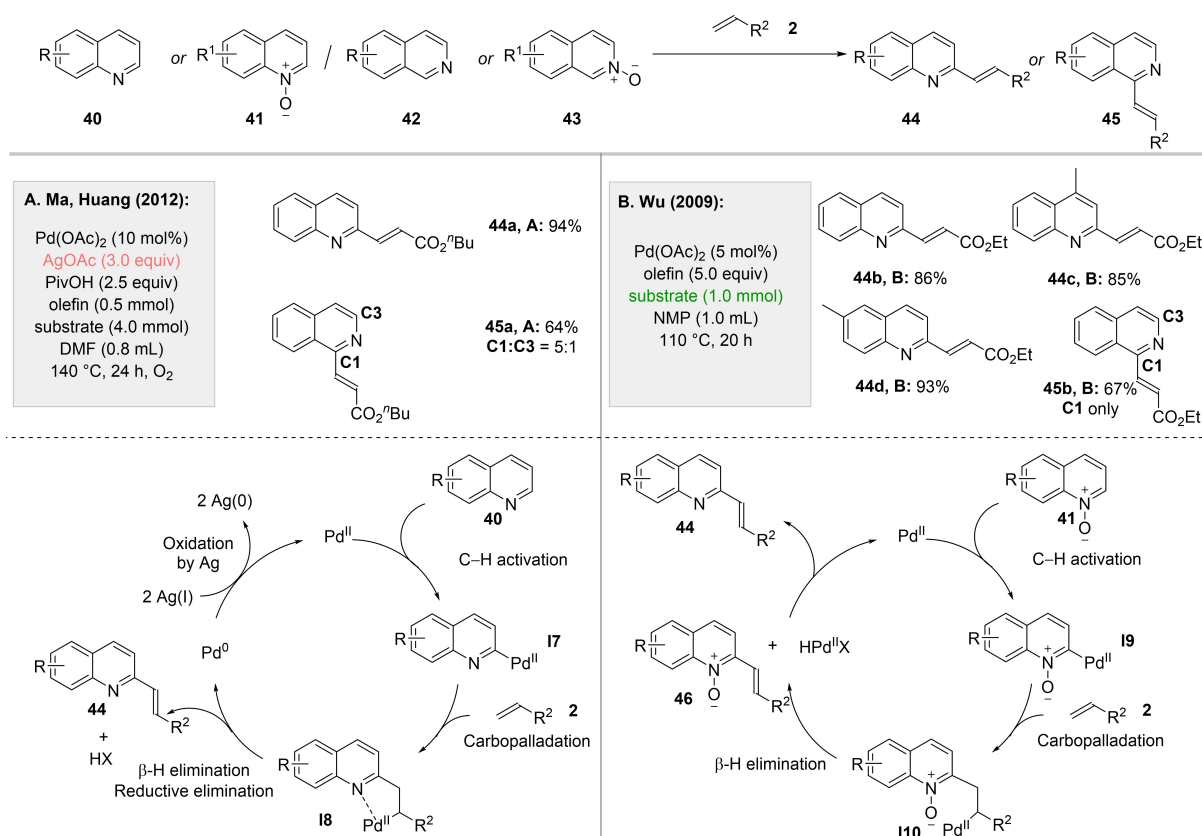
2.3. Replacement of Silver with Redox-Active Directing Groups

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 DGs 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 co-workers 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 **17** undergoes carbopalladation to produce **18**. A subsequent β-hydride elimination releases the product and finally a reductive elimination generates Pd⁰. The authors employed three equivalents of silver acetate for the re-oxidation step to achieve the optimal yield. A complementary study by Wu and co-workers employed the analogous N-oxides as starting materials and could thereby avoid the use of stoichiometric silver (Scheme 18B).^[74]

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 co-workers 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 **111** couples with the alkyne to generate **112**. After a reductive elimination, **112** releases the product **11** and forms Pd⁰. The silver oxide oxidizes Pd⁰ 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 co-workers reported a complementary study (in 2010) employing oxime esters as the redox-active DG (Scheme 19B).^[76] In the first step, the Pd⁰ is oxidized to Pd^{II} via an oxidative addition of the N–O bond giving intermediate **113**. The carbon–nitrogen double bond tautomerizes to a carbon–carbon double bond and the resulting intermediate **114** undergoes an *ortho*-C–H activation to generate **115**. Subsequently, a reductive elimination releases the product **11** and delivers Pd⁰, which can re-enter the catalytic cycle. The product **11r** was 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, respectively.

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

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 % yield, 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]

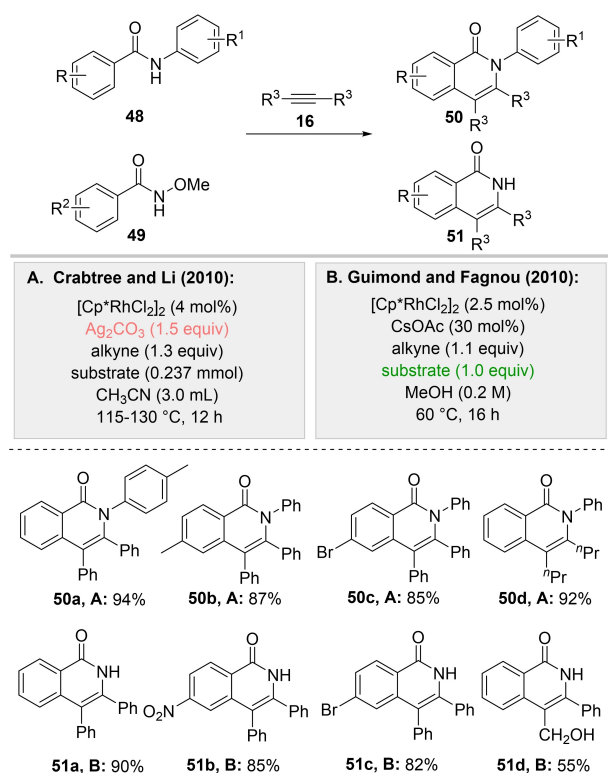
In the same year, Guimond and Fagnou reported the use of a redox-active DG containing an N–O bond

(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** was 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.

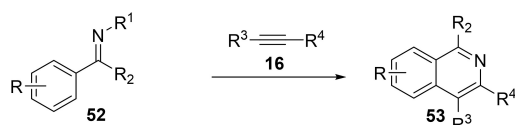
In analogy to the Rh-catalyzed synthesis of indoles from acetanilides and alkynes, the reaction of substrates containing a benzimine substructure can be used to access isoquinolines. Seminal reports by the groups of Fagnou and Miura used Cu^{II}-salts as oxidants towards this end, which have since been 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 co-workers reported a Rh-catalyzed [4+2] annulation of *N*-aryl benzamides 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 co-workers showed that a silver-free transformation is possible when an internal *O*-acyl oxime 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 co-workers showed that analogous transformations are possible 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 co-workers 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 co-workers (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.

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]

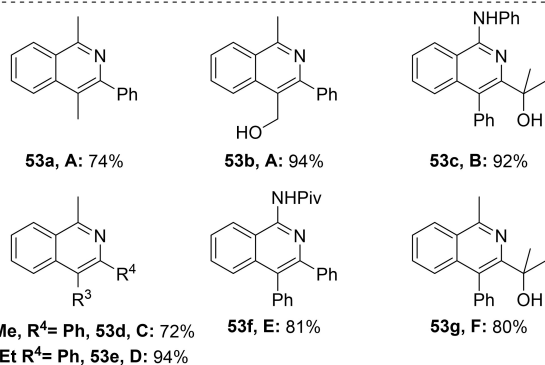
Based on this approach, Cavallo, Tantillo, Kapur, and co-workers reported a Rh-catalyzed *ortho*-C–H activation of



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



A. Yi (2018) [Cp*RhCl ₂] ₂ (10 mol%) AgOAc (1 equiv) alkyne (1 equiv) substrate R ¹ = OMe R ² = Me (0.2 mmol) MeOH (0.1 M), r.t., 24 h, N ₂	B. Cui, Wu (2021): [Cp*RhCl ₂] ₂ (5 mol%) PhCOOAg (60 mol%) alkyne (1.0 equiv) substrate R ¹ = H, R ² = NHA _r (0.1 mmol) PhCl (2.0 mL) 80 °C, 12 h, air
C. Chiba (2010): [Cp*RhCl ₂] ₂ (2.5 mol%) NaOAc (30 mol%) alkyne (1.2 equiv) substrate R ¹ = OAc (0.5 mmol) MeOH (0.2 M) 60 °C, 4–10 h, N ₂	D. Rovis (2011): [Cp*RhCl ₂] ₂ (1.25 mol%) K ₂ CO ₃ (200 mol%) alkyne (1.1 equiv) substrate R ¹ = OH (0.2 mmol) TFE (3.0 mL) 45 °C, 16 h
E. Miura (2011): [Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂ (4 mol%) PivOH (20 mol%), alkyne (1.1 equiv) substrate R ¹ /R ² = oxadiazole (0.1 mmol) PhCF ₃ (1.0 mL), 120 °C, 18 h	F. Zhao/Wang (2020): [Cp*RhCl ₂] ₂ (5 mol%) CsOAc (1.0 equiv) alkyne (1.5 equiv) substrate R ¹ /R ² = 3-arylisoxazolones (0.1 mmol) DCE (1.5 mL), 25 °C, 24 h



Scheme 21. A) Rh-catalyzed [4+2] annulation of *O*-methyl oxime and alkynes.^[81] B) Rh-catalyzed [4+2] annulation of *N*-aryl benzamides with propargyl alcohols.^[82] C) Rh-catalyzed synthesis of isoquinolines from aryl ketone *O*-acyl oxime 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]

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** were 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 co-workers, 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 state is restored by the N–N bond present in the DG. The second and third studies,

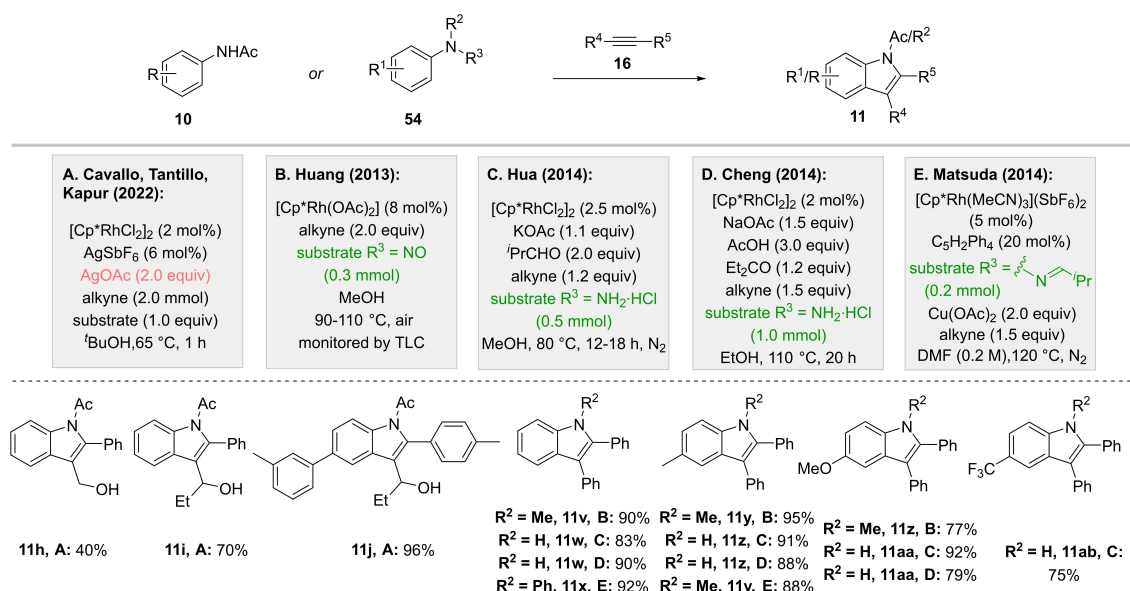
by Hua et al. and Cheng et al., employed arylhydrazines as starting material, in situ generating a hydrazone DG, which likewise contains a N–N bond (Scheme 22C^[89] and Scheme 22D^[90]). Finally, Matsuda and co-workers directly employed a hydrazone-based DG (Scheme 22E).^[91] The mechanisms of the last three studies strongly resemble the one described by Huang and co-workers. The products **11v–x** derived from monosubstituted 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 co-workers employed a Co-based catalyst for the synthesis of indole derivatives (Scheme 23A).^[92] Similar to the protocols from Cavallo, Tantillo, Kapur, and co-workers, 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 AgSbF₆ for the initial generation of active catalyst from a commercially available precatalyst. In 2016, Glorius and co-workers 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 monosubstituted 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 22B–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.

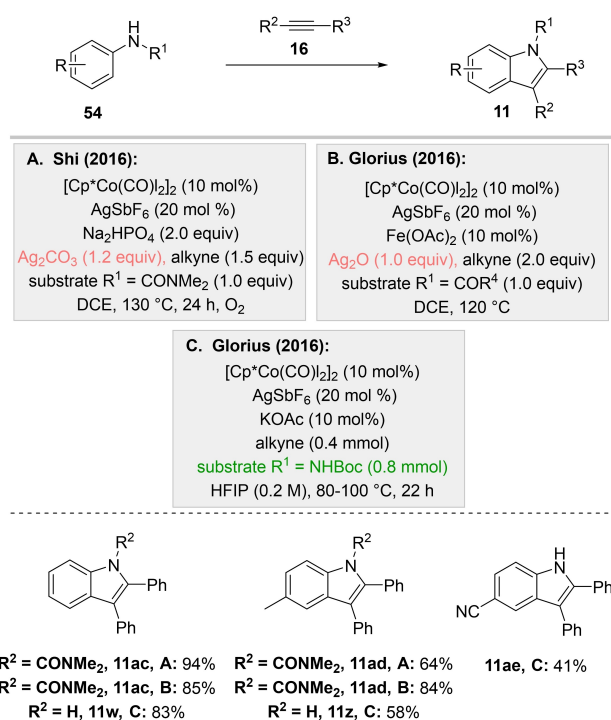
It should be noted that the use of redox-active DGs has been established as a highly valuable tool in C–H activation with many more applications described in literature, to which no immediate analogues based on the use of silver as terminal oxidant exist.^[71,72,95]

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/Ag⁰ is +0.79 V_{SHE},^[96] which is very close to the O₂/H₂O₂ and BQ/HQ systems (both +0.70 V_{SHE}).^[96] Considering these values,



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]

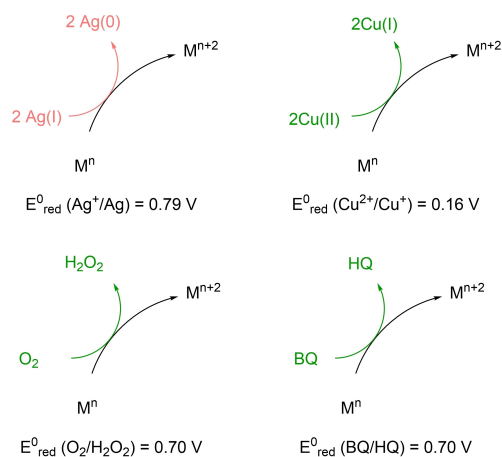


Scheme 23. A) Co-catalyzed oxidative coupling of *N*-aryl ureas and internal alkynes.^[92] B) Co-catalyzed synthesis of indols, *N*-acyl anilines and alkynes.^[93] C) Co-catalyzed C–H activation and redox-neutral indole synthesis from arylhydrazine derivatives.^[94]

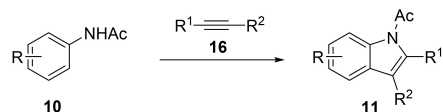
it seems reasonable that if the role of silver is exclusively that of an oxidant in a given reaction, it can potentially be replaced with O₂ and/or BQ as ecologically and economically more attractive oxidants (Scheme 24).

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 Pd⁰ 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 co-workers 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



Scheme 24. Comparison between alternative oxidants.

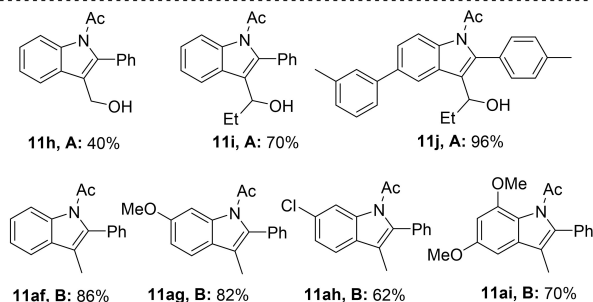


A. Cavallo, Tantillo, Kapur (2022):

[Cp* RhCl_2] $_2$ (2 mol%)
AgSbF $_6$ (6 mol%)
AgOAc (2.0 equiv)
alkyne (2.0 equiv)
substrate (1.0 equiv)
 $^t\text{BuOH}$, 65 $^\circ\text{C}$, 1 h

B. Stuart and Fagnou (2010):

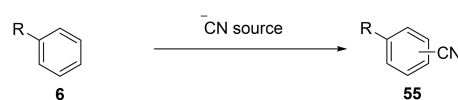
[Cp* RhCl_2] $_2$ (2.5 mol%)
AgSbF $_6$ (10 mol%)
Cu(OAc) $_2$ ·H $_2$ O (2.1 equiv)
alkyne (1.1 equiv)
substrate (1.0 equiv)
 $^t\text{Amyl-OH}$ (0.2 M), 120 $^\circ\text{C}$, 1–3 h



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]

with the seminal studies by Stuart, Fagnou, and co-workers 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 monosubstituted 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.

The replacement of silver with copper can also be used for Pd-catalysts. In 2019, van Gemmeren and co-workers 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



A. van Gemmeren (2019):

Pd(OAc) $_2$ (10 mol%)
Ac-Gly-OH (30 mol%), **L9** (20 mol %)
AgF (3.0–4.0 equiv),
CuCN or Zn(CN) $_2$ (2.0 equiv)
substrate (0.2 mmol)
HFIP (2.0 mL), 80–90 $^\circ\text{C}$, 18 h

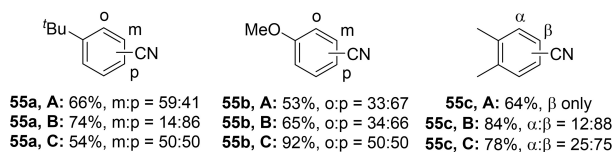
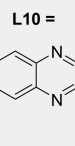
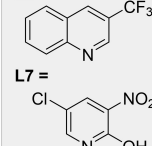
B. Yu (2019):

Pd(OAc) $_2$ (15 mol%)
L7 (30 mol %)
AgOAc (3.0 equiv),
AgCN (1.1 equiv)
substrate (0.2 mmol)
HFIP (0.4 M), 100 $^\circ\text{C}$, 24 h

C. Ritter (2019):

Pd(OPiv) $_2$ (10 mol%)
Ac-Ala-OH (20 mol%), **L10** (30 mol %)
K $_3\text{Fe}(\text{CN})_6$ (0.17 equiv)
KTFA (1.0 equiv), Cu(OAc) $_2$ (2.0 equiv)
substrate (1.0 equiv)
HFIP, 85 $^\circ\text{C}$, 24 h

L9 =



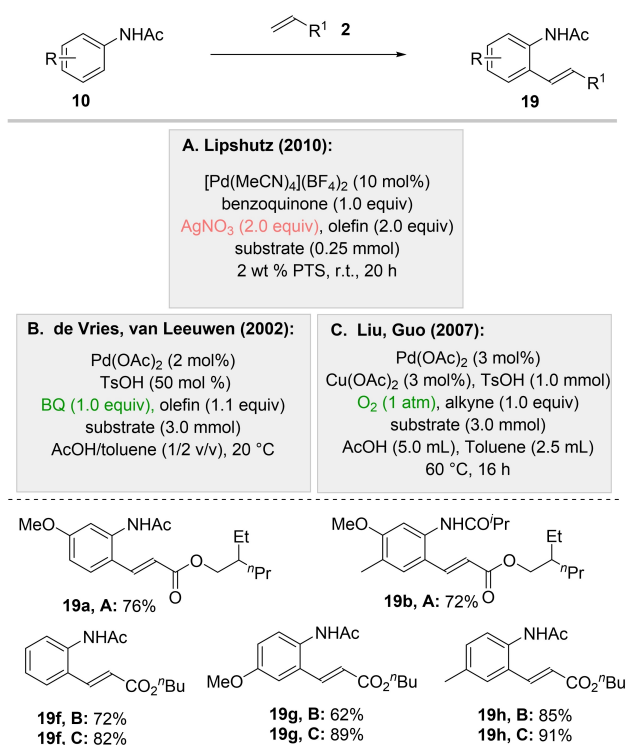
Scheme 26. A and B) Silver-based non-directed Pd-catalyzed C–H cyanation of arenes.^[100,102] C) Pd-catalyzed C–H cyanation of arenes with Cu additives.^[103]

authors employed three or four equivalents of silver fluoride for the oxidation step to obtain an optimal yield.

In a contemporary study, Yu and co-workers 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 co-workers, 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. Dialkyl-substituted arene formed product **55c**, maintaining steric control for the dual-ligand systems and electronic control in case of Pd–pyridone system.

In 2010, Lipshutz and co-workers 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 co-workers showed that benzoquinone can alternatively be used as organic oxidant (Scheme 27B),^[104] giving product **19f** with 72% yield.

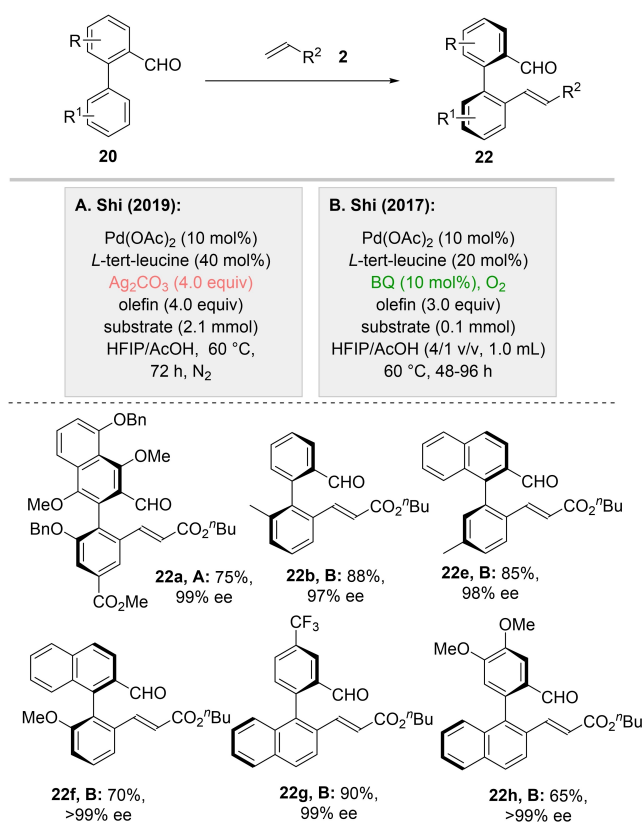
Electron-donating methoxy and methyl substituents on the arene were tolerated delivering the products **19g** and



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 O₂.^[105]

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 co-workers 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 O₂ (Scheme 28B).^[106] The reduced metal gets oxidized by BQ, the latter being reduced to HQ. Since the reduction potentials of BQ/HQ and O₂/H₂O₂ are similar, the HQ then gets oxidized back by O₂ 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 of 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 analogues based on the use of silver as terminal oxidant exist.^[107]



Scheme 28. A) Pd-catalyzed atroposelective C–H olefination with silver additive.^[47] B) Pd-catalyzed atroposelective C–H olefination using BQ and O₂.^[106]

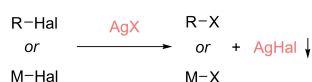
3. Silver as Halide Scavenger

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 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.

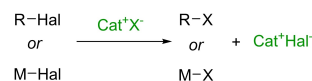
3.1. Replacement of Silver with Suitable Base

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

A: Removal of Halide Anions with Silver Additives



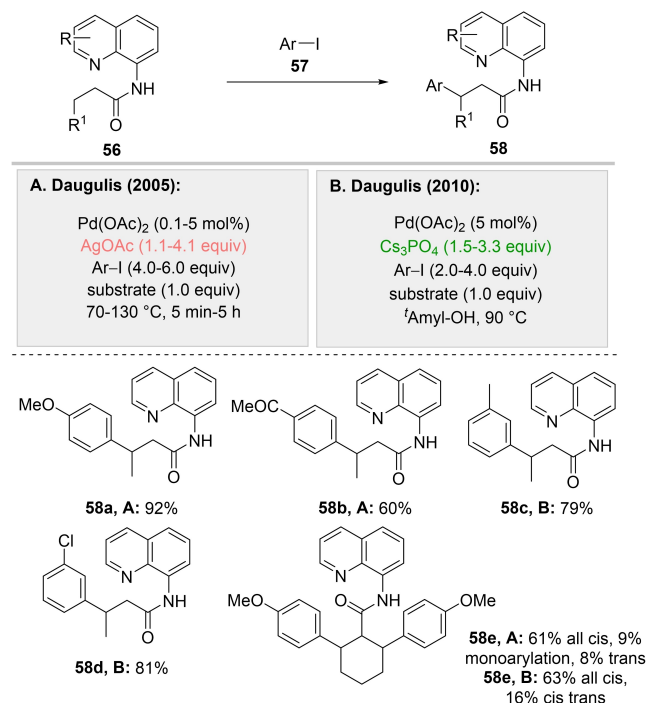
B: Removal of Halide Anions with Bases



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

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 co-workers reported an 8-aminoquinoline 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 diarylated 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



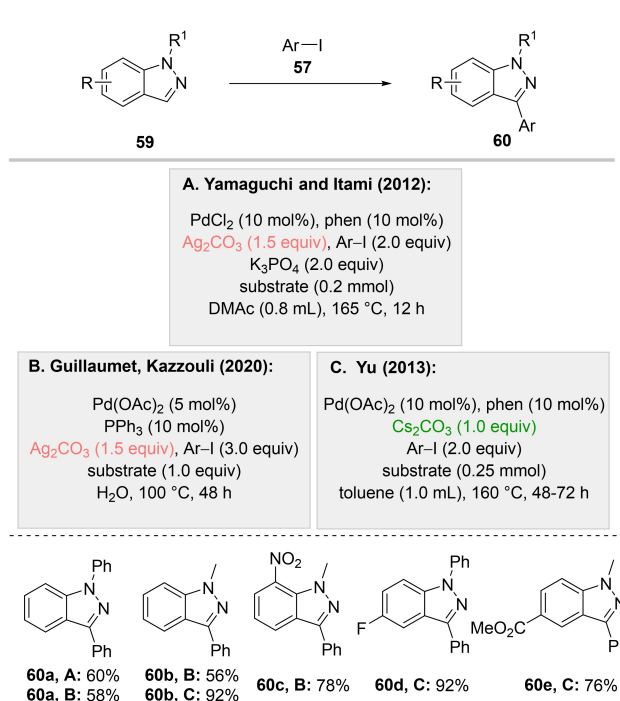
Scheme 30. A) Pd-catalyzed β -C–H arylation with 8-aminoquinoline DG.^[108] B) Pd-catalyzed β -C–H arylation with 8-aminoquinoline DG employing base as iodine scavenger.^[109]

excellent yield and selectivity. Alkyl and chloro groups were tolerated on the aryl iodide part.

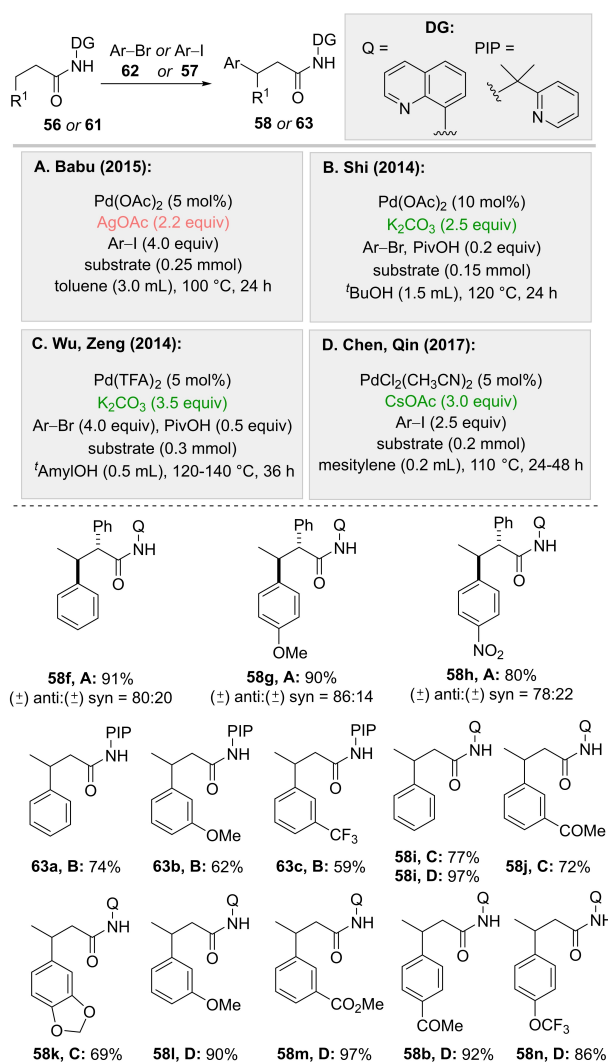
A C(sp²)–H activation/arylation with indazoles as substrates employing aryl iodide as the coupling partner and stoichiometric silver carbonate as halide scavenger was reported by Yamaguchi, Itami, and co-workers (Scheme 31A).^[110] The product **60a** derived from phenyl iodide was produced in 60 % yield. Recently, a modified version of this reaction was documented by Guillaumet, Kazzouli, and co-workers 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 to the silver additives in the other protocols.

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 co-workers, the group of Babu reported an 8-aminoquinoline-aided Pd-catalyzed diastereoselective β -arylation of the secondary C(sp³)–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



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]



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(sp³)–H bonds.^[114] C) Pd-catalyzed C–H arylation of C(sp³)–H bonds.^[115] D) Pd-catalyzed base-promoted C–H arylation of C(sp³)–H bonds.^[116]

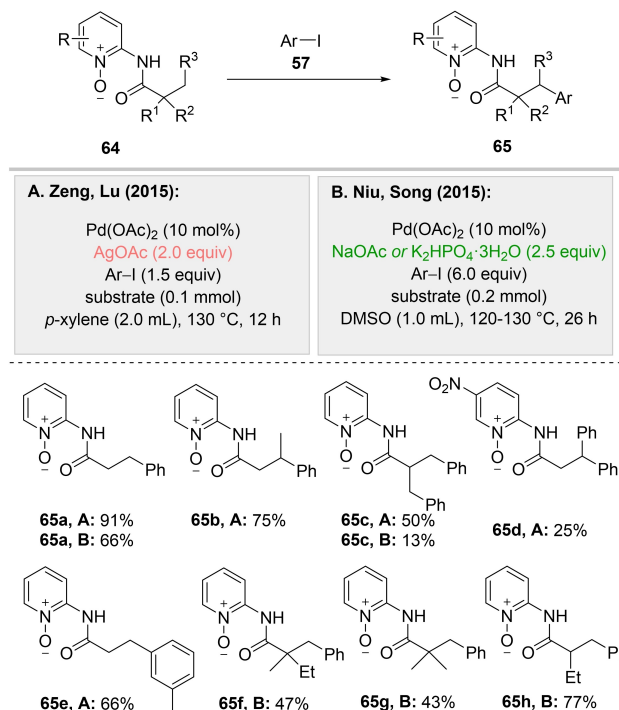
arene part are tolerated, generating products **58g** and **58h**, respectively.

In 2014, Shi and co-workers employed a PIP-amine based DG for the Pd-catalyzed arylation of unactivated methylene C(sp³)–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 co-workers 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 co-workers also employed potassium carbonate as the base, however

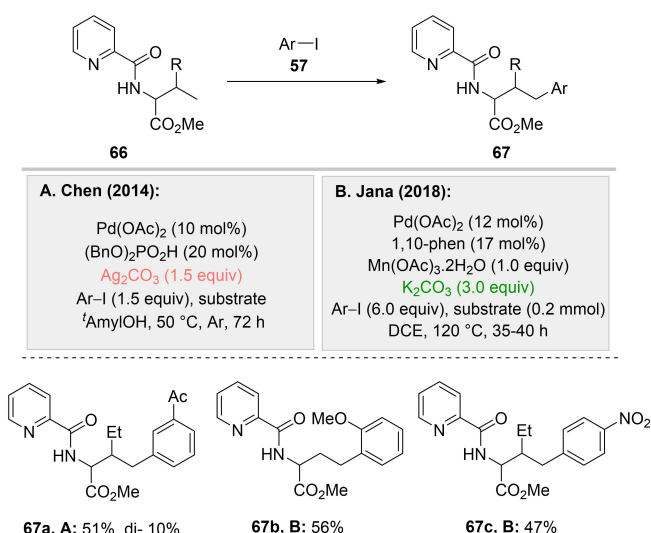
employing 8-aminoquinoline as the DG (Scheme 32C).^[115] With this protocol, the authors formed products **58i–k** in good to excellent yields. Finally, in 2017, Chen, Qin and co-workers reported a cesium acetate mediated Pd-catalyzed C(sp³)–H arylation of carboxylic acid derivatives (Scheme 32D).^[116] The product **58i** was prepared in 97 % yield. Similarly, methoxy, ester, ketone, and –OCF₃ substituents on the aryl iodide part produced products **58l**, **58m**, **58b**, and **58n**, respectively.

In 2015, Zeng, Lu, and co-workers employed a pyridine-*N*-oxide directed C–H arylation of β-C(sp³)–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 dipotassium hydrogen phosphate as base (Scheme 33B).^[118] The products **65f–h** were documented in the scope studies with synthetically useful yields.

In 2014, Chen and co-workers reported the total synthesis of Hibispeptin A via a Pd-catalyzed γ-C(sp³)–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 co-workers replaced the silver additive with potassium carbonate (Scheme 34B).^[120] Electron-donating methoxy as well as electron-withdrawing nitro groups were tolerated,



Scheme 33. A) Pd-catalyzed pyridine-*N*-oxide directed C–H arylation of C(sp³)–H bonds with silver additive.^[117] B) Pyridine-*N*-oxide directed Pd-catalyzed C(sp³)–H arylation with base.^[118]



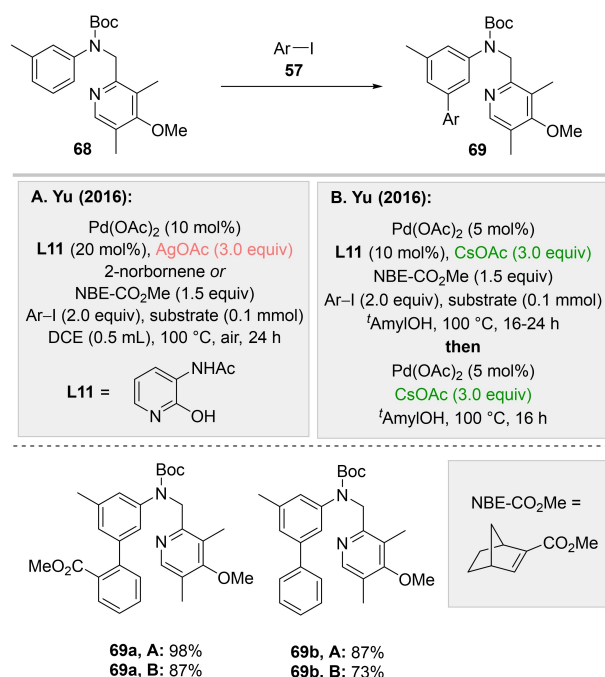
Scheme 34. A) Pd-catalyzed $\gamma\text{-C}(\text{sp}^3)\text{-H}$ arylation with silver.^[119] B) Ligand-promoted $\gamma\text{-C}(\text{sp}^3)\text{-H}$ arylation to access unnatural amino acid derivatives.^[120]

producing products **67b** and **67c** in synthetically useful yields.

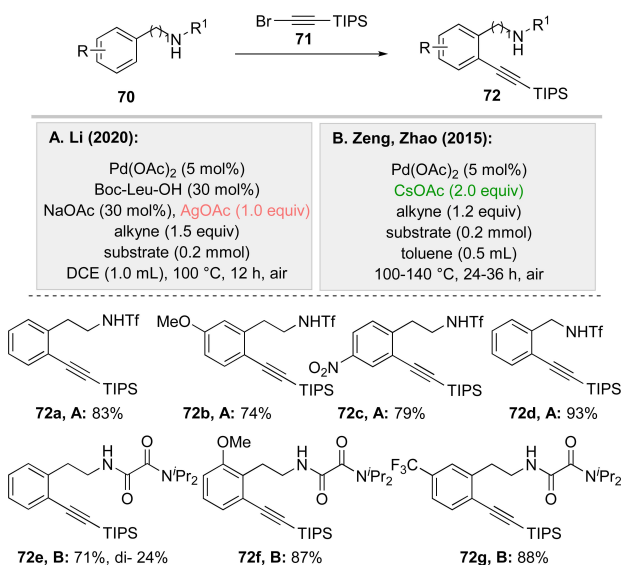
In 2016, Yu and co-workers reported a *meta*-C–H activation/arylation of arenes by merging *ortho*-C–H activation with a transient mediator norbornene, followed by coupling with a suitable aryl iodine source. Inside the same publication, the authors described the use of silver acetate and a silver-free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

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

Li and co-workers reported a Pd-catalyzed *ortho*-C–H alkylation 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 monosubstituted 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 alkylation protocol that is complementary with the method from Li. The authors employed cesium acetate for halide scavenging (Scheme 36B).^[123] Monosubstituted 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]



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 alkylation with silver additive.^[122] B) Silver-free Pd-catalyzed *ortho*-C–H alkylation.^[123]

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 co-workers 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.

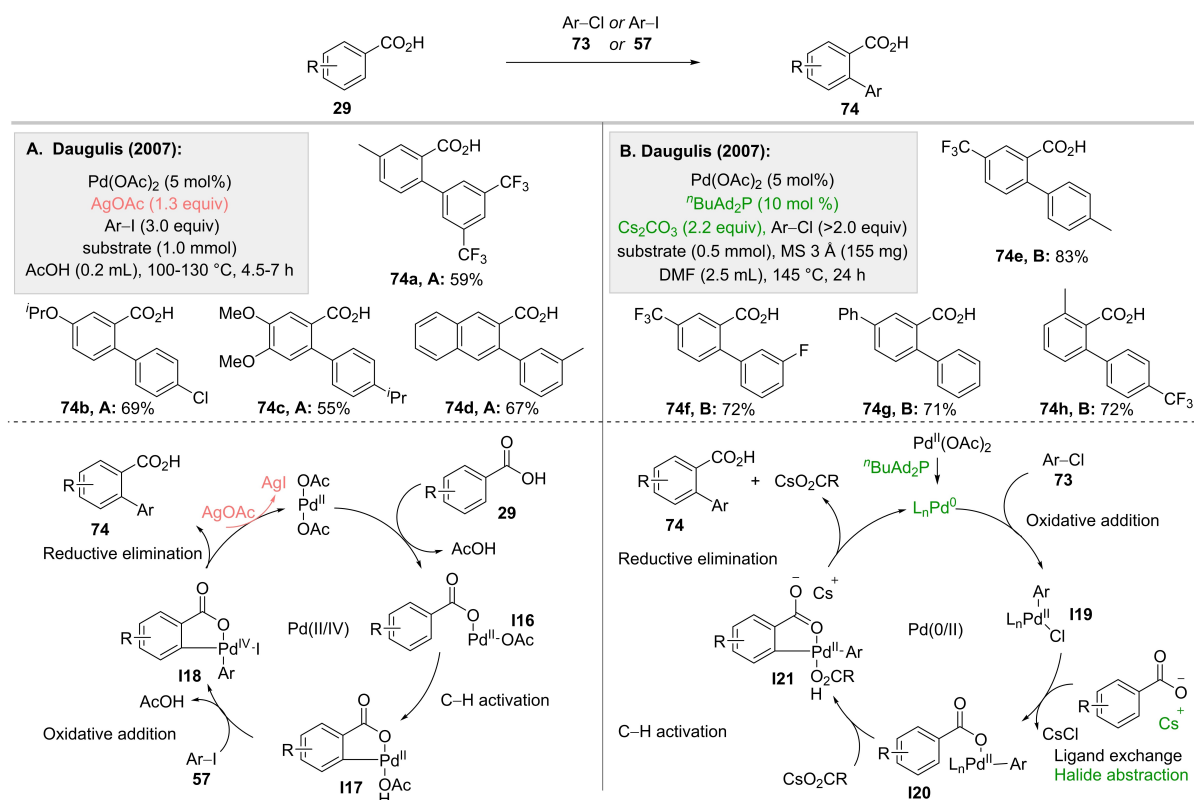
In the second protocol, the authors propose that Pd⁰ undergoes an oxidative addition with the aryl chloride to generate **I19** with a +2 oxidation state of Pd. Subsequently, a cesium salt of the substrate enters the catalytic cycle and the chloride gets abstracted by cesium to generate **I20**, which 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 for maintaining 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.

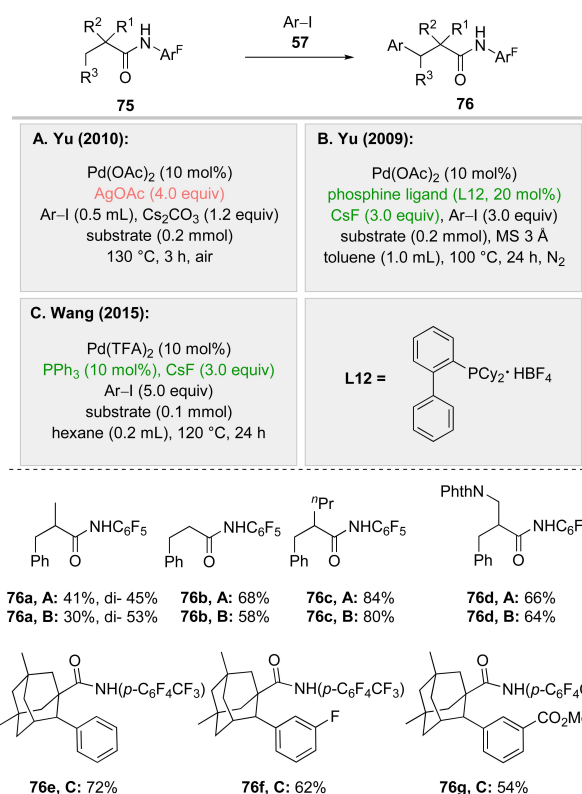
The concept was further extended to C–H functionalization of carboxylic acid derivatives. In 2010, the group of Yu reported a Pd-catalyzed C(sp³)–H arylation of amides

employing –CONHC₆H₅ 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 yields employing both the Pd^{II/IV} and Pd^{0/II} catalytic cycle. In 2015, Wang and co-workers applied the same strategy of using phosphine ligand and –CONHC₆H₅ as the DG for the arylation of the adamantyl scaffold (Scheme 38C).^[128] The products **76e–g** were 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 regeneration. The TDG reacts with the free amine to

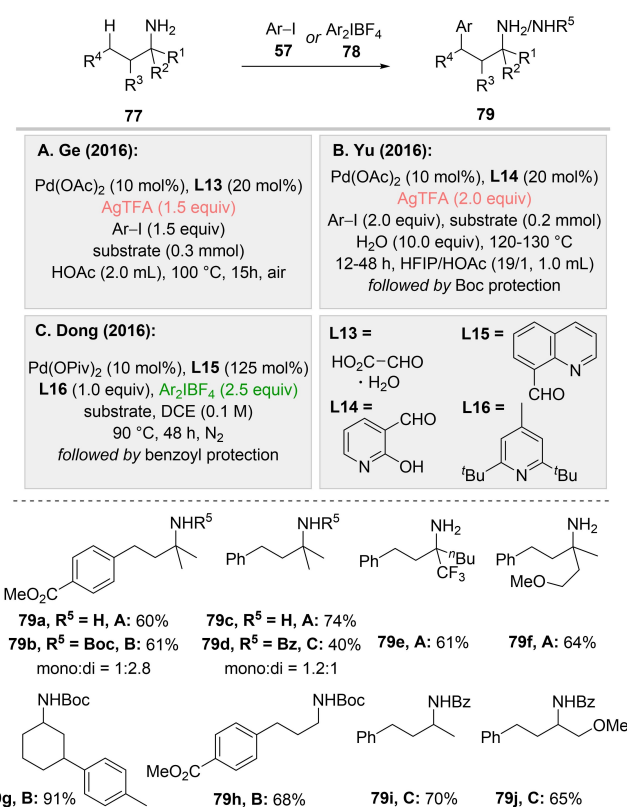




Scheme 38. A) Pd-catalyzed C(sp³)-H arylation of amides with silver additive in a Pd^{II/IV} cycle.^[126] B) Pd-catalyzed C(sp³)-H arylation of amides without silver additive.^[127] C) Pd-catalyzed methylene C(sp³)-H arylation of the adamantyl scaffold.^[128]

generate an imine-based DG in situ, which then directs a selective γ -C-H activation.

The products **79a** and **79c** were formed in 60% and 74% yield, respectively. Trifluoromethyl- and methoxy-containing substrates produced **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 regeneration. 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 the monoarylation 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 Ar₂IBF₄ as the arylating reagent (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 was tertiary. The products **79i-j**, derived from an α -non-tertiary amine, were formed with good to excellent efficiency.

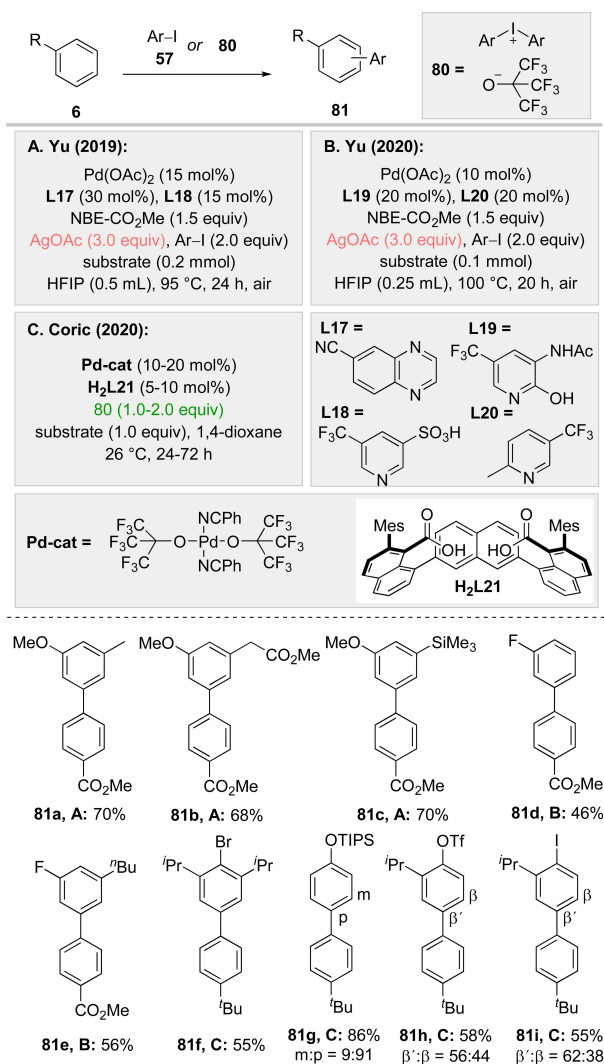


Scheme 39. A) Pd-catalyzed C-H arylation of primary aliphatic amines enabled by a TDG.^[129] B) Pd-catalyzed γ -C(sp³)-H arylation of free amines using a TDG.^[130] C) Silver-free Pd-catalyzed γ -C(sp³)-H arylation of free amines using a TDG.^[131]

In 2019, Yu and co-workers reported a Pd-catalyzed *meta*-C-H arylation of electron-rich arenes employing NBE-CO₂Me (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 co-workers replaced the silver additive by employing a modified reagent **80**, which does not contain halide ions (Scheme 40C).^[134]

The authors used the novel concept of spatial anion control to design catalytic sites for C-H bond activation, and achieved non-directed 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 analogues based on the use of silver as halide scavenger exist.^[135]



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]

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 the 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.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: C–H Activation • Catalysis • Electrosynthesis • Silver-Additives • Sustainability

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