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Green strategies for transition metal-catalyzed C–H activation in molecular syntheses

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Transition metal catalyzed C–H activation has surfaced as a powerful tool to improve the efficacy of molecular synthesis. Last two decades have witnessed a considerable progress in the activation of otherwise inert C–H bonds. However, during recent years, focus has shifted to address rising concerns to achieve high levels of resource economy in molecular syntheses. Herein, we discuss the advent and recent emerging strategies to improve the sustainability and environmentally benign nature of C–H activation manifolds.

The emergence of resource-economical, environmentally-benign strategies is one of the primary objectives in the field of organic synthesis for the construction of structurally complex and diverse molecules.¹ For instance, the tremendous progress in transition metal-catalyzed coupling reactions has propelled this discipline, enabling diverse applications in industries as well as in academia.² However, the pre-functionalization of starting materials and the formation of undesired byproducts jeopardize the overall efficiency of this approach. In stark contrast, catalyzed C–H activations³ has been recognized as an increasingly powerful alternative in terms of step- and atom-economy for the assembly of complex molecules,⁴ with transformative applications to among others late-stage diversification,⁵ material sciences,⁶ and pharmaceutical industries.⁷ This approach avoids the use of pre-functionalized starting materials, such as sensitive organometallic reagents, thereby preventing additional steps for pre-functionalizations and concurrent undesired waste generation.

Recent attention has shifted to improve the overall sustainability of the C–H activation approach using greener and more resource-economical strategies thus enabling lower E-factors.⁸ The use of non toxic, inexpensive Earth-abundant 3d metal catalysts⁹ as well as alternative energy¹⁰ sources are particularly attractive for environmentally benign transformations. Therefore, in this review we are focusing on the recent developments in the design of enabling green strategies for otherwise activation of the inert C–H bonds towards improved sustainability and resource-economy.¹¹

Environmentally-benign solvents

The tremendous progress of transition metal-catalysis is associated with an environmental disadvantage, because the use of organic solvents generates major amounts of waste, both in the chemical and pharmaceutical industries.¹² Unfortunately, the commonly used organic solvents are volatile, toxic and flammable, which potentially, constitutes a major safety hazard that is considered undesirable for large production.¹³ Therefore, environmentally-benign solvents are in high demand for transition metal-catalyzed C–H activations as a sustainable alternative.^{13d,g,14}

The application of environmentally-benign solvents¹⁵ in transition metal-catalyzed C–H activation is attractive, because they are readily available from biomass feedstocks and generally less toxic with high biodegradability, minimizing the environmental footprints.^{14b,16} Apart from bio-based solvents, water also has found applications in various C–H transformations.¹⁷

Polyethylene glycols (PEGs)

Polyethylene glycols (PEGs), available from inexpensive ethylene glycol,¹⁸ have gained considerable attention as green reaction media¹⁹ for organic transformations due to their favourable physiochemical properties and negligible toxicities. Commercially available PEGs have been recognized as promising green solvents in industries due to their non-flammable and non-corrosive nature.¹⁹

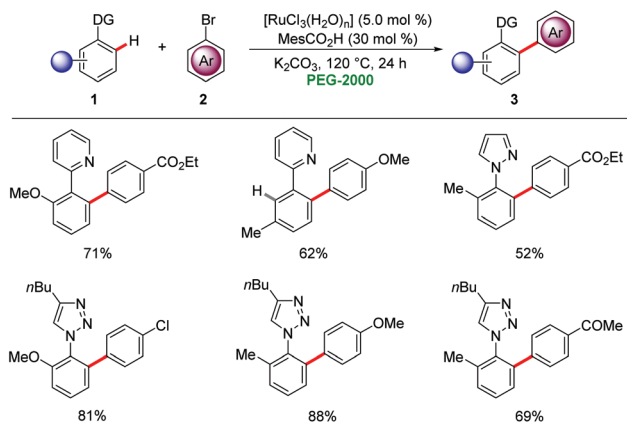
In 2009, Ackermann reported on the first transition metal-catalyzed C–H arylations in PEGs as reaction media (Scheme 1).²⁰ Chelation-assisted C–H arylations were achieved by the combination of catalytic amounts of [RuCl₃(H₂O)_n] and a co-catalytic amount of MesCO₂H (2,4,6-trimethylbenzoic acid) to furnish the desired biaryls **3** in high yields. Various

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Scheme 1 Ruthenium-catalyzed C–H arylation in PEG-2000.

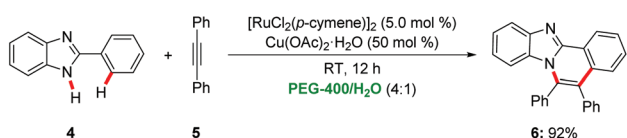
arenes **1** were arylated in a regioselective fashion by chelation-assisted ruthenium catalysis.

In a recent study, Li disclosed a related arylation of heteroarenes *via* C–H bond activation in PEG-400 with recyclable and inexpensive $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ ²¹ as the catalyst.²²

A green synthesis of benzimidazoisoquinolines²³ **6** was reported by Chandrasekhar *via* a ruthenium-catalyzed alkyne annulation with 2-aryl benzimidazoles **4** in a PEG-400/water reaction mixture at room temperature in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as oxidant (Scheme 2).²⁴ Notably, the catalyst could be recycled without significant loss of catalytic efficiency. In contrast, when using toluene as the solvent a reaction temperature of 111 °C was required.

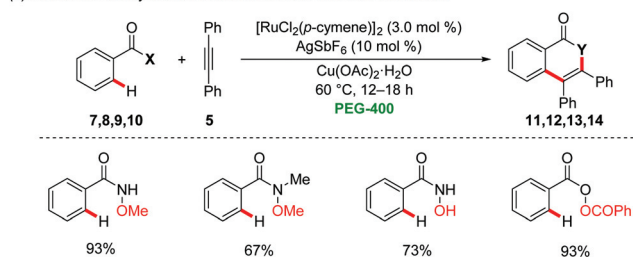
Bhanage employed recently a recyclable ruthenium/PEG-400 catalytic system for the oxidative annulation with internal alkynes **5** *via* directed C–H activation for the synthesis of isoquinolinones, isocoumarins, and *N*-methyl isoquinolinones²⁵ by the cleavage of C–H, N–O and O–O bonds (Scheme 3a).²⁶ Likewise, the oxidative alkenylation of *N*-methoxy-*N*-methylamides **8** with substituted styrenes **15** was achieved (Scheme 3b). Interestingly, the recyclability test for the ruthenium catalyst and PEG-400 provided satisfactory results without loss of the catalytic efficiency. The product isolation was conducted by extraction with diethyl ether, along with column chromatography using toluene and ethyl acetate as the eluents. In a recent study, the same group extended the approach towards *N*-tosylhydrazones for the synthesis of isoquinolinones *via* C–H/N–N activation.²⁷

In a related study, Cai reported on the synthesis of phthalides by recyclable ruthenium-catalyzed oxidative C–H alkeny-

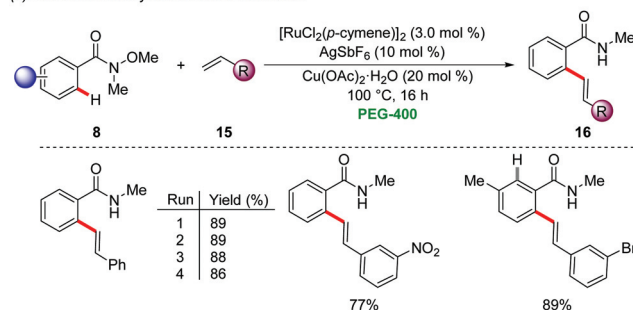


Scheme 2 Ruthenium-catalyzed oxidative annulation with alkynes **5** in PEG-400/ H_2O .

(a) Ruthenium catalyzed annulation of amides and acid derivatives



(b) Ruthenium catalyzed oxidative olefination

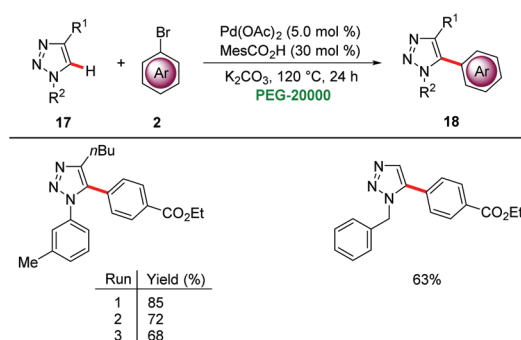


Scheme 3 Ruthenium-catalyzed oxidative annulation and olefination of amides in PEG-400.

lations in a PEG-400/water (3 : 2) mixture. Various substituted benzoic acids and electron-deficient alkenes were amenable substrates for the alkenylation to afford the desired phthalides in good yields.²⁸

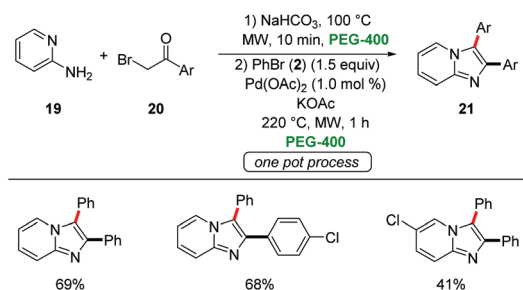
Ackermann demonstrated that PEGs are viable green reaction media for palladium-catalyzed C–H arylations. Co-catalytic amounts of MesCO_2H significantly improved the reaction efficiency for the direct arylation of triazoles **17** under aerobic conditions with 5.0 mol% of $\text{Pd}(\text{OAc})_2$ in PEG-20000 (Scheme 4).²⁰ The catalyst was found to be easily reusable, taking advantage of the physicochemical properties of PEG-20000 without significant loss in activity.

Berteina-Raboin developed a sequential one-pot synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines **21** starting from easily-accessible 2-amino pyridines **19**, α -bromo ketones **20** and aryl bromides **2** in PEG-400 (Scheme 5).²⁹ The use of $\text{Pd}(\text{OAc})_2$ as the catalyst and KOAc as the base at 220 °C under microwave irradiation for 1 h gave the optimal results.



Scheme 4 Palladium-catalyzed C–H arylation in PEG-20000.

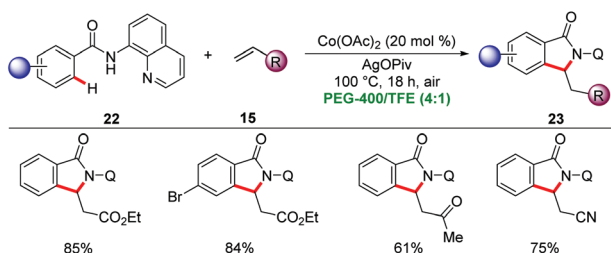




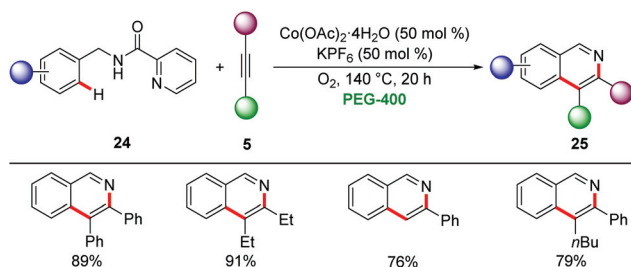
Scheme 5 One pot sequential approach for palladium-catalyzed arylation in PEG-400.

In 2015, Ackermann showed PEG-400 to be suitable solvent for Earth-abundant 3d metal-catalyzed C–H activation. Here, a combination of inexpensive $\text{Co}(\text{OAc})_2$ and sacrificial oxidant $\text{Mn}(\text{OAc})_2$ or AgOPiv afforded isoindolinone derivatives **23** from aromatic benzamides **22** by C–H/N–H annulation with alkenes **15** under aerobic conditions (Scheme 6).³⁰ Notably, organic solvents failed to provide the desired products in synthetically useful yields, highlighting the unique potential of PEG-400 as the reaction media. Several sensitive functional groups were well tolerated, providing versatile access to substituted isoindolinones **23**.

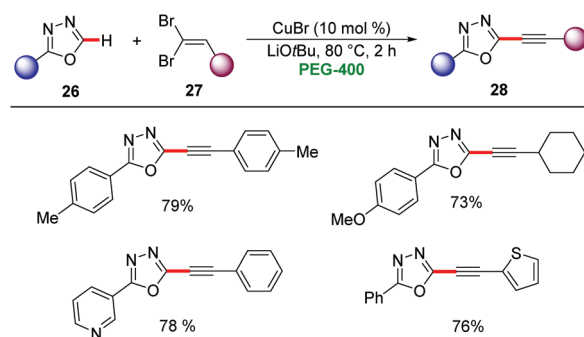
Later, Cui employed picolinamides as a traceless directing group for the cobalt-catalyzed synthesis of isoquinonlines **25** via C–H/N–H activation using oxygen as terminal oxidant (Scheme 7).³¹ The reaction proceeded efficiently for a broad range of substrates including terminal and internal alkynes **5** with excellent regioselectivities.



Scheme 6 Cobalt-catalyzed C–H/N–H annulation in PEG-400/TFE.



Scheme 7 Cobalt-catalyzed synthesis of isoquinonlines **25** in PEG-400.



Scheme 8 Copper-catalyzed alkynylation in PEG-400.

Furthermore, copper-catalysis was amenable for C–H alkylation in PEG-400. Here, catalytic amounts of CuBr were used for the kinetic C–H acidity guided alkynylation of 1,3,4-oxadiazoles **26** by *gem*-dibromoalkenes **27** to afford the desired products **28** in moderate to good yields (Scheme 8).³²

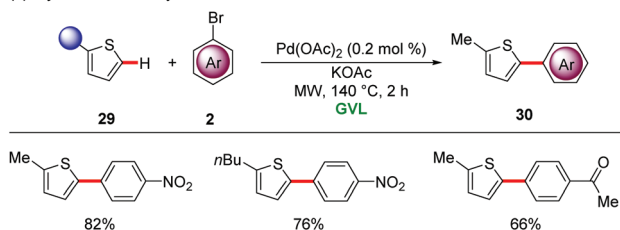
For the isolation of the desired products, simple extraction with ethereal solvents was carried out, followed by column chromatography.

γ -Valerolactone (GVL)

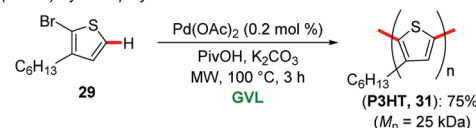
γ -Valerolactone's characteristic features include a high boiling point, a low vapour pressure, low toxicity along with high miscibility with water and most importantly it is highly biodegradable.³³ This environmentally-benign aprotic solvent is produced from levulinic acid which is itself derived from lignocellulosic biomasses.³⁴ Due to its physicochemical properties, GVL has found widespread applications as an alternative to hazardous organic solvents in transition metal-catalyzed transformations, including cross-coupling reactions,³⁵ hydroformylations³⁶ and aminocarbonylations.³⁷ In contrast, step-economical catalyzed C–H activations in renewable biomass derived solvent GVL have only recently been developed.

For instance, Larini and Cravotto disclosed the palladium-catalyzed C–H arylation of heterocycles **29** with aryl halides **2** in GVL as solvent (Scheme 9a).³⁸ Remarkably, only 0.2 mol%

(a) arylation of heterocycles



(b) C–H (hetero)arylation polymerization



Scheme 9 Palladium-catalyzed C–H arylation in GVL.



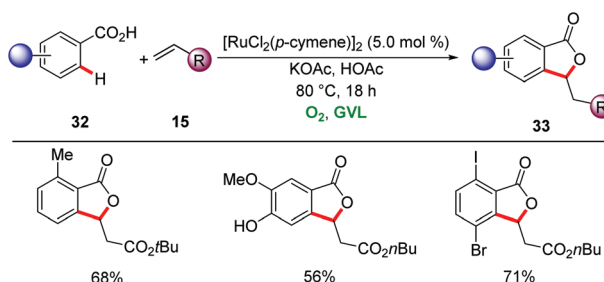
$\text{Pd}(\text{OAc})_2$ was sufficient for efficient regioselective C2 arylation of thiophenes **29** under microwave irradiation at 140 °C. The reaction conditions proved applicable to palladium-catalyzed synthesis of poly(3-hexyl)thiophene **31** by C–H (hetero)arylation polymerisation (Scheme 9b).

More cost-effective ruthenium-catalysts enabled the synthesis of phthalides **33** from aryl carboxylic acids **32** and alkenes **15** by Ackermann in biomass-derived GVL using molecular oxygen as the sole oxidant (Scheme 10).³⁹ The oxidative double C–H functionalization was characterized by high positional selectivity and functional group tolerance, with sensitive bromo, iodo and hydroxyl groups being tolerated. The reaction mixture was extracted with H_2O and *n*-hexane/MTBE to remove the GVL.

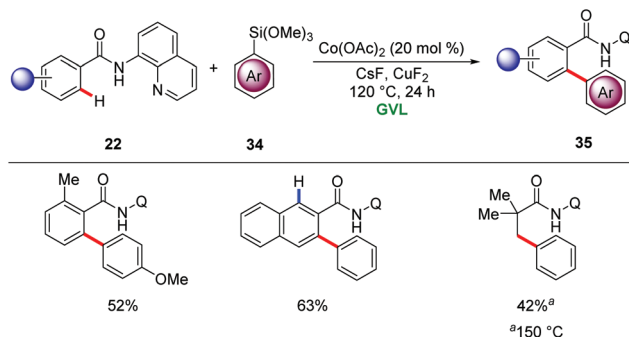
In a recent study, the same group found GVL as an effective solvent for the ruthenium(II)-catalyzed distal C–H alkenylation of arylacetamides *via* weakly coordinating amide assistance.⁴⁰

Ackermann also demonstrated GVL as a suitable solvent for Earth abundant 3d metal-catalyzed C–H activations. Thus, an *ortho* C–H arylation of benzamide **22** in GVL was realized (Scheme 11).⁴¹ In addition, challenging $\text{C}(\text{sp}^3)\text{--H}$ bond arylations were also achieved with arylsiloxanes in GVL as reaction media albeit at a higher temperature.

Furthermore, GVL has also found applications to heterogeneous palladium-catalyzed C–H activations as well as in the field of electrochemistry to enhance the sustainability in molecular synthesis (*vide infra*).



Scheme 10 Ruthenium-catalyzed green synthesis of phthalides **33** in GVL.



Scheme 11 Cobalt-catalyzed *ortho*-C–H arylation of benzamide **22** in GVL.

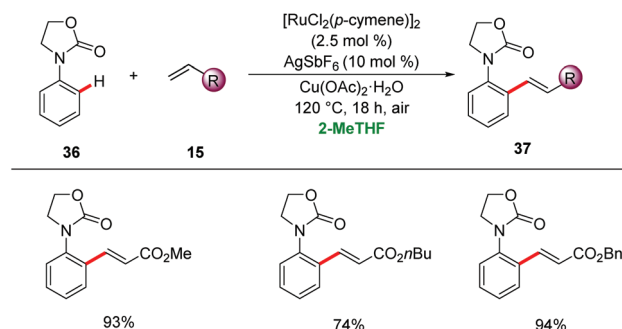
2-Methyltetrahydrofuran (2-MeTHF)

2-Methyltetrahydrofuran (2-MeTHF) is largely produced from renewable lignocellulosic biomasses.⁴² Favourable physicochemical properties of 2-MeTHF render it as an eco-friendly alternative to THF with lower miscibility with water and higher boiling point.⁴³ In this section, we summarize the potential of 2-MeTHF as a green reaction media for catalyzed C–H activation.

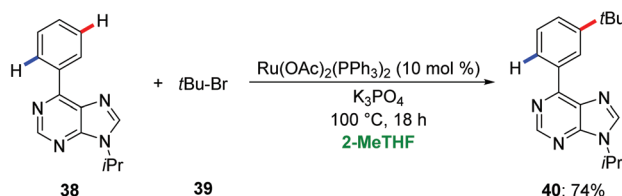
McMullin, Williams and Frost disclosed *ortho*-C–H alkenylation of a variety of *N*-aryloxazolinone **36** using $[\text{RuCl}_2(p\text{-cymene})]_2$ as a catalyst in 2-MeTHF (Scheme 12).⁴⁴ 2-MeTHF showed superior efficacy to typically used organic solvents for the desired alkenylated product with high levels of monoselectivity.

Ackermann employed 2-MeTHF for ruthenium-catalyzed remote *meta*-C–H functionalization of purines **38**.⁴⁵ Hence, the arene-ligand free complex $[\text{Ru}(\text{OAc})_2(\text{PPh}_3)_2]$ enabled the *meta*-C–H alkylation of purines **38** *via* a ruthenium(II/III) manifold with excellent levels of chemo- and *meta*-selectivity (Scheme 13).

Sommer demonstrated a sustainable synthesis of n-type conjugated copolymers PNDIT2 **43** from 2,6-dibromonaphthalene diimide **42** using palladium-catalyzed direct arylations in 2-MeTHF (Scheme 14).⁴⁶ The palladium catalyst delivered the desired product PNDIT2 **43** in 98% yield and with molecular weight of $M_n \sim 20$ kDa. Later, the synthesis of benzodithiophene-*alt*-diketopyrrolopyrrole copolymer was achieved *via* a palladium-catalyzed direct heteroarylation polymerization (DHAP) in 2-MeTHF.⁴⁷

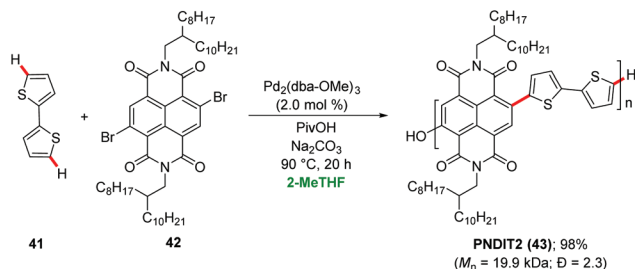


Scheme 12 *ortho*-C–H alkenylation of a variety of *N*-aryloxazolinone **36** in 2-MeTHF.



Scheme 13 Ruthenium-catalyzed *meta*-selective C–H alkylation in 2-MeTHF.





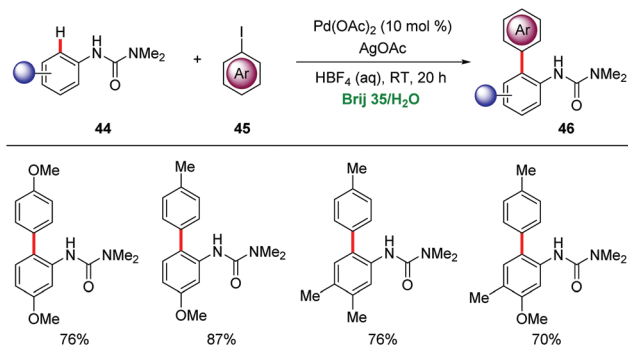
Scheme 14 Palladium-catalyzed direct C–H arylation polymerization in 2-MeTHF.

The Cook group employed an inexpensive and non-toxic iron catalyst for the *ortho*-alkylation of aromatic amides with alkyl bromides in biomass-derived 2-MeTHF as a green reaction media *via* bidentate 8-AQ assistance. The combination of catalytic amounts of Fe(acac)₃ as catalyst and dppe as ligand enabled primary and secondary alkylations in high yields and excellent regioselectivities.⁴⁸

Water:micellar catalysis

Water is nontoxic, non-flammable, non-corrosive, naturally abundant and cost-efficient, providing key advantages as a sustainable, safe and environmentally-benign solvent.¹⁷ The eco-friendly nature of water emphasizes its significant potential as reaction media for organic transformations, particularly in combination with non-renewable organic solvents for the workup procedures. However, the solubility and instability of organic or organometallic compounds in water often imposes significant limitations for the use of water as a solvent.⁴⁹ Therefore, surfactants have emerged as enabling tools for realizing homogenous metal catalysis in water. In this section, we discuss micellar catalysis for transition metal-catalyzed C–H activations in water.

A mixture of 2% surfactant/H₂O was employed in the palladium-catalyzed C–H arylations of anilides **44** to provide diversely substituted biaryl compounds **46** (Scheme 15).⁵⁰ Brij 35 was found by Lipshutz as an efficient surfactant for the C–H arylation with AgOAc as a stoichiometric additive at room temperature.



Scheme 15 Palladium-catalyzed C–H arylation of anilides **44** in Brij 35/H₂O.

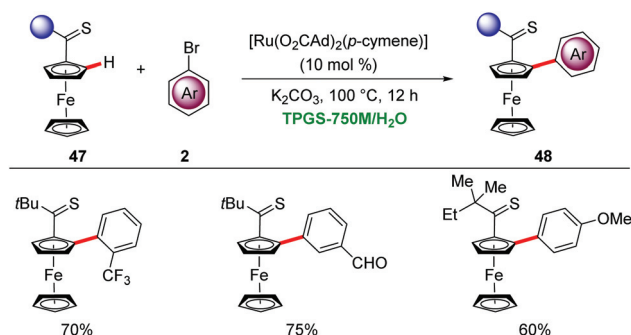
Later, *ortho*-acylations of anilides were also achieved in an aqueous solution of a surfactant *via* a palladium-catalyzed cross dehydrogenative coupling between anilides and aromatic aldehydes.⁵¹

Ackermann devised a ruthenium-catalyzed C–H arylation in water through micellar catalysis.⁵² The presence of a single component ruthenium catalyst and K₂CO₃ as base gave optimal results for the C–H arylation of sensitive ferrocenes **47** through weak thioketone assistance in a solution of 2% TPGS-750 in H₂O (Scheme 16).

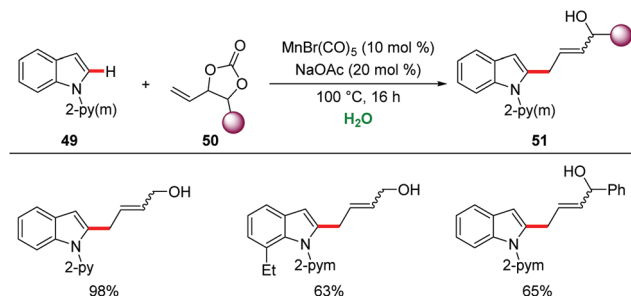
Water itself has been found applications as a reaction medium for a variety of C–H bond functionalization reactions, catalyzed by palladium,⁵³ rhodium,⁵⁴ iridium⁵⁵ and ruthenium.⁵⁶ Similarly, water has also been found as an amenable solvent for Earth-abundant 3d metal-catalyzed C–H functionalization.⁵⁷

In this context, in 2017, decarboxylative C–H/C–O functionalizations by manganese catalysis in H₂O were realized by Ackermann.⁵⁸ Air- and water-tolerant manganese(I) catalysis enabled versatile C–H allylations of indole **49** with high levels of chemo- and regioselectivity (Scheme 17).

In addition, water-tolerant manganese(I)-catalysis was easily expanded to the unprecedented C–C activation of alcohol, leading to the allylated and hydroarylated arenes.⁵⁹ It is noteworthy that similar reactivity of sequential C–H and C–C/C–Het bond activation was demonstrated by Glorius under neat reaction conditions.⁶⁰



Scheme 16 Ruthenium-catalyzed C–H arylation in TPGS-750M/H₂O.



Scheme 17 Manganese(I)-catalyzed C–H allylation in H₂O.



Generally speaking, green solvents have emerged as viable reaction medium for C–H activation reactions. However, to unleash the full potential, toxic organic solvents should ideally be avoided during the workup procedures for the isolation and purification of the target products.

Heterogeneous catalytic system

Despite significant advances in C–H functionalization with homogenous catalysts, a major challenge for large-scale applications is associated with the limited recyclability of the often expensive catalysts and difficult removal of undesired trace metal impurities.⁶¹ Hence, heterogeneous catalysts are in high demand for sustainable molecular synthesis. Further recyclable heterogeneous catalysts provide an opportunity for innovative transformations through the design of hybrid metal catalysts.⁶²

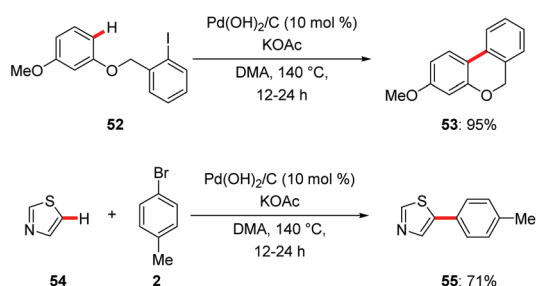
An early report on C–H arylations by Fagnou proved viable with the commercially available heterogeneous palladium catalyst Pd(OH)₂/C.⁶³ Pearlman's catalyst allowed for efficient intra- and intermolecular C–H arylation with aryl iodides **52** and bromides **2** (Scheme 18). Detailed experimental studies revealed *in situ* formation of the active homogenous palladium species. In a related work, C-2 selective arylations of NH-free pyrroles were realized with the Pearlman's catalyst.⁶⁴

In 2015, the Glorius group disclosed C–H arylations of triphenylene, naphthalenes and anthracene with the combination of diaryliodonium salts and catalytic amounts of Pd/C.⁶⁵

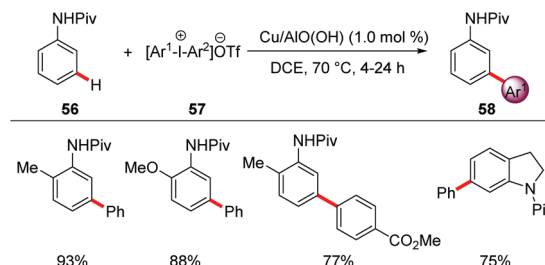
Aimed at improving catalyst recyclability, chemists have focused their attention on using different types of heterogeneous palladium sources for efficient arylation.⁶⁶ Along with heterogeneous palladium sources, the addition of catalytic amounts of copper has also been beneficial for the regio- and chemoselective arylations.⁶⁷

For example, a reusable copper-based catalyst system was used for the direct arylation of anilides **56** with *meta*-selectivity using reusable heterogeneous copper nanoparticles (Scheme 19).⁶⁸

In subsequent studies, Wang further achieved the C–H arylation of various heterocycles in the presence of a heterogeneous catalyst CuO nano spindles in diglyme.⁶⁹ Furthermore, heterogeneous MOF based copper catalysts have found suitable application for the direct C–H arylation of heteroarenes.⁷⁰



Scheme 18 Heterogeneous palladium-catalyzed C–H arylation.



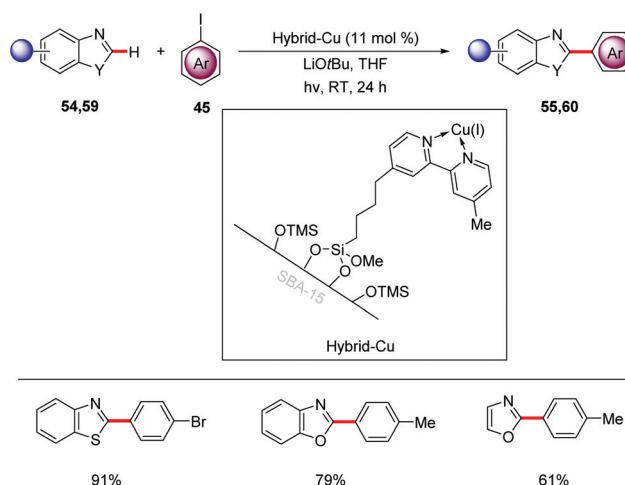
Scheme 19 *meta*-C–H arylation of anilides **56** with heterogeneous copper nanoparticles.

Very recently, Ackermann achieved heterogeneous photo-induced copper-catalyzed C–H arylation of heteroarenes **54**, **59** with aryl iodides **45** at room temperature (Scheme 20).⁷¹ This photo-catalysis strategy proved to be highly robust leading to minimal leaching and enabling the recycling of the catalyst without loss of its efficiency.

While a significant number of heterogeneous catalytic based systems are based mainly on the arylation of aromatic substrates,⁷² recent interest on other types of C–C and C–Het bond formation reactions using recyclable heterogeneous catalysis has gained considerable attention.⁷³

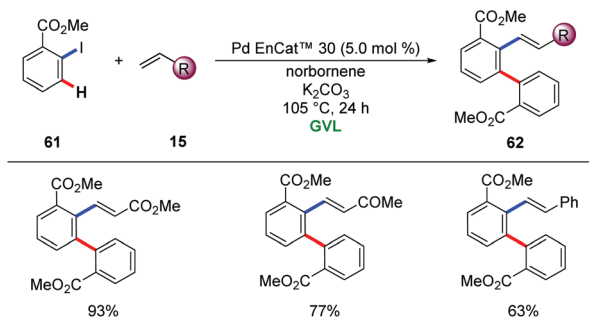
In 2016, Ackermann and Vaccaro realized the heterogeneous palladium catalysis for the Catellani reaction in the renewable biomass derived green solvent GVL.⁷⁴ The authors employed two different heterogeneous palladium sources, namely, Pd/Al₂O₃ and Pd EnCat™ 30, to enable difunctionalization with a variety of alkenes **15**, providing access to diverse *meta*-substituted arenes **62**. Notably, biomass-derived GVL proved to be the superior solvent among other typical organic solvents (Scheme 21).

The same groups reported heterogeneous Pd/C for the C–H arylation of 1,2,3-triazoles with aryl bromides in GVL. Co-catalytic amount of MesCO₂H and CF₃CO₂K were used as ligand



Scheme 20 Heterogeneous copper-catalyzed photo-induced C–H arylation.





Scheme 21 Heterogeneous palladium-catalyzed Catellani reaction in GVL.

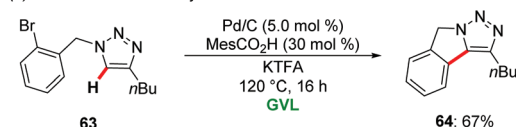
and base respectively for the direct arylation to provide access to fully decorated 1,2,3-triazoles in good to excellent yields with good functional group tolerance. Interestingly, the heterogeneous palladium catalyst was also applicable for the intramolecular C–H arylation of the substrate **63** to afford isoindole motif **64** in good yield (Scheme 22a).⁷⁵ Later, Ackermann and Vaccaro further extended the heterogeneous palladium-catalyzed direct C–H functionalization of 1,2,3-triazoles **65** using continuous flow regime in GVL as a green reaction media (Scheme 22b).⁷⁶

The Glorius group employed Pd/Al₂O₃ as a heterogeneous catalyst for the direct C–H thiolation and selenation reactions.⁷⁷ The combination of Pd/Al₂O₃ and CuCl₂ in dichloroethane or toluene gave optimal results for the synthesis of sulfenylated **69** and selenylated products **70** (Scheme 23).

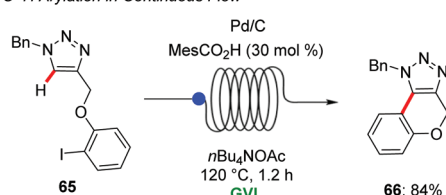
Furthermore, C–H cyanations were achieved by heterogeneous palladium(II) and magnesium–lanthanum mixed oxide.⁷⁸ The combination of NH₄HCO₃ and DMSO served as cyano source to allow for regioselective C–H cyanations of heteroarenes **1** (Scheme 24).

C–H halogenations were achieved using an easily synthesized Pd@MOF nano catalysts by Martín-Matute.⁷⁹ The halogenation reaction was conveniently performed with the robust MOF-based heterogeneous catalysts to deliver the desired products **73** and **74** under very mild conditions with excellent mono- and di-selectivities (Scheme 25). It is worth

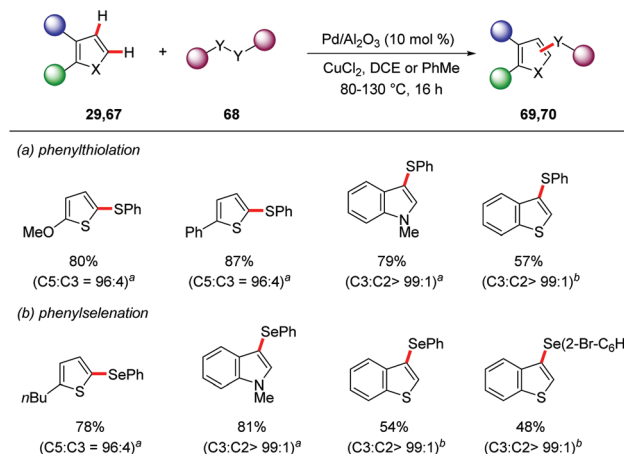
(a) Intramolecular C–H arylation



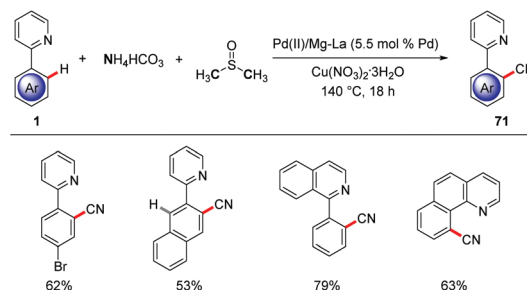
(b) C–H Arylation in Continuous Flow



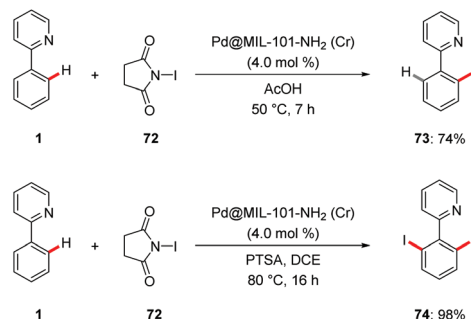
Scheme 22 Heterogeneous palladium-catalyzed C–H arylation in GVL.



Scheme 23 Heterogeneous palladium-catalyzed direct C–H thiolation and selenylation. ^a DCE, 80 °C, ^b PhMe, 130 °C.



Scheme 24 Heterogeneous palladium-catalyzed C–H cyanation.

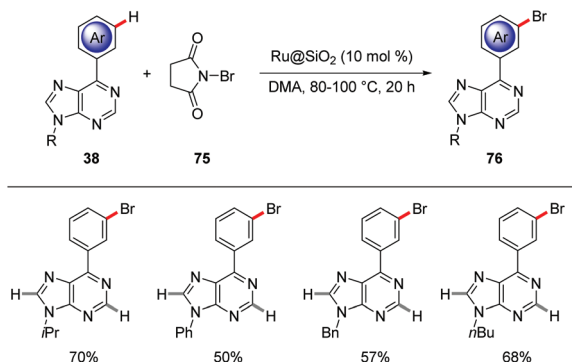


Scheme 25 C–H halogenation by Pd@MOF nano catalysts.

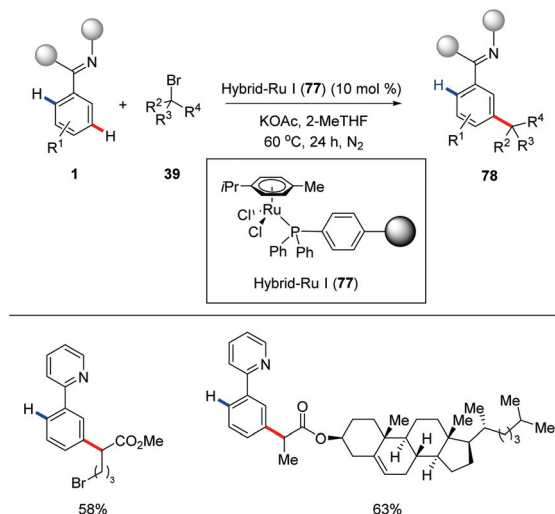
mentioning that the MOFs were recycled and reused without loss of efficacy.

meta-C–H Brominations of aryl substituted purine bases **38** were devised by Ackermann using a heterogeneous ruthenium catalyst (Scheme 26).⁸⁰ The robust heterogeneous Ru@SiO₂ catalyst proved broadly applicable for the *meta*-selective bromination with NBS with excellent level of positional selectivity to furnish the *meta*-brominated purine bases **76**. Interestingly, the catalyst was easily recovered and reused without loss of catalytic efficiency.





Scheme 26 *meta*-C–H Bromination using heterogenous ruthenium catalyst.



Scheme 27 *meta*-C–H Activation by recyclable hybrid-ruthenium catalysis.

In a very recent study, the same group reported the first recyclable hybrid-ruthenium catalysis for distal *meta*-C–H activation (Scheme 27).⁸¹ It is noteworthy to mention that *meta*-C–H alkylation was achievable under photoinduced conditions with the hybrid-ruthenium-catalysis manifold.

To extend the synthetic utility of the heterogenous catalysts, C–H oxygenation⁸² and C–H borylation⁸³ were also developed with easily recyclable heterogenous palladium and iridium catalysts respectively.

Overall, significant momentum was gained in C–H activation by heterogenous catalysis to reduce the undesired trace metal impurities, and enable the efficient recycling and reuse of the transition metal catalysts.

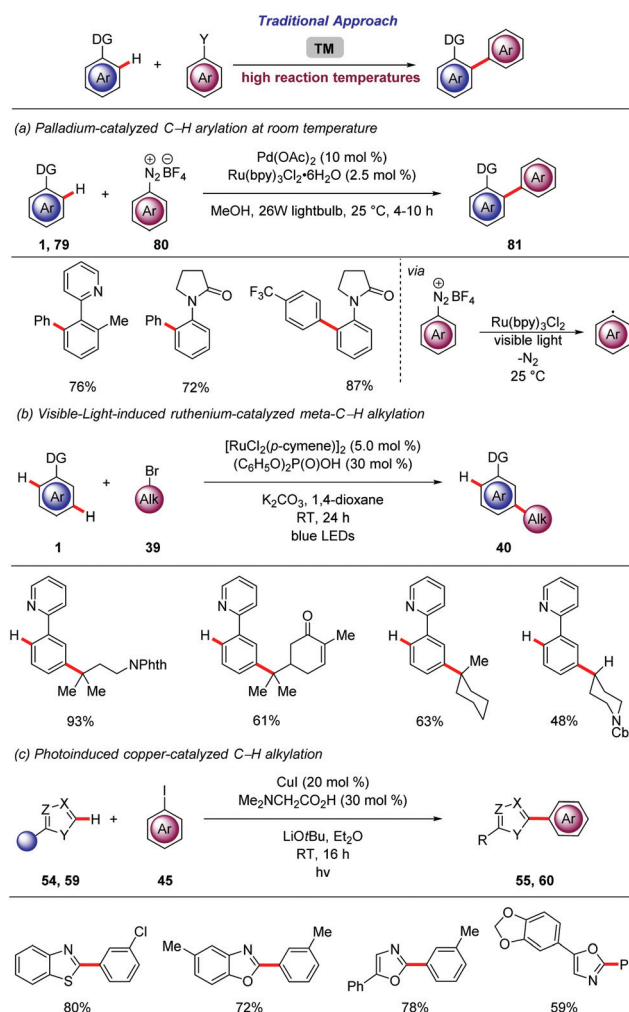
Photocatalytic C–H activation

In the last fifteen years, photochemistry has witnessed a renaissance. Thus, photocatalysis was identified as a mild and

efficient tool for challenging transformations.⁸⁴ The merger of photocatalysis with transition metal-catalyzed⁸⁵ cross coupling unlocked a dormant area of the chemical space.⁸⁶

The generation of aryl radicals from aryldiazonium salts and subsequent addition of these radicals to various acceptors, in a Meerwein type arylation, is well established.⁸⁷ In 2011, Sanford merged the versatile palladium-catalyzed C–H activation regime with photocatalytic generation of aryl radical (Scheme 28a).⁸⁸ The use of Ru(bpy)₃Cl₂ as an effective photocatalyst for the controlled generation of the aryl radicals under mild reaction conditions was crucial. The *ortho*-arylation of arenes bearing various directing groups was achieved by means of catalytic amounts of Pd(OAc)₂ and Ru(bpy)₃Cl₂ in MeOH, at room temperature under CFL (compact fluorescent lamp) irradiation.

The proximity-induced regime for the functionalization of inert C–H bonds is restricted to the *ortho* position in relation to the directing group. To bypass this limitation many strategies have been developed⁸⁹ including, use of templates,⁹⁰ non-covalent interactions between the ligand and the sub-

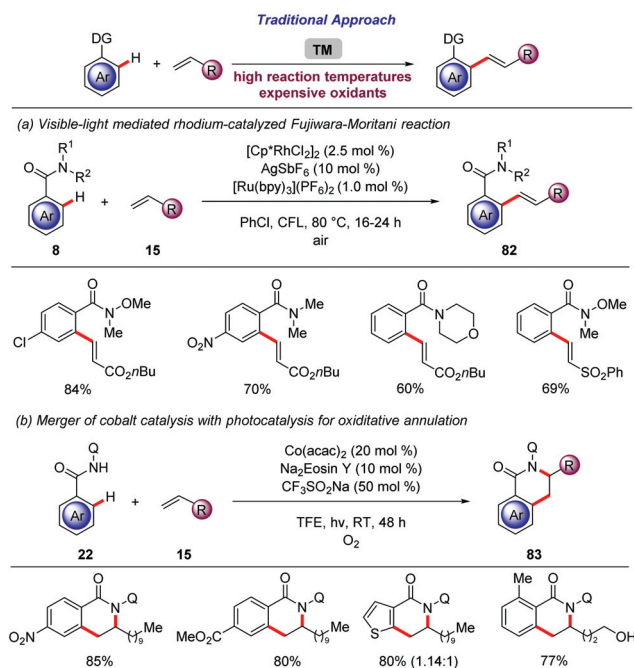


Scheme 28 Redox-neutral photocatalytic C–H activation.



strate,⁹¹ mediators⁹² for Catellani type reaction⁹³ and σ -activation.⁹⁴ Generally, these reactions require elevated reaction temperatures that restrict the synthetic utility of those highly sought transformations. Thus, Ackermann demonstrated that the *meta*-C–H functionalization regime that have already shaped into a powerful strategy for remote functionalization can be further improved by the merger with photocatalysis.⁹⁵ Thus, the *meta*-selective C–H alkylation of arenes **1** was achieved under exceedingly mild reactions conditions *via* visible-light irradiation at room temperature, without the aid of an exogenous photocatalyst (Scheme 28b). After extensive optimization, catalytic amounts of $[\text{RuCl}_2(p\text{-cymene})]_2$ and $(\text{C}_6\text{H}_5\text{O})_2\text{P}(\text{O})\text{OH}$ were found to promote not only the acid-assisted C–H cycloruthenation but also the visible-light induced homolytic cleavage of the alkyl bromides **39**. With the optimized conditions in hand, the robustness of the methodology was demonstrated by the ample scope. Remarkably, compared to the previously developed ruthenium-catalyzed *meta*-C–H that require 100–140 °C, this reaction was conducted at room temperature. Subsequently, Greaney independently reported similar reactivity under blue-light irradiation.⁹⁶ The same authors exploited the visible-light irradiation for the ruthenium-catalyzed *ortho*-C–H arylation of heteroarenes. The robust C–H arylation occurred at ambient temperature, enabled by an unprecedented inner-sphere electron transfer from biscyclometalated ruthenacycles.⁹⁷ In sharp contrast, the differentiation of C–H bonds based on their electronic environment is a common strategy. Thus azoles, bearing a relatively acidic C–H bond have been functionalized, without the assistance of a chelating group, by means of various transition metals under rather forcing reaction conditions.⁹⁸ Thus, Ackermann reported on the photoinduced copper-catalyzed C–H arylation of azoles **54**, **59** at room temperature, using cost-effective CuI (Scheme 28c).⁹⁹ Detailed optimization studies revealed the essential nature of the *N,N*-dimethylglycine as a ligand and LiOtBu as a base. The mild nature and robustness of the protocol was reflected by the complete tolerance of various functional groups, the expedient and chemoselective synthesis of alkaloids. Interestingly, challenging oxazolines proved likewise to be viable substrates for this C–H arylation.

The productive merger of photocatalysis with C–H activation is not only restricted to redox-neutral reactions, but can also be expanded to oxidative reactions. The rhodium-catalyzed oxidative alkenylation of arenes bearing various directing groups is well established,¹⁰⁰ but stoichiometric amounts of oxidants are required and generally elevated temperatures are employed in order to achieve high conversion.¹⁰¹ Thus, Rueping disclosed a rhodium-catalyzed Fujiwara–Moritani reaction enabled by visible light (Scheme 29a).¹⁰² The authors reasoned that the rhodium hydride species produced after β -hydride elimination can be recycled towards the active species by a photocatalytic oxidation, where O_2 acts as the terminal oxidant. After extensive optimization, benzamides **8** were efficiently converted to the desired *E*-olefins with catalytic amounts of $[\text{Cp}^*\text{RhCl}_2]_2$, AgSbF_6 and $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$ in chlorobenzene at 80 °C under air. Under the optimized reaction



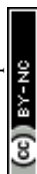
Scheme 29 Oxidative photocatalytic C–H activation.

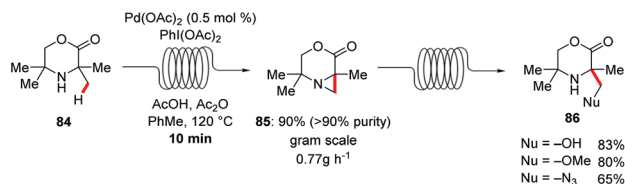
conditions a plethora of functional groups were tolerated on the arene moiety and various alkenes **15** were also employed.¹⁰³ Subsequently, Rueping and Sundararaju employed this strategy, for high valent cobalt catalysis with photocatalysis (Scheme 29b).¹⁰⁴ This approach represents a sustainable protocol with an earth-abundant cobalt catalyst in combination with an organic dye. Indeed, catalytic quantities of $\text{Co}(\text{acac})_2$ and $\text{Na}_2\text{Eosin Y}$ in combination with $\text{CF}_3\text{SO}_2\text{Na}$ in TFE were effective to promote this oxidative cyclisation at room temperature.

C–H activation in flow

A straightforward transfer of the enormous potential of C–H activation from academia to the industries is through the use of flow technology,¹⁰⁵ because flow setups improve heat and mass transfer, are generally safer as batch processes and are well suited for the use of highly reactive intermediates. Moreover, the inherent scalability of flow procedures represents an additional asset.

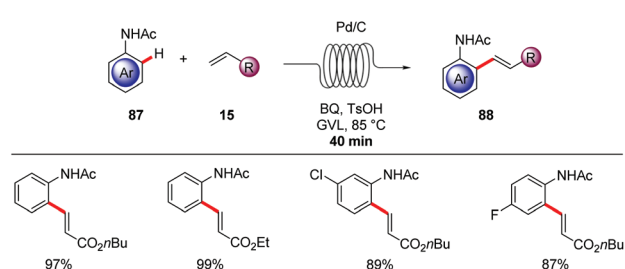
In this context, Gaunt and Lapkin developed an oxidative palladium-catalyzed C–H aziridination and subsequent ring opening in flow.¹⁰⁶ In order to transform the process from the batch conditions,¹⁰⁷ to the desired flow setup the authors performed DFT calculations and constructed a predictive kinetic model that enabled the facile transfer to the flow conditions (Scheme 30). Under the optimized reaction conditions consisting of catalytic amounts of $\text{Pd}(\text{OAc})_2$ and stoichiometric $\text{PhI}(\text{OAc})_2$, Ac_2O and AcOH , that was crucial for reducing the concentration of the off-cycle resting state of the catalyst, the desired aziridine **85** was isolated in 90% yield in only



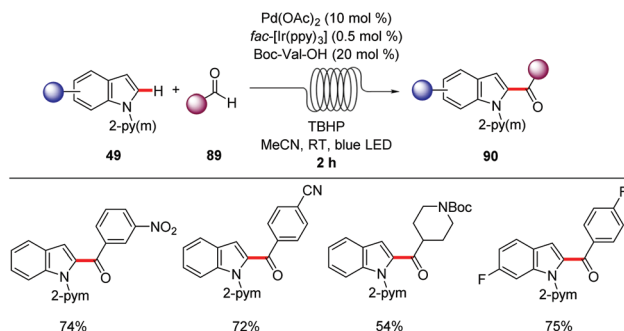


Scheme 30 Continuous-flow synthesis of aziridines.

10 minutes. In addition, the authors were able to devise a purification system in flow by connecting one column packed with a palladium scavenger and a second column with an amine scavenger. Flow technology offers unique opportunities for immobilizing a heterogeneous catalyst, enabling the facile reuse of the catalyst. Thus, after developing the directed Fujiwara–Moritani reaction catalyzed by simple palladium on carbon for batch synthesis Ackermann and Vaccaro probed the possibility of immobilizing the heterogeneous catalyst in a coil and performing the reaction in flow.¹⁰⁸ Remarkably, their batch conditions consisting of Pd/C, benzoquinone as the oxidant, *p*-toluenesulfonic acid and GVL as solvent, were easily transferred to the flow setup with the catalyst was immobilised to the coil (Scheme 31). The reaction between anilides **87** and acrylate **15** was run for 29 hours to produce up to 109 g of the alkenylated product. Control experiments demonstrated that the leaching of the palladium catalyst was minimal in GVL (up to 4 ppm) compared to other commonly used polar aprotic solvents such as DMF and NMP, clearly showcasing the enhanced durability of the heterogeneous catalyst in GVL. The high surface-area-to-volume ratio typical of flow reactors is ideal for performing photochemical reactions, since photochemical reaction are very difficult to be scaled up in batch setups, thus photochemical protocols that are developed in flow are more likely to be adopted from industries. To this end, Noël and Van der Eycken reported on the photocatalytic C-2 acylation of indole derivatives **49** under palladium catalysis with aldehydes serving as acyl radical surrogates (Scheme 32).¹⁰⁹ The authors optimized the reaction conditions for the acylation in batch, and were delighted to observe that the reaction conditions were compatible for reactions in flow as well, while observing an increased rate. With the optimized conditions in hand, consisting of catalytic amounts of Pd(OAc)₂, Boc-Val-OH, *fac*-[Ir(ppy)₃] as photocatalyst and *tert*-butyl hydroperoxide as terminal oxidant in acetonitrile, they



Scheme 31 Heterogeneous C–H alkenylations in continuous flow.

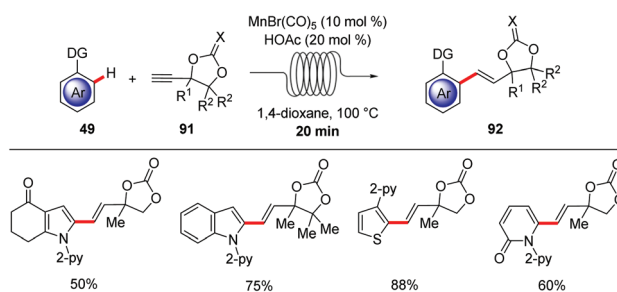


Scheme 32 C–H acylation of indoles by dual photoredox/transition metal catalysis.

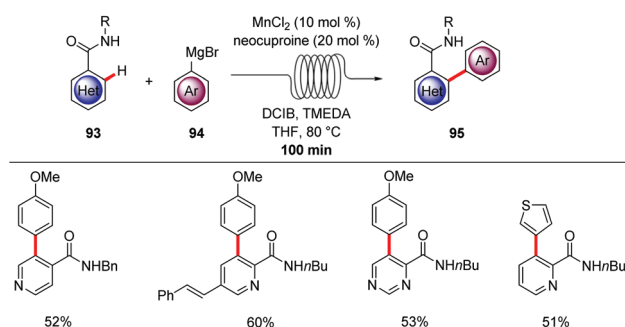
expanded the scope of the acylation in batch and in flow. Interestingly, the isolated yields were comparable but the required 2 hours, which the batch protocol called for 20 hours. In addition, the mild reaction conditions enabled the acylation with α,α -disubstituted aldehydes to occur without any noticeable decarbonylation.

Despite the fact that the majority of C–H activation protocols has been developed with precious transition metals, C–H activation by 3d-transition metals has gained immense momentum during the last 10 years, due to its cost-effective and less-toxic nature.^{9,110} Thus, in 2017 Ackermann developed the manganese(I) hydroarylation of propargylic carbonates **91** in flow (Scheme 33a).¹¹¹ Fine-tuning of the reaction conditions were required to bypass the inherent pathway for the β -oxygen elimination that leads to allene products, gratifyingly, the synergistic catalysis between MnBr(CO)₅ and a Brønsted acid

(a) Manganese(I)-catalyzed hydroarylations in flow



(b) Manganese(II)-catalyzed C–H arylations in flow



Scheme 33 Manganese-catalyzed C–H activation in flow.



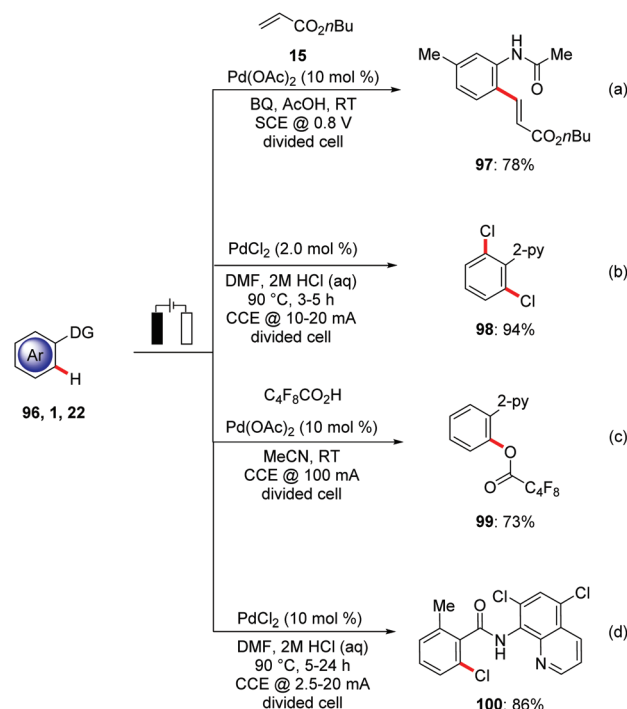
promoted the key protodemetalation in favour of the undesired β -oxygen elimination. With the synergistic regime in hand, various arenes and propargylic carbonates were efficiently coupled in only 20 minutes. In addition, metal impurities could be easily removed by implementing a scavenger column in flow. Remarkably, high levels of chemo-, site- and regio-selectivities were observed in only 1 minute, albeit at higher temperatures. Whereas, manganese(i)-catalyzed C–H activation offers a wide range of reactivity, due to the fact that the mechanistic pathways are presumably redox-neutral, arylation reactions are still elusive. Hence, in 2018 Ackermann reported on the directed C–H arylation of heteroarenes **93** with the aid of weakly-coordinating amides using the cost effective MnCl_2 as catalyst and neocuproine as ligand (Scheme 33b).¹¹² The methodology features the use of a flow-setup in order to minimize safety concerns, since Grignard reagents were used. In addition, improved heat and mass transfer allowed the completion of the reaction in 100 min compared to the batch setup that required 16 h. Importantly, pyridines, pyrimidines and thiophenes were well tolerated showing the potential for medicinal chemistry.

Metallaelectro-catalyzed C–H activation

Transition metal-catalyzed C–H activation has emerged as viable tool for molecular synthesis by reducing the formation of undesired byproducts.³ Yet, synthetically attractive oxidative C–H transformations pose significant limitation in terms of oxidant economy.¹¹³ The oxidative C–H activation primarily relies on stoichiometric amounts of expensive and toxic chemical oxidants including hypervalent iodine(III), copper(II), or silver(I) salts jeopardizing the overall sustainable nature of the C–H activation approach. While in few cases molecular oxygen has been used as terminal oxidant,¹¹⁴ this imposes additional restriction for its fixed redox potential and major safety hazard with flammable organic solvents.¹¹⁵ Since the pioneering studies of Kolbe¹¹⁶ and Shono,¹¹⁷ organic electrosynthesis¹¹⁸ has undergone a considerable recent renaissance. Particularly, the merger of transition metal catalysis with electrosynthesis¹¹ has enormous potential for the development of environmentally-benign diverse C–H functionalizations to form C–C or C–Het bonds using electrons as formal redox reagent for the re-oxidation of the metal centre. Thereby, super stoichiometric amounts of chemical oxidants can be avoided, thus enabling lower E-factors⁸ for resource economical synthesis.^{118d,i,119}

In this context, Amatore and Jutand achieved the electrochemical palladium(II)-catalyzed C–H bond olefination of *N*-acetylanilines **96** in AcOH in a divided cell set-up. Co-catalytic amounts of *p*-benzoquinone were needed as a redox mediator which can be regenerated at the anode to recycle the palladium(II) species in the catalytic cycle (Scheme 34a).¹²⁰

Palladium-catalyzed electrochemical oxidations with HX were accomplished by Kakiuchi.¹²¹ It is worth noting that in this protocol electricity was primarily responsible for the for-



Scheme 34 Palladaelectro-catalyzed C–H activation.

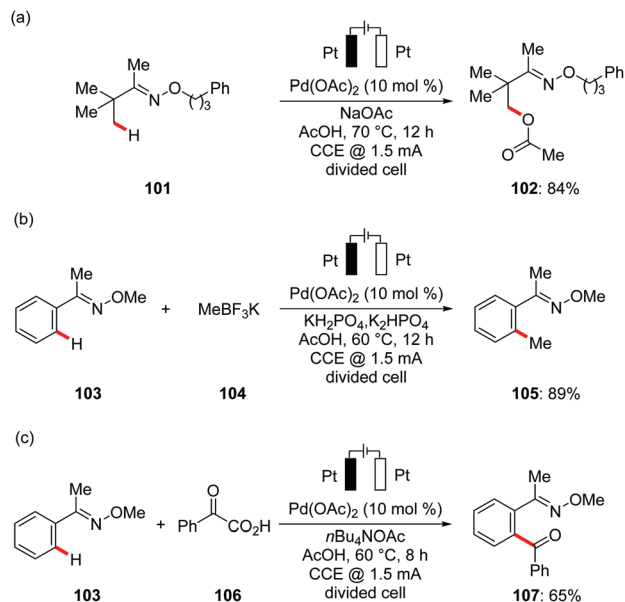
mation of the electrophilic Cl^+ species (Scheme 34b). This protocol enhanced the atom-economy, since the lengthy and costly use of electrophilic halogenation reagents can be circumvented. Later, a related C–H perfluoroalkoxylation of phenyl pyridines **1** was achieved with perfluoroalkylated acids by Budnikova (Scheme 34c).¹²²

In a recent study, Kakiuchi used the bidentate chlorinated 8-aminoquinoline directing group for the electrochemical *ortho*-selective chlorination of electronically poor benzamides **22** for the synthesis of Vismodegib (Scheme 34d).¹²³

In subsequent studies, Mei developed for the first time palladium-catalyzed $\text{C}(\text{sp}^3)$ –H oxygenation of oxime derivatives **101** using anodic oxidation instead of stoichiometric amounts of toxic metal oxidants. The combination of catalytic amounts of $\text{Pd}(\text{OAc})_2$, carboxylic acids and their corresponding sodium salts gave optimal results again in a divided cell set-up (Scheme 35a).¹²⁴ Other commonly employed chemical oxidants, such as $\text{PhI}(\text{OAc})_2$, *t*-BuOOAc, or NaNO_3/O_2 , provided the desired product **102** in significantly lower yields, highlighting the unique potential of electricity as green terminal oxidant. Based on their initial findings, Mei reported the palladium-catalyzed oxidative $\text{C}(\text{sp}^2)$ –H methylation **105** and benzoylation **107** of oximes with methyltrifluoroborates **104** and benzoyl acetic acids **106** respectively (Scheme 35b and c).¹²⁵

All palladaelectrocatalytic C–H transformations require a strong N-coordination and a divided cell set up. However, organic electrochemical C–H activation is not limited to the strong nitrogen-centred directing groups. In recent years, ruthenium,¹²⁶ rhodium¹²⁷ and iridium¹²⁸ catalysts have enabled the efficient electrooxidative C–H transformations





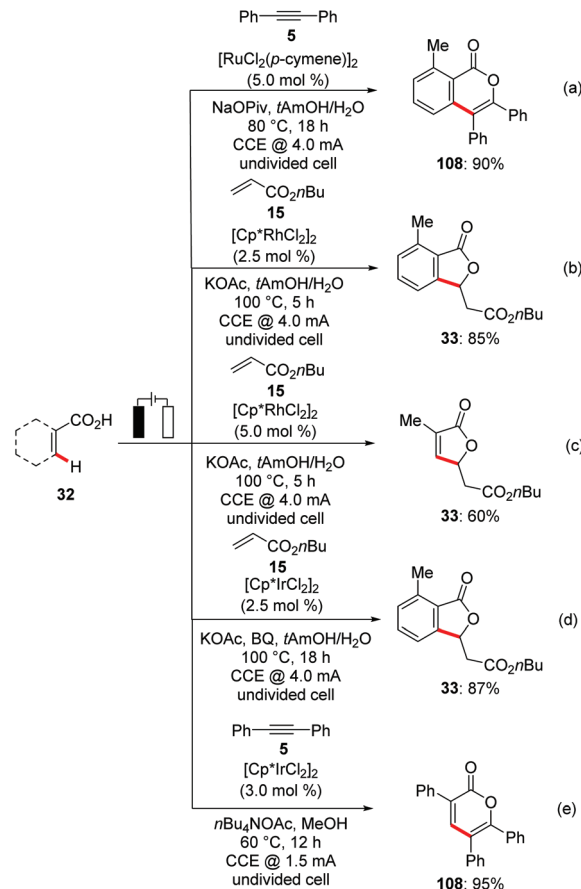
Scheme 35 Palladaelectro-catalyzed C–H activation using oxime as directing group.

with weakly coordinating substrates. Very recently, Ackermann reported on the first transition metal-catalyzed electrocatalytic organometallic C–H activation *via* weakly co-ordinating oxygen based carboxylic acids.^{126h} Thus, an inexpensive ruthenium(II) catalyst in combination with NaOPiv, enabled the C–H/O–H functionalization of synthetically meaningful benzoic acids **32** for alkyne **5** annulations with high levels of efficacy, thereby avoiding the use of sacrificial metal oxidants, namely Cu(OAc)₂·H₂O¹²⁹ (Scheme 36a).

Along the same lines, Ackermann devised an unprecedented rhodium(III)-catalyzed electrooxidative C–H/O–H alkenylation between benzoic acids **32** and acrylates **15** *via* weakly co-ordinating *O*-chelation with H₂ as the sole by-product (Scheme 36b and c).^{127f}

Furthermore, the same group demonstrated the first electrocatalytic iridium-catalyzed C–H/O–H annulation of benzoic acids **32** and acrylates **15**.^{128b} Catalytic amounts of *p*-benzoquinone were exploited as a redox catalyst to increase the turnover number (Scheme 36d). In a recent study Mei extended the iridium-catalyzed electrochemical vinylic C–H/O–H annulation with alkynes **5** and synthetically useful acrylic acids to afford α -pyrones **108** in good to excellent yields (Scheme 36e).^{128a} The authors showed that under otherwise identical reaction conditions, commonly used chemical oxidants in combination with cobalt or ruthenium catalysis yielded poor regioselectivities with unsymmetrical internal alkynes, which demonstrates the advantage of this strategy over previously reported annulation protocols.^{129,130}

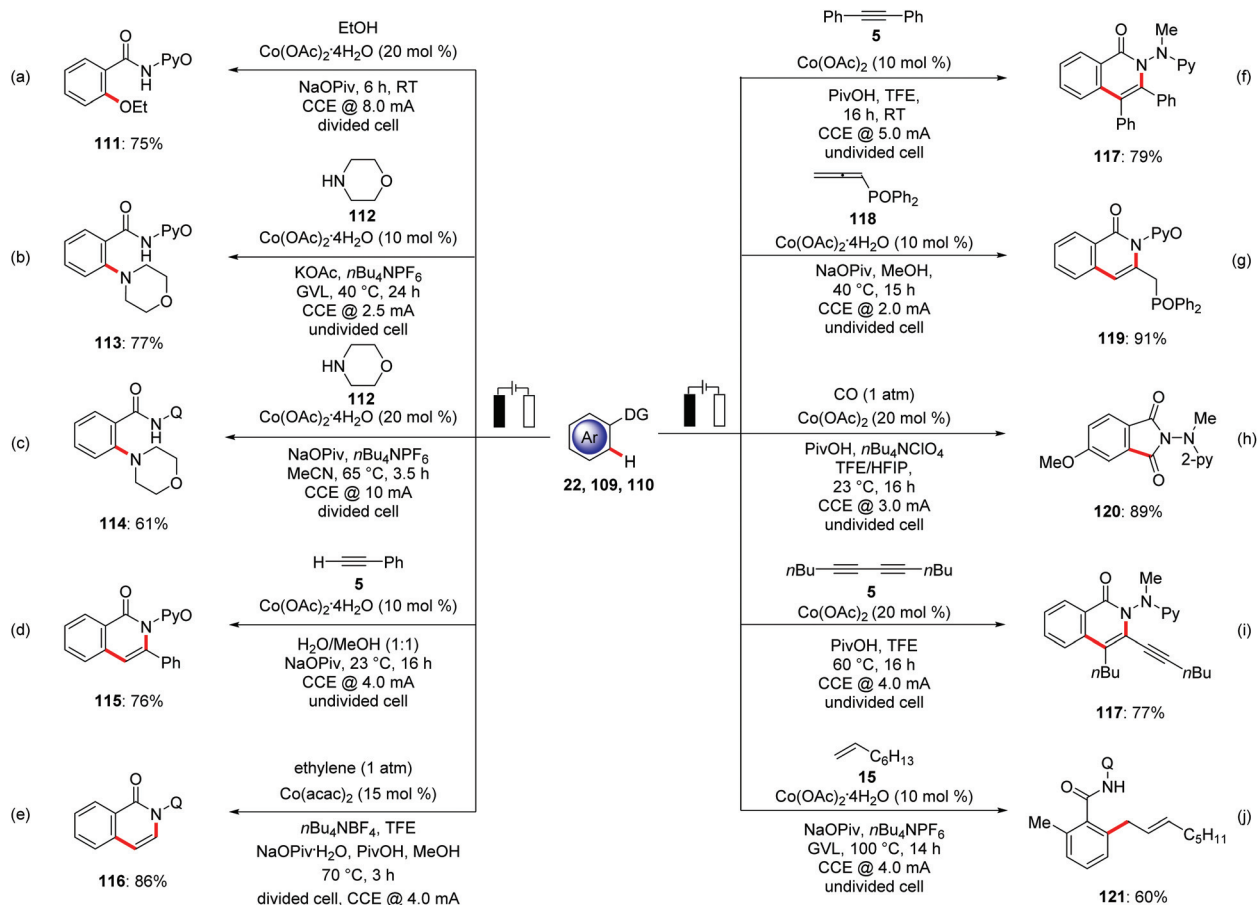
While electrocatalysis has largely relied on precious and toxic 4d and 5d transition metals, in recent years, momentum has been gained by identifying Earth-abundant and less-toxic 3d metals as viable catalysts for molecular C–H transformations.¹³¹



Scheme 36 Metallalectro-catalyzed C–H/O–H annulations with acids.

In 2017, Ackermann reported on the first electrochemical C–H activation by Earth-abundant metal catalysis.¹³² Here, the authors employed Cp*-free Co(OAc)₂·4H₂O as an inexpensive precatalyst for the electrochemical C–H oxygenation of benzamides **111** with alcohols (Scheme 37a). The reaction proceeded with a broad range of substrates and high levels of functional group tolerance at room temperature. In contrast, previous studies by Song and Niu required high reaction temperatures in the presence of stoichiometric amounts of silver(I) chemical oxidants.¹³³ Intrigued by this report, the electrooxidative¹³⁴ direct C–H amination of otherwise inert C–H bonds of aromatic benzamides **32** was subsequently reported.¹³⁵ Ackermann hence demonstrated for the use of biomass-derived, renewable solvent GVL in electrocatalysis for the amination of benzamides **109** with secondary amines **112** at a low temperature of 40 °C with H₂ as the stoichiometric byproduct by cathodic reduction (Scheme 37b), representing a notable advancement towards sustainability, since previous amination protocols were largely restricted to the use of superstoichiometric chemical oxidant in organic solvent at higher temperature.¹³⁶ Concurrently, Lei utilized 8-AQ as directing group for the C–H amination with cyclic secondary amines **112** in acetonitrile media at an elevated reaction temperature of



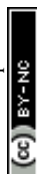


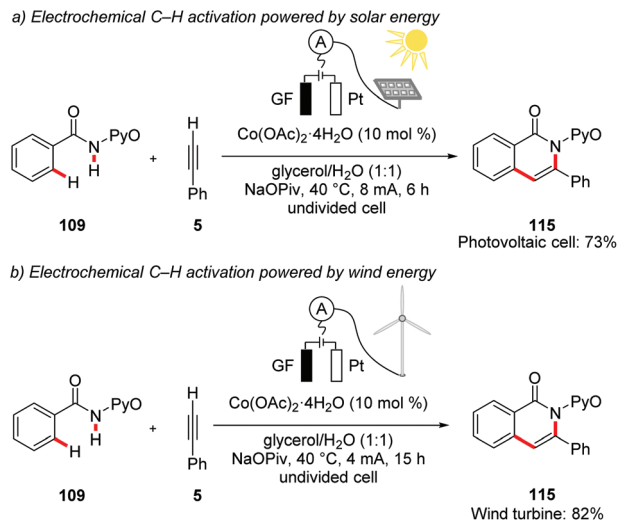
Scheme 37 Cobalt electro-catalyzed C–H activation.

65 °C (Scheme 37c).¹³⁷ The Ackermann group realized an electrochemical annulation of C–H and N–H bond with alkynes **5** using electricity as the sole oxidant (Scheme 37d).¹³⁸ This environmentally-benign cobalt catalysis was performed in non-toxic H_2O as the reaction medium at room temperature. Benzamides, heterocycles and alkenes bearing pyridine *N*-oxide were found as amenable substrates for the electrochemical annulation to gain access to isoquinolone **115** motifs. Later along these lines, Lei extended this approach towards the C–H/N–H annulation of ethylene and ethyne by amides **32** (Scheme 37e).¹³⁹ The electrochemical C–H/N–H annulation was not limited to terminal alkynes. Ackermann rationalized electro-oxidative internal alkyne annulation with electro-reductive removable benzhydrazide **110**, demonstrating the unique potential of electricity (Scheme 37f).¹⁴⁰ It is noteworthy that the authors employed an electroreductive hydrazide cleavage approach by the use of catalytic amounts of SmI_2 to cleave the benzhydrazides in a traceless manner. Considering the unique key structural motifs of allenes, Ackermann delineated the first direct use of allenes **118** for electrochemical C–H functionalization.¹⁴¹ An unprecedented electrochemical cobalt-catalyzed C–H activation with allenes **118** was realized with high regio- and site-selectivity under

exceedingly mild reaction conditions in the absence of toxic chemical oxidants (Scheme 37g). Later, the oxidative C–H/N–H carbonylation with carbon monoxide as a readily available inexpensive C1 building block proved viable. In addition to carbon monoxide, Ackermann likewise showed the versatility of cobalt catalysis by using synthetically useful isocyanides (Scheme 37h).¹⁴² Mei and Ackermann disclosed C–H/N–H activations of hydrazides **110** with 1,3-diynes **5** using a robust earth-abundant cobalt catalyst to furnish the desired products **117** in good to excellent yields (Scheme 37i).¹⁴³ In a very recent study by the Ackermann group the potential of cobalt catalysts in an electrocatalytic C–H allylation of benzamides **32** with nonactivated alkenes **15** was disclosed in bio-mass derived green solvent GVL (Scheme 37j).¹⁴⁴ In stark contrast, previous methods for C–H allylations were limited to the use of silver(I) chemical oxidants in organic solvents, jeopardizing the innate sustainability of C–H activation approach.¹⁴⁵

In a recent proof-of-concept study, Ackermann demonstrated the utilization of renewable solar and wind energy for electrocatalytic oxidative C–H activations. As a model study, the authors performed the cobalt electro-catalyzed C–H/N–H annulation of amide **109** with alkyne **5** in biomass derived glycerol as reaction media. The reaction was powered by either a



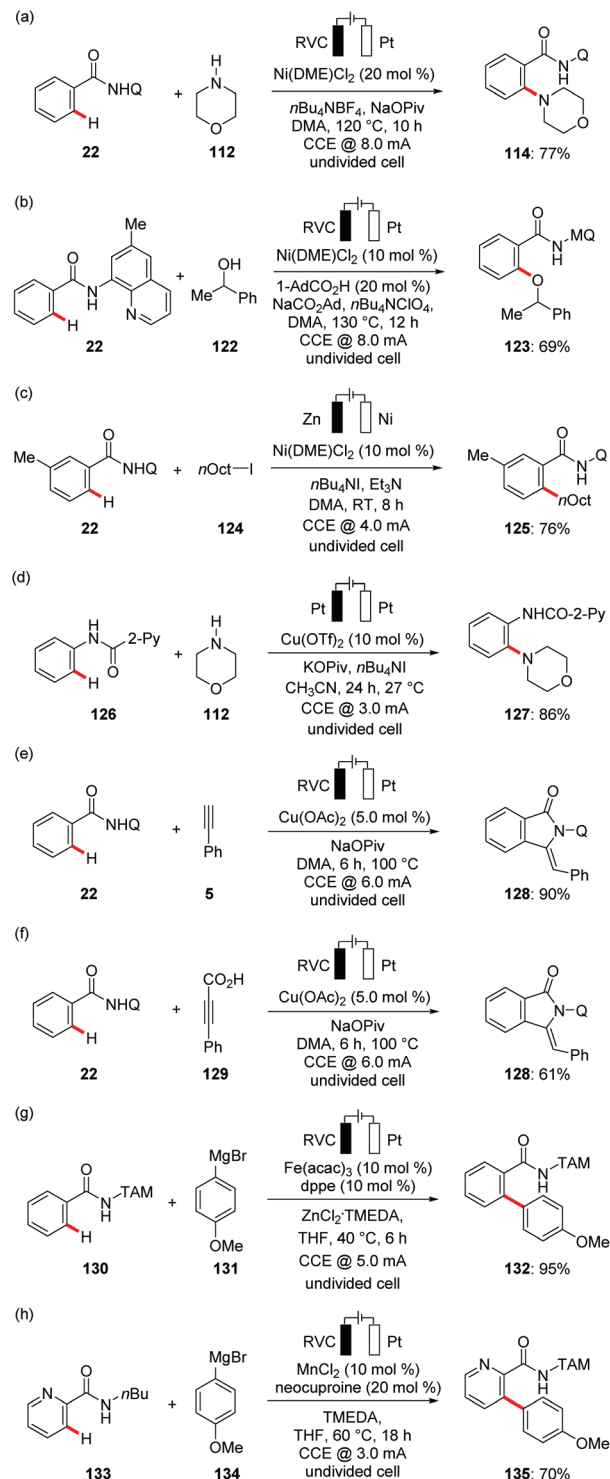


Scheme 38 Electrochemical C–H activation powered by renewable electricity.

commercially available photovoltaic module or a commercially available wind turbine to drive to the desired transformation (Scheme 38).¹⁴⁶

With notable progress in Earth-abundant cobalt catalysis for sustainable electrocatalysis, there has been strong interest in further developing metallaelectro-catalyzed C–H transformations. Ackermann devised less toxic, cost-effective nickel complexes as efficient catalysts for the electrochemical C–H activations.¹⁴⁷ In 2018, Ackermann reported first electrochemical nickel-catalyzed C–H amination of benzamides **22** (Scheme 39a).¹⁴⁸ The nickelalectro-catalyzed chemo- and position-selective amination proceeded with a broad range of functional group tolerance. Along this line, the same group reported on nickelalectro-oxidative C–H alkoxylation with challenging secondary alcohols **122** with H₂ as the sole byproduct (Scheme 39b).¹⁴⁹ It is worth noting that the chemical oxidants AgOAc, Cu(OAc)₂, molecular oxygen, PhI(OAc)₂, or K₂S₂O₈ provided significantly lower yield of the desired product. Detailed mechanistic studies revealed an oxidation-induced reductive elimination at a nickel(III) center. Furthermore, the nickel-catalyzed C–H alkylation of benzamide **22** was achieved with broad functional group tolerance at room temperature in user-friendly undivided cell setup (Scheme 39c).¹⁵⁰ In contrast, previous studies were largely limited to the use of strong bases and considerably higher reaction temperatures for nickel-catalyzed C–H alkylations.¹⁵¹

Recently, Mei exploited copper catalysis for the electrochemical C–H aminations of electron-rich anilides **126** with electricity as terminal oxidant (Scheme 39d).¹⁵² In a related work, Nicholls and coworkers reported electro-oxidative amination of anilides with amines producing H₂ as the sole byproduct.¹⁵³ Concurrently, the Ackermann group disclosed cupraelectro-catalyzed C–H alkynylations of electron-rich and electron-deficient benzamides **22** for the synthesis of synthetically meaningful isoindolones **128** (Scheme 39e).¹⁵⁴ Notably,

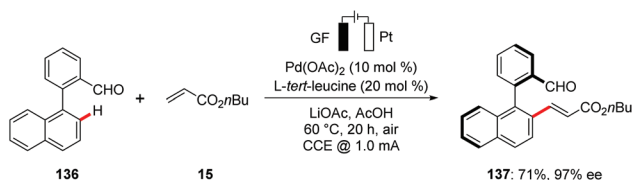


Scheme 39 3d metal-catalyzed C–H activation.

the authors also demonstrated C–H/C–C functionalizations in a decarboxylative fashion with alkynyl carboxylic acids to afford the desired isoindolone **128** products (Scheme 39f).

Recently, iron catalysis has found considerable applications in molecular synthesis due to its low cost, low toxicity and as the most naturally abundant transition metal on Earth.¹⁵⁵





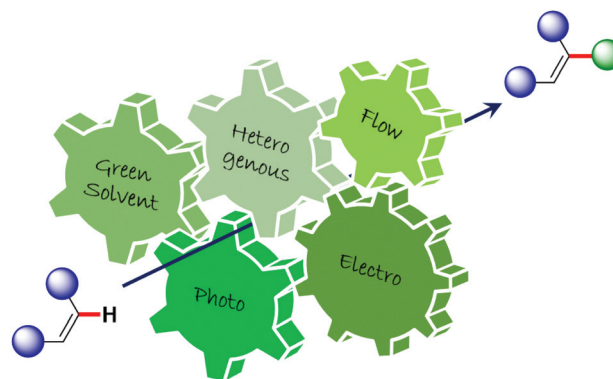
Scheme 40 Atroposelective palladaelectro-catalyzed C–H activation.

Despite the recent attention iron-catalyzed C–H activation has gained, superstoichiometric use of corrosive, expensive chemical oxidants pose a major limitation to organometallic iron catalysis.¹⁵⁶ To overcome these challenges, Ackermann reported the unprecedented ferraelectro-catalyzed C–H arylations at mild temperature using electricity as a green oxidant (Scheme 39g).¹⁵⁷ Interestingly, the electro-oxidative arylations proceeded efficiently in the biomass-derived solvent 2-MeTHF. Ackermann enhanced the versatility of metallaelectrocatalysis by the merger of electrocatalysis with environmentally-benign manganese catalysis. Non-toxic MnCl_2 was utilized for the electrochemical C–H arylation of amides **133** in the absence of any zinc additives (Scheme 39f).¹⁵⁷

Despite significant advances of metallaelectrocatalysis, reports on enantioselective electrochemical transformations are scarce.¹⁵⁸ Recently, the Ackermann group reported on the first asymmetric metallaelectro-catalyzed C–H activation.¹⁵⁹ The authors disclosed the unprecedented use of transient directing groups for the asymmetric palladaelectro-catalyzed C–H olefinations for the synthesis of enantiomerically-enriched axially chiral biaryls and heterobiaryls **137** scaffolds under mild conditions (Scheme 40). Late-stage diversification of the products enabled the synthesis of highly enantio-enriched BINOLs, dicarboxylic acids and helicenes.

Conclusions

During the last decade transition metal-catalyzed C–H activation has emerged as a transformative platform for molecular syntheses. However, despite significant advances in C–H activations, the quest for sustainable and environmentally-benign strategies continues to be of central importance for resource economical C–H activations. Herein, we have highlighted key aspects for eco-friendly metal-catalyzed C–H activation (Scheme 41). The strategies discussed herein provide guidance towards more sustainable C–H transformations. Each approach, by itself, does not necessarily ensure ideal greenness, but their combination will lead to improved levels of sustainability. Namely, the following five key trends have been summarized: (1) the use of biomass-derived solvents is an important aspect to reduce the consumption of toxic organic solvents. This is particularly the case in industrial scale, since typical isolation methods, such as column chromatography generally employed in academic settings, are replaced by more sustainable methods. Particularly, in many cases similar trends have been observed for GVL compared to commonly



Scheme 41 Green strategies for sustainable C–H activation.

employed polar aprotic solvents, such as DMF, DMA, and NMP. Similarly, biomass-derived 2-MeTHF is a safer alternative to flammable THF in many C–H activation processes. These empirical observations can encourage the practitioner to use these class of solvents more frequently. (2) The facile recyclability of the catalyst is another key aspect, potentially even for large scale applications. In recent years, heterogeneous catalysts have emerged for various C–C and C–heteroatom bond forming reactions with efficient recycling of the catalysts. (3) Furthermore, the merger of transition metal catalysis with photocatalysis has considerably enhanced the reactivity under exceedingly mild conditions. (4) The recent use of flow technologies for metal-catalyzed C–H activation reactions has shown enormous potential for the straightforward scale-up with safer setups and shorter reaction times. (5) Last but not least, metallaelectrocatalysis avoids the use of toxic chemical oxidants or metal promoters by electricity as traceless inexpensive oxidant, representing a significant advance for resource-economical C–H activations. Very recently, metallaelectrocatalysis has been realized with 3d metal catalysts as well as in green reaction medium, showcasing the high sustainability of the process. In view of current metal-catalyzed C–H activation portfolio, it is evident that the exponential growth for sustainable strategies in organic synthesis has gained considerable attention for resource economical transformations. Given the topical interest in resource-economical C–H activation, future exciting advances are expected in this rapidly evolving research arena, including, enantioselective heterogeneous catalysis and Earth-abundant electrocatalysis.

Conflicts of interest

There are no conflicts to declare.

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