

## REVIEW

View Article Online  
View Journal | View IssueCite this: *Org. Chem. Front.*, 2021, **8**, 4886Received 10th May 2021,  
Accepted 2nd June 2021

DOI: 10.1039/d1qo00727k

rsc.li/frontiers-organic

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

Uttam Dhawa,<sup>a</sup> Nikolaos Kaplaneris<sup>a</sup> and Lutz Ackermann<sup>\*a,b</sup>

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.<sup>1</sup> 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.<sup>2</sup> 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 activations<sup>3</sup> has been recognized as an increasingly powerful alternative in terms of step- and atom-economy for the assembly of complex molecules,<sup>4</sup> with transformative applications to among others late-stage diversification,<sup>5</sup> material sciences,<sup>6</sup> and pharmaceutical industries.<sup>7</sup> 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.<sup>8</sup> The use of non toxic, inexpensive Earth-abundant 3d metal catalysts<sup>9</sup> as well as alternative energy<sup>10</sup> 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.<sup>11</sup>

<sup>a</sup>Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstraße 2, 37077 Göttingen, Germany.

E-mail: Lutz.Ackermann@chemie.uni-goettingen.de; <http://www.ackermann.chemie.uni-goettingen.de/index.html>

<sup>b</sup>Woehler Research Institute for Sustainable Chemistry (WISCh), Georg-August-Universität Göttingen, Tammannstraße 2, 37077 Göttingen, Germany

## 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.<sup>12</sup> 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.<sup>13</sup> Therefore, environmentally-benign solvents are in high demand for transition metal-catalyzed C–H activations as a sustainable alternative.<sup>13d,g,14</sup>

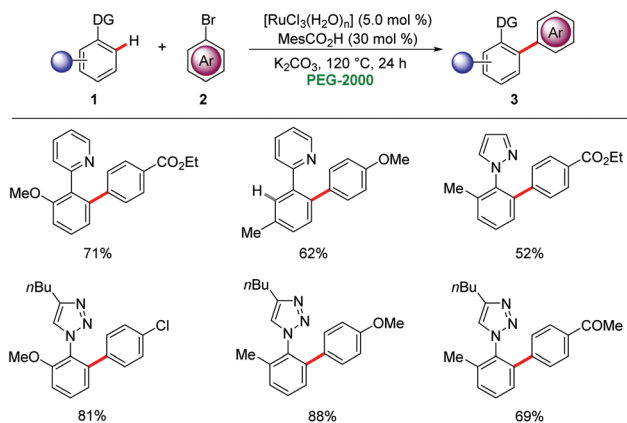
The application of environmentally-benign solvents<sup>15</sup> in transition metal-catalyzed C–H activation is attractive, because they are readily available from biomass feedstocks and generally less toxic with high biodegradability, minimizing the environmental footprints.<sup>14b,16</sup> Apart from bio-based solvents, water also has found applications in various C–H transformations.<sup>17</sup>

## Polyethylene glycols (PEGs)

Polyethylene glycols (PEGs), available from inexpensive ethylene glycol,<sup>18</sup> have gained considerable attention as green reaction media<sup>19</sup> 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.<sup>19</sup>

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





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

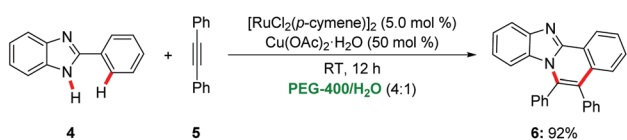
arenes **1** were arylated in a regioselective fashion by chelation-assisted ruthenium catalysis.

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

A green synthesis of benzimidazoisoquinolines<sup>23</sup> **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).<sup>24</sup> 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.

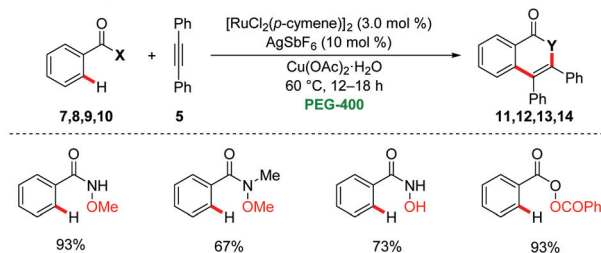
Bhanage employed recently a recyclable ruthenium/PEG-400 catalytic system for the oxidative annulation with internal alkynes **5** *via* directed C–H activation for the synthesis of isoquinolinones, isocoumarins, and *N*-methyl isoquinolinones<sup>25</sup> by the cleavage of C–H, N–O and O–O bonds (Scheme 3a).<sup>26</sup> 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.<sup>27</sup>

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

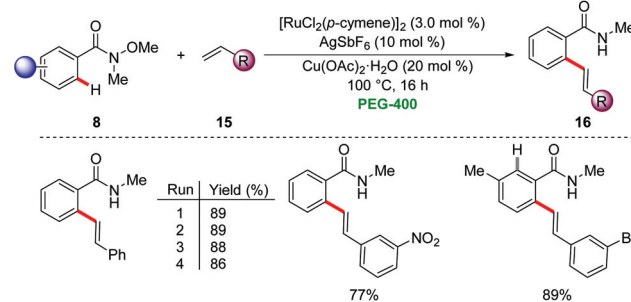


**Scheme 2** Ruthenium-catalyzed oxidative annulation with alkynes **5** in PEG-400/ $\text{H}_2\text{O}$ .

(a) Ruthenium catalyzed annulation of amides and acid derivatives



(b) Ruthenium catalyzed oxidative olefination

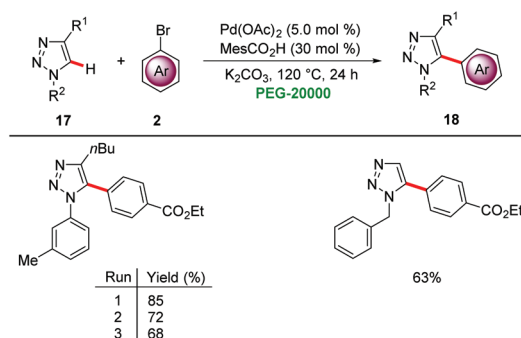


**Scheme 3** Ruthenium-catalyzed oxidative annulation and olefination of amides in PEG-400.

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.<sup>28</sup>

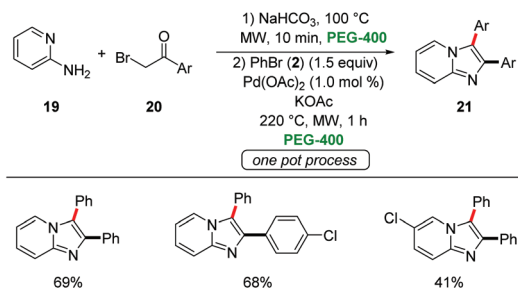
Ackermann demonstrated that PEGs are viable green reaction media for palladium-catalyzed C–H arylations. Co-catalytic amounts of  $\text{MesCO}_2\text{H}$  significantly improved the reaction efficiency for the direct arylation of triazoles **17** under aerobic conditions with 5.0 mol% of  $\text{Pd}(\text{OAc})_2$  in PEG-20000 (Scheme 4).<sup>20</sup> 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**,  $\alpha$ -bromo ketones **20** and aryl bromides **2** in PEG-400 (Scheme 5).<sup>29</sup> The use of  $\text{Pd}(\text{OAc})_2$  as the catalyst and  $\text{KOAc}$  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.

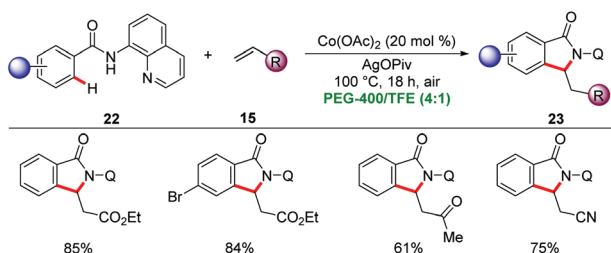




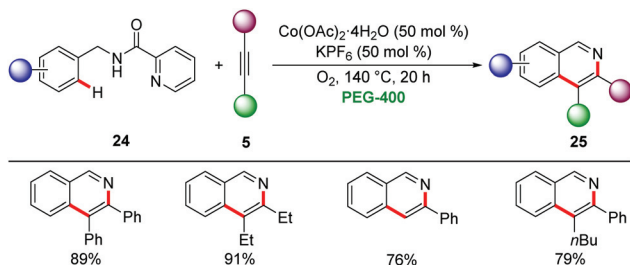
**Scheme 5** One pot sequential approach for palladium-catalyzed arylation in PEG-400.

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  $\text{AgOPiv}$  afforded isoindolinone derivatives **23** from aromatic benzamides **22** by C–H/N–H annulation with alkenes **15** under aerobic conditions (Scheme 6).<sup>30</sup> 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).<sup>31</sup> 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 alkylation in PEG-400.

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

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

### $\gamma$ -Valerolactone (GVL)

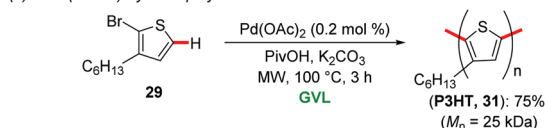
$\gamma$ -Valerolactone's characteristic features include a high boiling point, a low vapour pressure, low toxicity along with high miscibility with water and most importantly it is highly biodegradable.<sup>33</sup> This environmentally-benign aprotic solvent is produced from levulinic acid which is itself derived from lignocellulosic biomasses.<sup>34</sup> 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,<sup>35</sup> hydroformylations<sup>36</sup> and aminocarbonylations.<sup>37</sup> 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).<sup>38</sup> Remarkably, only 0.2 mol%

#### (a) arylation of heterocycles



#### (b) C–H (hetero)arylation polymerization



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



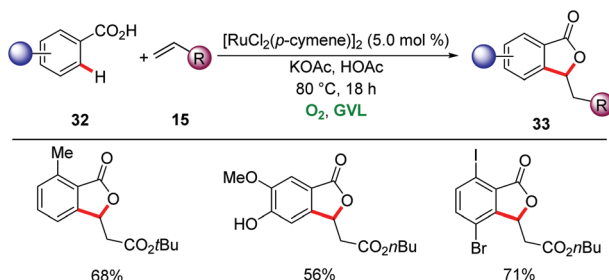
$\text{Pd}(\text{OAc})_2$  was sufficient for efficient regioselective C2 arylation of thiophenes **29** under microwave irradiation at 140 °C. The reaction conditions proved applicable to palladium-catalyzed synthesis of poly(3-hexyl)thiophene **31** by C–H (hetero)arylation polymerisation (Scheme 9b).

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).<sup>39</sup> 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  $\text{H}_2\text{O}$  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.<sup>40</sup>

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).<sup>41</sup> 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.

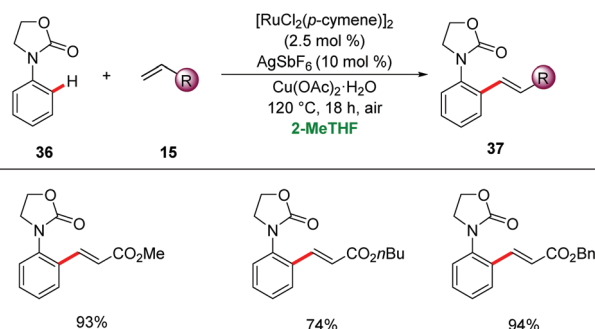
## 2-Methyltetrahydrofuran (2-MeTHF)

2-Methyltetrahydrofuran (2-MeTHF) is largely produced from renewable lignocellulosic biomasses.<sup>42</sup> Favourable physico-chemical properties of 2-MeTHF render it as an eco-friendly alternative to THF with lower miscibility with water and higher boiling point.<sup>43</sup> 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).<sup>44</sup> 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**.<sup>45</sup> 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).<sup>46</sup> 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.<sup>47</sup>

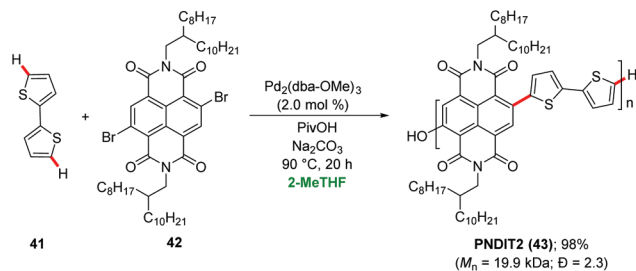


**Scheme 12** *ortho*-C–H alkenylation of a variety of *N*-aryloxazolinone **36** in 2-MeTHF.



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





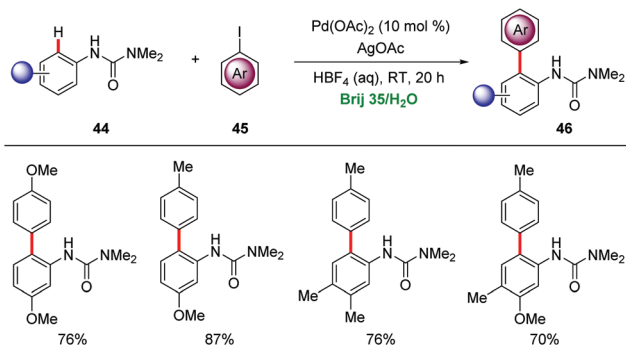
**Scheme 14** Palladium-catalyzed direct C–H arylation polymerization in 2-MeTHF.

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)<sub>3</sub> as catalyst and dppe as ligand enabled primary and secondary alkylations in high yields and excellent regioselectivities.<sup>48</sup>

### 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.<sup>17</sup> 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.<sup>49</sup> 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/H<sub>2</sub>O was employed in the palladium-catalyzed C–H arylations of anilides 44 to provide diversely substituted biaryl compounds 46 (Scheme 15).<sup>50</sup> 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/H<sub>2</sub>O.

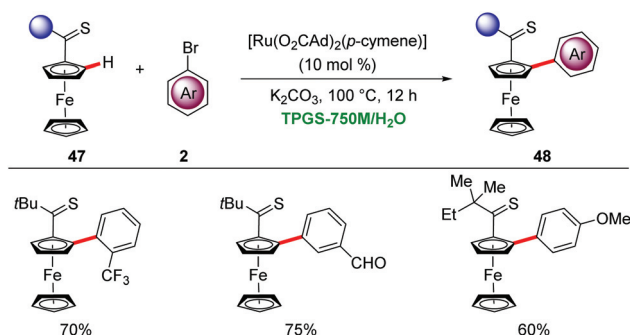
Later, *ortho*-acylations of anilides were also achieved in an aqueous solution of a surfactant *via* a palladium-catalyzed cross dehydrogenative coupling between anilides and aromatic aldehydes.<sup>51</sup>

Ackermann devised a ruthenium-catalyzed C–H arylation in water through micellar catalysis.<sup>52</sup> The presence of a single component ruthenium catalyst and K<sub>2</sub>CO<sub>3</sub> 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 H<sub>2</sub>O (Scheme 16).

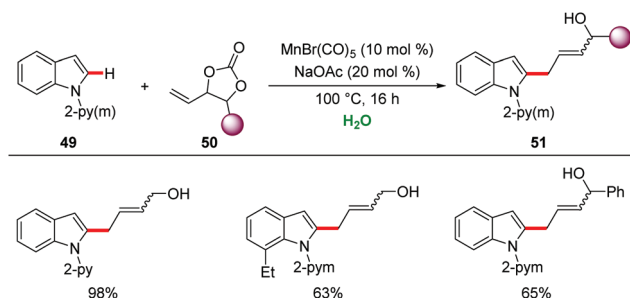
Water itself has been found applications as a reaction medium for a variety of C–H bond functionalization reactions, catalyzed by palladium,<sup>53</sup> rhodium,<sup>54</sup> iridium<sup>55</sup> and ruthenium.<sup>56</sup> Similarly, water has also been found as an amenable solvent for Earth-abundant 3d metal-catalyzed C–H functionalization.<sup>57</sup>

In this context, in 2017, decarboxylative C–H/C–O functionalizations by manganese catalysis in H<sub>2</sub>O were realized by Ackermann.<sup>58</sup> 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.<sup>59</sup> 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.<sup>60</sup>



**Scheme 16** Ruthenium-catalyzed C–H arylation in TPGS-750M/H<sub>2</sub>O.



**Scheme 17** Manganese(I)-catalyzed C–H allylation in H<sub>2</sub>O.



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.<sup>61</sup> 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.<sup>62</sup>

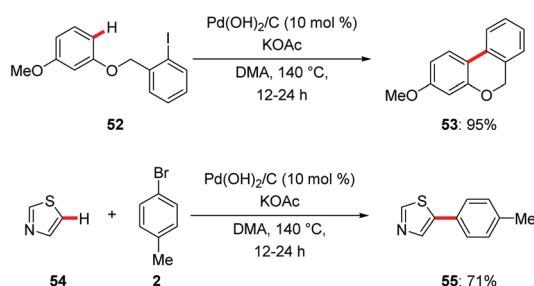
An early report on C–H arylations by Fagnou proved viable with the commercially available heterogeneous palladium catalyst Pd(OH)<sub>2</sub>/C.<sup>63</sup> Pearlman's catalyst allowed for efficient intra- and intermolecular C–H arylation with aryl iodides **52** and bromides **2** (Scheme 18). Detailed 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.<sup>64</sup>

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.<sup>65</sup>

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

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).<sup>68</sup>

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.<sup>69</sup> Furthermore, heterogeneous MOF based copper catalysts have found suitable application for the direct C–H arylation of heteroarenes.<sup>70</sup>



Scheme 18 Heterogeneous palladium-catalyzed C–H arylation.



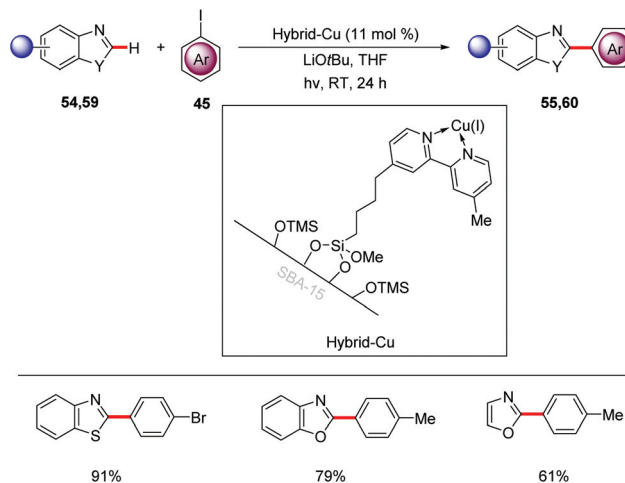
Scheme 19 *meta*-C–H arylation of anilides **56** with heterogeneous copper nanoparticles.

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).<sup>71</sup> 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,<sup>72</sup> recent interest on other types of C–C and C–Het bond formation reactions using recyclable heterogeneous catalysis has gained considerable attention.<sup>73</sup>

In 2016, Ackermann and Vaccaro realized the heterogeneous palladium catalysis for the Catellani reaction in the renewable biomass derived green solvent GVL.<sup>74</sup> The authors employed two different heterogeneous palladium sources, namely, Pd/Al<sub>2</sub>O<sub>3</sub> 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 MesCO<sub>2</sub>H and CF<sub>3</sub>CO<sub>2</sub>K 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).<sup>75</sup> 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).<sup>76</sup>

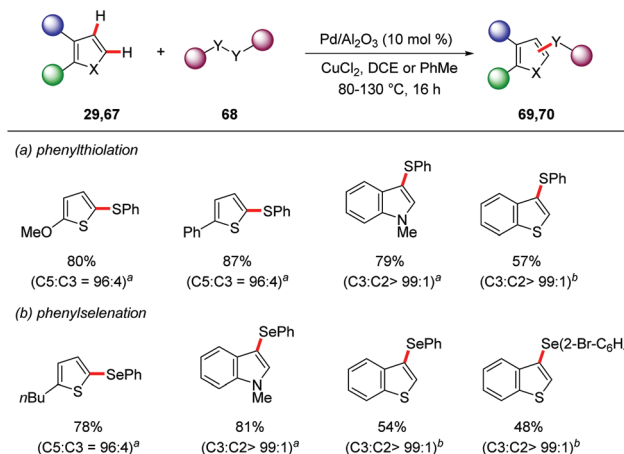
The Glorius group employed Pd/Al<sub>2</sub>O<sub>3</sub> as a heterogeneous catalyst for the direct C–H thiolation and selenation reactions.<sup>77</sup> The combination of Pd/Al<sub>2</sub>O<sub>3</sub> and CuCl<sub>2</sub> in dichloroethane or toluene gave optimal results for the synthesis of sulfenylated **69** and selenylated products **70** (Scheme 23).

Furthermore, C–H cyanations were achieved by heterogeneous palladium(II) and magnesium–lanthanum mixed oxide.<sup>78</sup> The combination of NH<sub>4</sub>HCO<sub>3</sub> and DMSO served as cyano source to allow for regioselective C–H cyanations of heteroarenes **1** (Scheme 24).

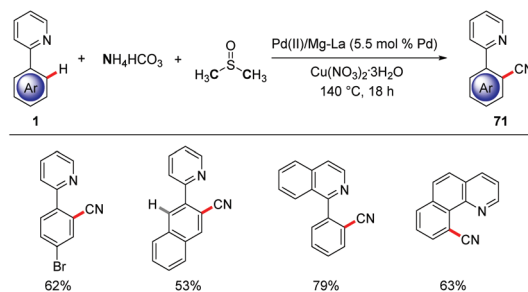
C–H halogenations were achieved using an easily synthesized Pd@MOF nano catalysts by Martín-Matute.<sup>79</sup> The halogenation reaction was conveniently performed with the robust MOF-based heterogeneous catalysts to deliver the desired products **73** and **74** under very mild conditions with excellent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



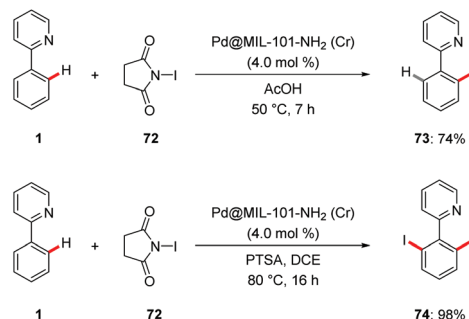
**Scheme 22** Heterogeneous palladium-catalyzed C–H arylation in GVL.



**Scheme 23** Heterogeneous palladium-catalyzed direct C–H thiolation and selenylation. <sup>a</sup> DCE, 80 °C, <sup>b</sup> PhME, 130 °C.



**Scheme 24** Heterogeneous palladium-catalyzed C–H cyanation.

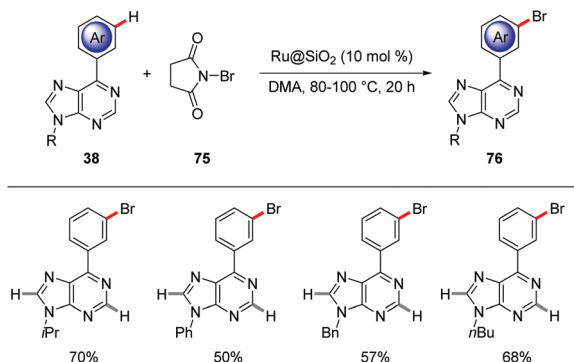


**Scheme 25** C–H halogenation by Pd@MOF nano catalysts.

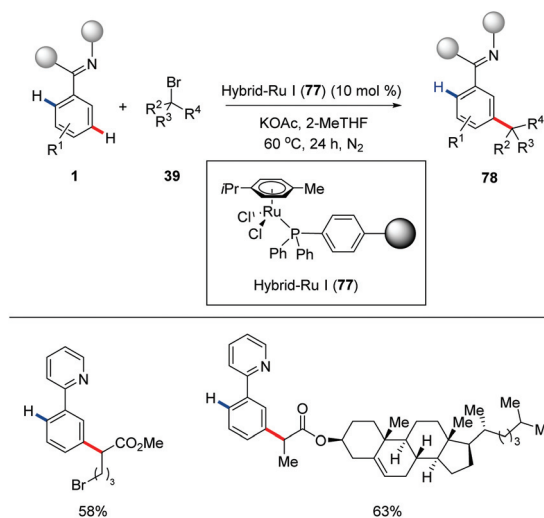
mentioning that the MOFs were recycled and reused without loss of efficacy.

*meta*-C–H Brominations of aryl substituted purine bases **38** were devised by Ackermann using a heterogeneous ruthenium catalyst (Scheme 26).<sup>80</sup> The robust heterogeneous Ru@SiO<sub>2</sub> 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).<sup>81</sup> 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 oxygenation<sup>82</sup> and C–H borylation<sup>83</sup> 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.

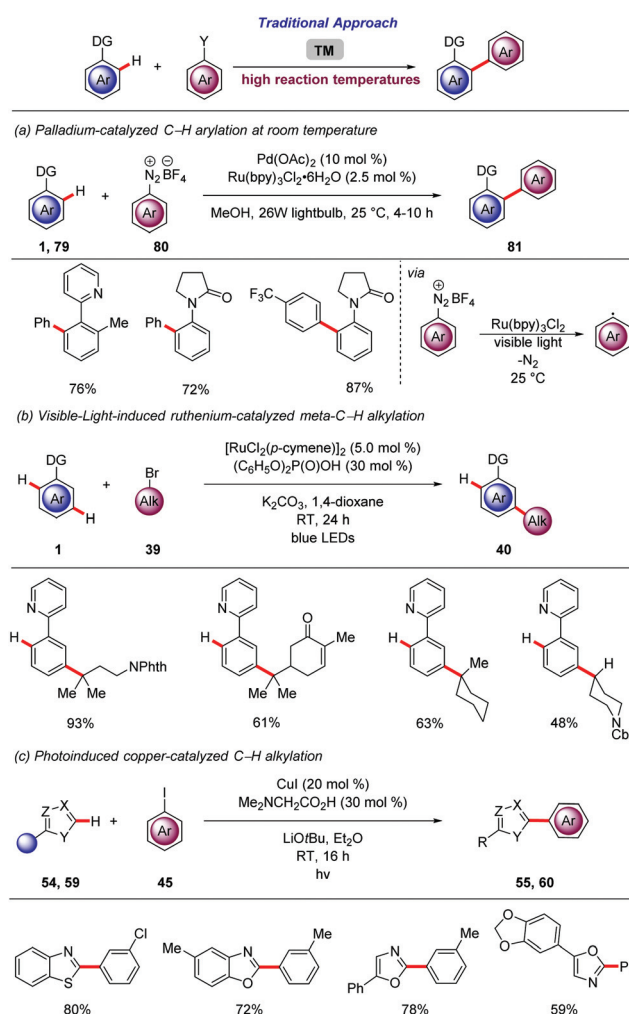
## Photocatalytic C–H activation

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

efficient tool for challenging transformations.<sup>84</sup> The merger of photocatalysis with transition metal-catalyzed<sup>85</sup> cross coupling unlocked a dormant area of the chemical space.<sup>86</sup>

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.<sup>87</sup> In 2011, Sanford merged the versatile palladium-catalyzed C–H activation regime with photocatalytic generation of aryl radical (Scheme 28a).<sup>88</sup> The use of Ru(bpy)<sub>3</sub>Cl<sub>2</sub> 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)<sub>2</sub> and Ru(bpy)<sub>3</sub>Cl<sub>2</sub> 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 developed<sup>89</sup> including, use of templates,<sup>90</sup> non-covalent interactions between the ligand and the sub-



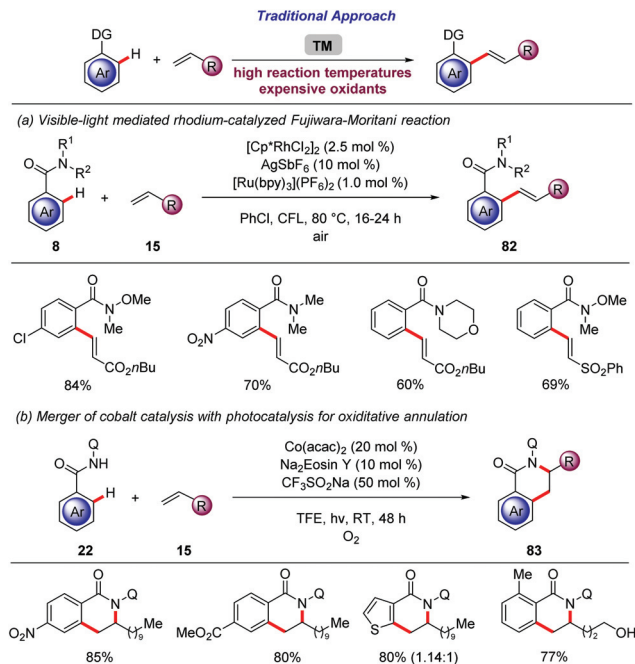
**Scheme 28** Redox-neutral photocatalytic C–H activation.





strate,<sup>91</sup> mediators<sup>92</sup> for Catellani type reaction<sup>93</sup> and  $\sigma$ -activation.<sup>94</sup> 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.<sup>95</sup> 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 [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> and (C<sub>6</sub>H<sub>5</sub>O)<sub>2</sub>P(O)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.<sup>96</sup> 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.<sup>97</sup> 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.<sup>98</sup> Thus, Ackermann reported on the photoinduced copper-catalyzed C–H arylation of azoles **54**, **59** at room temperature, using cost-effective CuI (Scheme 28c).<sup>99</sup> 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,<sup>100</sup> but stoichiometric amounts of oxidants are required and generally elevated temperatures are employed in order to achieve high conversion.<sup>101</sup> Thus, Rueping disclosed a rhodium-catalyzed Fujiwara–Moritani reaction enabled by visible light (Scheme 29a).<sup>102</sup> The authors reasoned that the rhodium hydride species produced after  $\beta$ -hydride elimination can be recycled towards the active species by a photocatalytic oxidation, where O<sub>2</sub> acts as the terminal oxidant. After extensive optimization, benzamides **8** were efficiently converted to the desired *E*-olefins with catalytic amounts of [Cp\**Rh*Cl<sub>2</sub>]<sub>2</sub>, AgSbF<sub>6</sub> and [Ru(bpy)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub> in chlorobenzene at 80 °C under air. Under the optimized reaction



Scheme 29 Oxidative photocatalytic C–H activation.

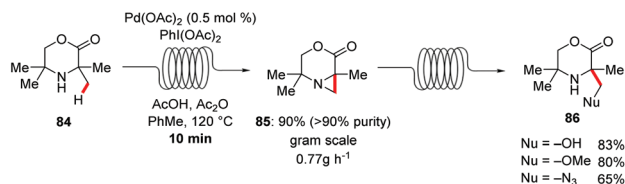
conditions a plethora of functional groups were tolerated on the arene moiety and various alkenes **15** were also employed.<sup>103</sup> Subsequently, Rueping and Sundararaju employed this strategy, for high valent cobalt catalysis with photocatalysis (Scheme 29b).<sup>104</sup> This approach represents a sustainable protocol with an earth-abundant cobalt catalyst in combination with an organic dye. Indeed, catalytic quantities of Co(acac)<sub>2</sub> and Na<sub>2</sub>Eosin Y in combination with CF<sub>3</sub>SO<sub>2</sub>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,<sup>105</sup> 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.

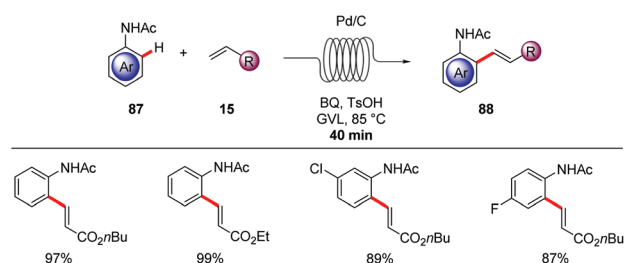
In this context, Gaunt and Lapkin developed an oxidative palladium-catalyzed C–H aziridination and subsequent ring opening in flow.<sup>106</sup> In order to transform the process from the batch conditions,<sup>107</sup> to the desired flow setup the authors performed DFT calculations and constructed 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 Pd(OAc)<sub>2</sub> and stoichiometric PhI(OAc)<sub>2</sub>, Ac<sub>2</sub>O 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



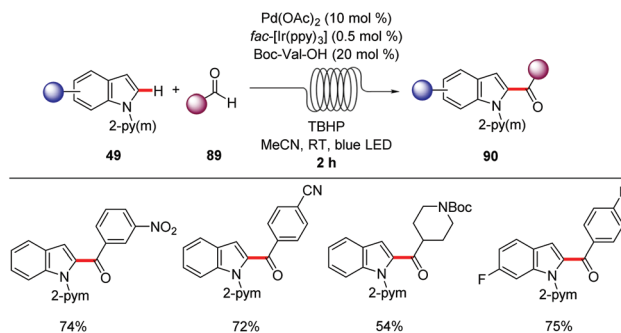


**Scheme 30** Continuous-flow synthesis of aziridines.

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.<sup>108</sup> 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 reactions 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).<sup>109</sup> 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)<sub>2</sub>, Boc-Val-OH, *fac*-[Ir(ppy)<sub>3</sub>] as photocatalyst and *tert*-butyl hydroperoxide as terminal oxidant in acetonitrile, they



**Scheme 31** Heterogeneous C–H alkenylations in continuous flow.

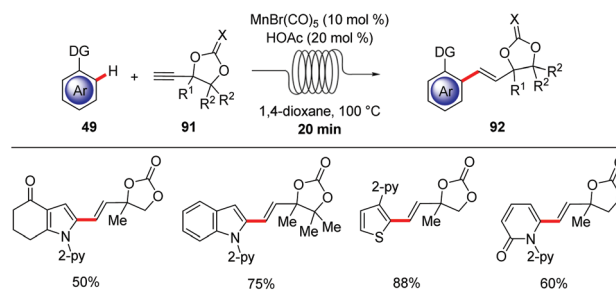


**Scheme 32** C–H acylation of indoles by dual photoredox/transition metal catalysis.

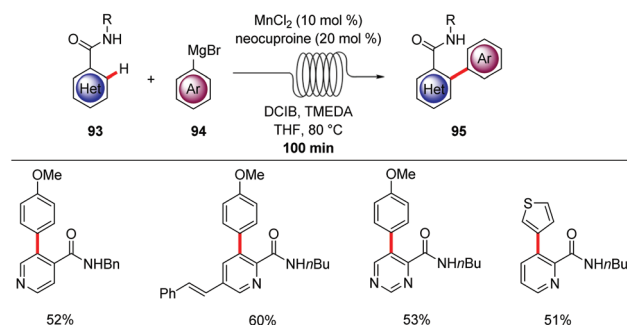
expanded the scope of the acylation in batch and in flow. Interestingly, the isolated yields were comparable but the required 2 hours, which the batch protocol called for 20 hours. In addition, the mild reaction conditions enabled the acylation with  $\alpha,\alpha$ -disubstituted aldehydes to occur 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.<sup>9,110</sup> Thus, in 2017 Ackermann developed the manganese(I) hydroarylation of propargylic carbonates **91** in flow (Scheme 33a).<sup>111</sup> Fine-tuning of the reaction conditions were required to bypass the inherent pathway for the  $\beta$ -oxygen elimination that leads to allene products, gratifyingly, the synergistic catalysis between  $\text{MnBr}(\text{CO})_5$  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.



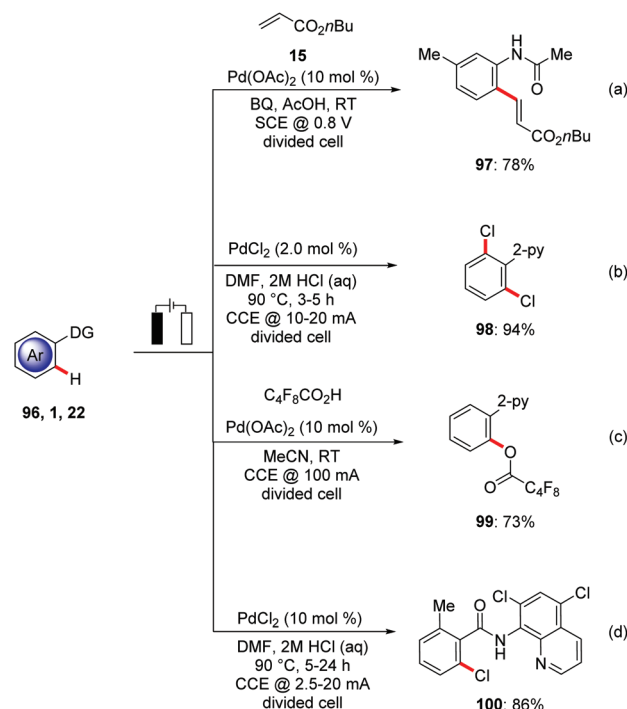
promoted the key protodemetalation in favour of the undesired  $\beta$ -oxygen elimination. With the synergistic regime in hand, various arenes and propargylic carbonates were efficiently coupled in only 20 minutes. In addition, metal impurities could be easily removed by implementing a scavenger column 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  $\text{MnCl}_2$  as catalyst and neocuproine as ligand (Scheme 33b).<sup>112</sup> 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.<sup>3</sup> Yet, synthetically attractive oxidative C–H transformations pose significant limitation in terms of oxidant economy.<sup>113</sup> 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,<sup>114</sup> this imposes additional restriction for its fixed redox potential and major safety hazard with flammable organic solvents.<sup>115</sup> Since the pioneering studies of Kolbe<sup>116</sup> and Shono,<sup>117</sup> organic electrosynthesis<sup>118</sup> has undergone a considerable recent renaissance. Particularly, the merger of transition metal catalysis with electrosynthesis<sup>11</sup> 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-factors<sup>8</sup> for resource economical synthesis.<sup>118d,i,119</sup>

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).<sup>120</sup>

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



Scheme 34 Palladaelectro-catalyzed C–H activation.

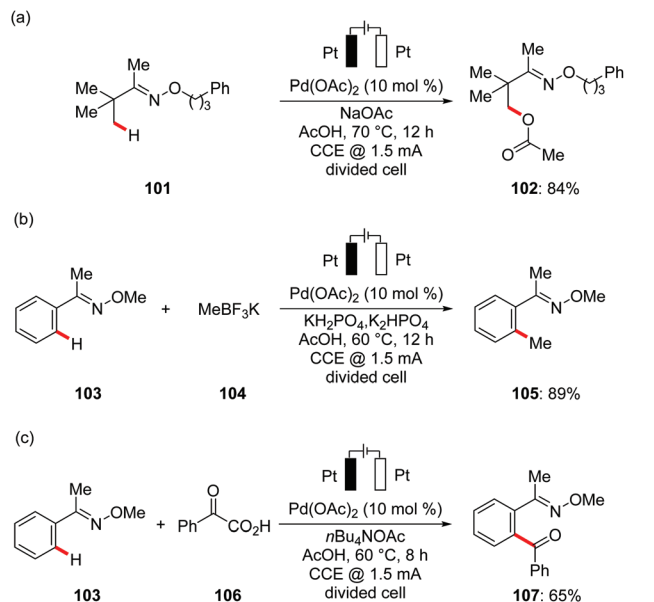
mation of the electrophilic  $\text{Cl}^+$  species (Scheme 34b). This protocol enhanced the atom-economy, since the lengthy and costly use of electrophilic halogenation reagents can be circumvented. Later, a related C–H perfluoroalkoxylation of phenyl pyridines **1** was achieved with perfluoroalkylated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

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).<sup>123</sup>

In subsequent studies, Mei developed for the first time palladium-catalyzed  $\text{C}(\text{sp}^3)\text{--H}$  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).<sup>124</sup> Other commonly employed chemical oxidants, such as  $\text{PhI}(\text{OAc})_2$ , *t*-BuOOAc, or  $\text{NaNO}_3/\text{O}_2$ , 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  $\text{C}(\text{sp}^2)\text{--H}$  methylation **105** and benzylation **107** of oximes with methyltrifluoroborates **104** and benzoyl acetic acids **106** respectively (Scheme 35b and c).<sup>125</sup>

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,<sup>126</sup> rhodium<sup>127</sup> and iridium<sup>128</sup> catalysts have enabled the efficient electrooxidative C–H transformations





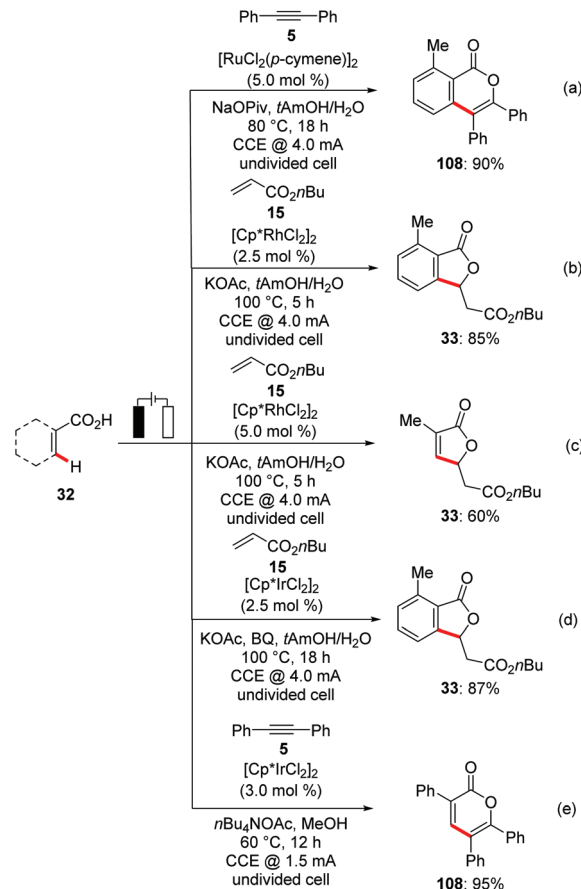
**Scheme 35** Palladaelectro-catalyzed C–H activation using oxime as directing group.

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.<sup>126h</sup> 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)<sub>2</sub>·H<sub>2</sub>O<sup>129</sup> (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 H<sub>2</sub> as the sole by-product (Scheme 36b and c).<sup>127f</sup>

Furthermore, the same group demonstrated the first electrocatalytic iridium-catalyzed C–H/O–H annulation of benzoic acids **32** and acrylates **15**.<sup>128b</sup> 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  $\alpha$ -pyrones **108** in good to excellent yields (Scheme 36e).<sup>128a</sup> 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.<sup>129,130</sup>

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.<sup>131</sup>



**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.<sup>132</sup> Here, the authors employed Cp\*-free Co(OAc)<sub>2</sub>·4H<sub>2</sub>O 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.<sup>133</sup> Intrigued by this report, the electrooxidative<sup>134</sup> direct C–H amination of otherwise inert C–H bonds of aromatic benzamides **32** was subsequently reported.<sup>135</sup> 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 H<sub>2</sub> 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.<sup>136</sup> 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).<sup>137</sup> 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).<sup>138</sup> This environmentally-benign cobalt catalysis was performed in non-toxic H<sub>2</sub>O 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).<sup>139</sup> 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).<sup>140</sup> It is noteworthy that the authors employed an electroreductive hydrazide cleavage approach by the use of catalytic amounts of SmI<sub>2</sub> 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.<sup>141</sup> 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).<sup>142</sup> Mei and Ackermann disclosed C–H/N–H activations of hydrazides **110** with 1,3-diyne **5** using a robust earth-abundant cobalt catalyst to furnish the desired products **117** in good to excellent yields (Scheme 37i).<sup>143</sup> 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).<sup>144</sup> 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.<sup>145</sup>

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



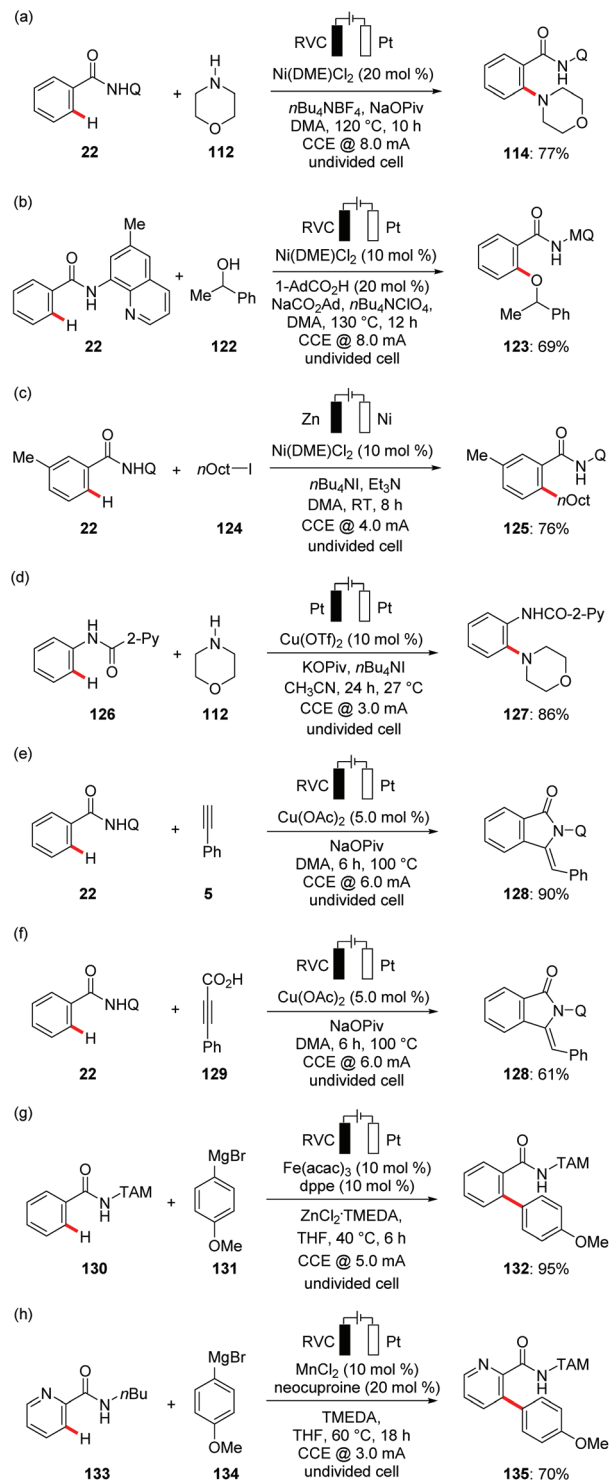


**Scheme 38** Electrochemical C–H activation powered by renewable electricity.

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

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.<sup>147</sup> In 2018, Ackermann reported first electrochemical nickel-catalyzed C–H amination of benzamides **22** (Scheme 39a).<sup>148</sup> 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 H<sub>2</sub> as the sole by product (Scheme 39b).<sup>149</sup> It is worth noting that the chemical oxidants AgOAc, Cu(OAc)<sub>2</sub>, molecular oxygen, PhI(OAc)<sub>2</sub>, or K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> 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).<sup>150</sup> In contrast, previous studies were largely limited to the use of strong bases and considerably higher reaction temperatures for nickel-catalyzed C–H alkylations.<sup>151</sup>

Recently, Mei exploited copper catalysis for the electrochemical C–H aminations of electron-rich anilides **126** with electricity as terminal oxidant (Scheme 39d).<sup>152</sup> In a related work, Nicholls and coworkers reported electro-oxidative amination of anilides with amines producing H<sub>2</sub> as the sole byproduct.<sup>153</sup> 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).<sup>154</sup> Notably,



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

the authors also demonstrated C–H/C–C functionalizations in a decarboxylative fashion with alkyne 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.<sup>155</sup>





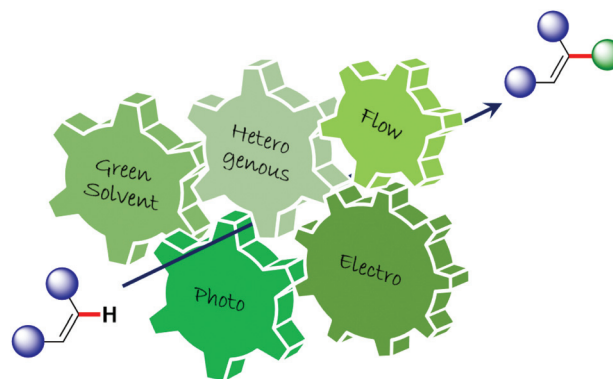
**Scheme 40** Atroposelective palladaelectro-catalyzed C–H activation.

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.<sup>156</sup> To overcome these challenges, Ackermann reported the unprecedented ferralectro-catalyzed C–H arylations at mild temperature using electricity as a green oxidant (Scheme 39g).<sup>157</sup> 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  $\text{MnCl}_2$  was utilized for the electrochemical C–H arylation of amides **133** in the absence of any zinc additives (Scheme 39f).<sup>157</sup>

Despite significant advances of metalla-electrocatalysis, reports on enantioselective electrochemical transformations are scarce.<sup>158</sup> Recently, the Ackermann group reported on the first asymmetric metallaelectro-catalyzed C–H activation.<sup>159</sup> 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.

## Acknowledgements

Generous support by the DFG (Gottfried-Wilhelm-Leibniz award), the DAAD (fellowship to U. D.) and the Onassis Foundation (fellowship to N. K.) is gratefully acknowledged.



## Notes and references

- 1 (a) R. A. Sheldon, Metrics of Green Chemistry and Sustainability: Past, Present, and Future, *ACS Sustainable Chem. Eng.*, 2018, **6**, 32–48; (b) P. A. Wender, Toward the ideal synthesis and molecular function through synthesis-informed design, *Nat. Prod. Rep.*, 2014, **31**, 433–440; (c) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize, *Angew. Chem., Int. Ed.*, 2012, **51**, 5062–5085; (d) P. T. Anastas and M. M. Kirchhoff, Origins, Current Status, and Future Challenges of Green Chemistry, *Acc. Chem. Res.*, 2002, **35**, 686–694; (e) B. M. Trost, Atom Economy—A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259–281; (f) B. M. Trost, The atom economy—a search for synthetic efficiency, *Science*, 1991, **254**, 1471–1477.
- 2 (a) A. Suzuki, Cross-Coupling Reactions Of Organoboranes: An Easy Way To Construct C–C Bonds (Nobel Lecture), *Angew. Chem., Int. Ed.*, 2011, **50**, 6722–6737; (b) E.-i. Negishi, Magical Power of Transition Metals: Past, Present, and Future (Nobel Lecture), *Angew. Chem., Int. Ed.*, 2011, **50**, 6738–6764; (c) A. Zapf and M. Beller, The development of efficient catalysts for palladium-catalyzed coupling reactions of aryl halides, *Chem. Commun.*, 2005, 431–440; (d) K. C. Nicolaou, P. G. Bulger and D. Sarlah, Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442–4489; (e) A. de Meijere and F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, WILEY-VCH, 2nd edn, 2004.
- 3 (a) S. Rej, Y. Ano and N. Chatani, Bidentate Directing Groups: An Efficient Tool in C–H Bond Functionalization Chemistry for the Expedient Construction of C–C Bonds, *Chem. Rev.*, 2020, **120**, 1788–1887; (b) A. Dey, S. K. Sinha, T. K. Achar and D. Maiti, Accessing Remote meta- and para-C(sp<sup>2</sup>)-H Bonds with Covalently Attached Directing Groups, *Angew. Chem., Int. Ed.*, 2019, **58**, 10820–10843; (c) Y. Xu and G. Dong, sp<sup>3</sup> C–H activation via exo-type directing groups, *Chem. Sci.*, 2018, **9**, 1424–1432; (d) C. Sambriago, D. Schönbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, A comprehensive overview of directing groups applied in metal-catalysed C–H functionalisation chemistry, *Chem. Soc. Rev.*, 2018, **47**, 6603–6743; (e) P. Gandeepan and L. Ackermann, Transient Directing Groups for Transformative C–H Activation by Synergistic Metal Catalysis, *Chem*, 2018, **4**, 199–222; (f) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, Recent Advances in Radical C–H Activation/Radical Cross-Coupling, *Chem. Rev.*, 2017, **117**, 9016–9085; (g) Y. Park, Y. Kim and S. Chang, Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications, *Chem. Rev.*, 2017, **117**, 9247–9301; (h) J. R. Hummel, J. A. Boerth and J. A. Ellman, Transition-Metal-Catalyzed C–H Bond Addition to Carbonyls, Imines, and Related Polarized  $\pi$  Bonds, *Chem. Rev.*, 2017, **117**, 9163–9227; (i) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, Palladium-Catalyzed Transformations of Alkyl C–H Bonds, *Chem. Rev.*, 2017, **117**, 8754–8786; (j) H. M. L. Davies and D. Morton, Collective Approach to Advancing C–H Functionalization, *ACS Cent. Sci.*, 2017, **3**, 936–943; (k) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, Mild metal-catalyzed C–H activation: examples and concepts, *Chem. Soc. Rev.*, 2016, **45**, 2900–2936; (l) P. Gandeepan and C.-H. Cheng, Transition-Metal-Catalyzed  $\pi$ -Bond-Assisted C–H Bond Functionalization: An Emerging Trend in Organic Synthesis, *Chem. – Asian J.*, 2015, **10**, 824–838; (m) O. Daugulis, J. Roane and L. D. Tran, Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon–Hydrogen Bonds, *Acc. Chem. Res.*, 2015, **48**, 1053–1064; (n) C. S. Yeung and V. M. Dong, Catalytic Dehydrogenative Cross-Coupling: Forming Carbon–Carbon Bonds by Oxidizing Two Carbon–Hydrogen Bonds, *Chem. Rev.*, 2011, **111**, 1215–1292; (o) L. Ackermann, Carboxylate-Assisted Transition-Metal-Catalyzed C–H Bond Functionalizations: Mechanism and Scope, *Chem. Rev.*, 2011, **111**, 1315–1345; (p) I. A. I. Mkhaliid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, C–H Activation for the Construction of C–B Bonds, *Chem. Rev.*, 2010, **110**, 890–931; (q) T. W. Lyons and M. S. Sanford, Palladium-Catalyzed Ligand-Directed C–H Functionalization Reactions, *Chem. Rev.*, 2010, **110**, 1147–1169; (r) A. Gunay and K. H. Theopold, C–H Bond Activations by Metal Oxo Compounds, *Chem. Rev.*, 2010, **110**, 1060–1081; (s) D. A. Colby, R. G. Bergman and J. A. Ellman, Rhodium-Catalyzed C–C Bond Formation via Heteroatom-Directed C–H Bond Activation, *Chem. Rev.*, 2010, **110**, 624–655; (t) L. Ackermann, R. Vicente and A. R. Kapdi, Transition-Metal-Catalyzed Direct Arylation of (Hetero)Arenes by C–H Bond Cleavage, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (u) R. G. Bergman, C–H activation, *Nature*, 2007, **446**, 391–393; (v) L. Ackermann, Catalytic Arylations with Challenging Substrates: From Air-Stable HASPO Preligands to Indole Syntheses and C–H-Bond Functionalizations, *Synlett*, 2007, 507–526.
- 4 (a) E. R. Welin, A. Ngamnthiporn, M. Klatté, G. Lapointe, G. M. Pototschnig, M. S. J. McDermott, D. Conklin, C. D. Gilmore, P. M. Tadross, C. K. Haley, K. Negoro, E. Glibstrup, C. U. Grünanger, K. M. Allan, S. C. Virgil, D. J. Slamon and B. M. Stoltz, Concise total syntheses of (–)-jorunnamycin A and (–)-jorunmycin enabled by asymmetric catalysis, *Science*, 2019, **363**, 270; (b) A. Çapcı, M. M. Lorion, H. Wang, N. Simon, M. Leidenberger, M. C. Borges Silva, D. R. M. Moreira, Y. Zhu, Y. Meng, J. Y. Chen, Y. M. Lee, O. Friedrich, B. Kappes, J. Wang, L. Ackermann and S. B. Tsogoeva, Artemisinin–(Iso)quinoline Hybrids by C–H Activation and Click Chemistry:





- Combating Multidrug-Resistant Malaria, *Angew. Chem., Int. Ed.*, 2019, **58**, 13066–13079.
- 5 (a) J. Börgel and T. Ritter, Late-Stage Functionalization, *Chem*, 2020, **6**, 1877–1887; (b) W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi and L. Ackermann, Late-Stage Peptide Diversification by Position-Selective C–H Activation, *Angew. Chem., Int. Ed.*, 2018, **57**, 14700–14717; (c) A. F. M. Noisier and M. A. Brimble, C–H Functionalization in the Synthesis of Amino Acids and Peptides, *Chem. Rev.*, 2014, **114**, 8775–8806.
- 6 (a) J.-R. Pouliot, F. Grenier, J. T. Blaskovits, S. Beaupré and M. Leclerc, Direct (Hetero)arylation Polymerization: Simplicity for Conjugated Polymer Synthesis, *Chem. Rev.*, 2016, **116**, 14225–14274; (b) D. J. Schipper and K. Fagnou, Direct Arylation as a Synthetic Tool for the Synthesis of Thiophene-Based Organic Electronic Materials, *Chem. Mater.*, 2011, **23**, 1594–1600.
- 7 (a) S. D. Friis, M. J. Johansson and L. Ackermann, Cobalt-catalysed C–H methylation for late-stage drug diversification, *Nat. Chem.*, 2020, **12**, 511–519; (b) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson and A. Wood, Organic synthesis provides opportunities to transform drug discovery, *Nat. Chem.*, 2018, **10**, 383–394; (c) M. Seki, A New Catalytic System for Ru-Catalyzed C–H Arylation Reactions and Its Application in the Practical Syntheses of Pharmaceutical Agents, *Org. Process Res. Dev.*, 2016, **20**, 867–877; (d) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, The medicinal chemist's toolbox for late stage functionalization of drug-like molecules, *Chem. Soc. Rev.*, 2016, **45**, 546–576; (e) L. Ackermann, Robust Ruthenium(II)-Catalyzed C–H Arylations: Carboxylate Assistance for the Efficient Synthesis of Angiotensin-II-Receptor Blockers, *Org. Process Res. Dev.*, 2015, **19**, 260–269.
- 8 R. A. Sheldon, The E factor 25 years on: the rise of green chemistry and sustainability, *Green Chem.*, 2017, **19**, 18–43.
- 9 (a) S. M. Khake and N. Chatani, Nickel-Catalyzed C–H Functionalization Using A Non-directed Strategy, *Chem*, 2020, **6**, 1056–1081; (b) Ł. Woźniak and N. Cramer, Enantioselective CH Bond Functionalizations by 3d Transition-Metal Catalysts, *Trends Chem.*, 2019, **1**, 471–484; (c) J. Loup, U. Dhawa, F. Pesciaioli, J. Wencel-Delord and L. Ackermann, Enantioselective C–H Activation with Earth-Abundant 3d Transition Metals, *Angew. Chem., Int. Ed.*, 2019, **58**, 12803–12818; (d) S. M. Khake and N. Chatani, Chelation-Assisted Nickel-Catalyzed C–H Functionalizations, *Trends Chem.*, 2019, **1**, 524–539; (e) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, 3d Transition Metals for C–H Activation, *Chem. Rev.*, 2019, **119**, 2192–2452; (f) P. M. Edwards and L. L. Schafer, Early transition metal-catalyzed C–H alkylation: hydroaminoalkylation for Csp<sup>3</sup>–Csp<sup>3</sup> bond formation in the synthesis of selectively substituted amines, *Chem. Commun.*, 2018, **54**, 12543–12560; (g) T. Yoshino and S. Matsunaga, (Pentamethylcyclopentadienyl)cobalt(III)-Catalyzed C–H Bond Functionalization: From Discovery to Unique Reactivity and Selectivity, *Adv. Synth. Catal.*, 2017, **359**, 1245–1262; (h) M. Moselage, J. Li and L. Ackermann, Cobalt-Catalyzed C–H Activation, *ACS Catal.*, 2016, **6**, 498–525; (i) W. Liu and L. Ackermann, Manganese-Catalyzed C–H Activation, *ACS Catal.*, 2016, **6**, 3743–3752; (j) G. Cera and L. Ackermann, Iron-Catalyzed C–H Functionalization Processes, *Top. Curr. Chem.*, 2016, **374**, 57; (k) K. Gao and N. Yoshikai, Low-Valent Cobalt Catalysis: New Opportunities for C–H Functionalization, *Acc. Chem. Res.*, 2014, **47**, 1208–1219; (l) C.-L. Sun, B.-J. Li and Z.-J. Shi, Direct C–H Transformation via Iron Catalysis, *Chem. Rev.*, 2011, **111**, 1293–1314; (m) A. A. Kulkarni and O. Daugulis, Direct Conversion of Carbon-Hydrogen into Carbon-Carbon Bonds by First-Row Transition-Metal Catalysis, *Synthesis*, 2009, 4087–4109.
- 10 (a) J. L. Howard, Q. Cao and D. L. Browne, Mechanochemistry as an emerging tool for molecular synthesis: what can it offer?, *Chem. Sci.*, 2018, **9**, 3080–3094; (b) C. Bolm and J. G. Hernández, From Synthesis of Amino Acids and Peptides to Enzymatic Catalysis: A Bottom-Up Approach in Mechanochemistry, *ChemSusChem*, 2018, **11**, 1410–1420; (c) N. A. Romero and D. A. Nicewicz, Organic Photoredox Catalysis, *Chem. Rev.*, 2016, **116**, 10075–10166; (d) M. D. Kärkäs, J. A. Porco and C. R. J. Stephenson, Photochemical Approaches to Complex Chemotypes: Applications in Natural Product Synthesis, *Chem. Rev.*, 2016, **116**, 9683–9747.
- 11 T. H. Meyer, I. Choi, C. Tian and L. Ackermann, Powering the Future: How Can Electrochemistry Make a Difference in Organic Synthesis?, *Chem*, 2020, **6**, 2484–2496.
- 12 (a) C. J. Clarke, W.-C. Tu, O. Levers, A. Bröhl and J. P. Hallett, Green and Sustainable Solvents in Chemical Processes, *Chem. Rev.*, 2018, **118**, 747–800; (b) C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry To Drive More Sustainable Processes, *Org. Process Res. Dev.*, 2011, **15**, 912–917.
- 13 (a) L. Soh and M. J. Eckelman, Green Solvents in Biomass Processing, *ACS Sustainable Chem. Eng.*, 2016, **4**, 5821–5837; (b) F. P. Byrne, S. Jin, G. Paggiola, T. H. M. Petchey, J. H. Clark, T. J. Farmer, A. J. Hunt, C. Robert McElroy and J. Sherwood, Tools and techniques for solvent selection: green solvent selection guides, *Sustainable Chem. Processes*, 2016, **4**, 7; (c) M. Tobiszewski, S. Tsakovski, V. Simeonov, J. Namieśnik and F. Pena-Pereira, A solvent selection guide based on chemometrics and multicriteria decision analysis, *Green Chem.*, 2015, **17**, 4773–4785; (d) D. Prat, O. Pardigon, H.-W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek, Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes, *Org. Process Res. Dev.*, 2013, **17**, 1517–1525; (e) L. Moity, M. Durand, A. Benazzouz, C. Pierlot, V. Molinier and



- J.-M. Aubry, Panorama of sustainable solvents using the COSMO-RS approach, *Green Chem.*, 2012, **14**, 1132–1145; (f) P. J. Dunn, The importance of Green Chemistry in Process Research and Development, *Chem. Soc. Rev.*, 2012, **41**, 1452–1461; (g) P. G. Jessop, Searching for green solvents, *Green Chem.*, 2011, **13**, 1391–1398; (h) K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation, *Green Chem.*, 2008, **10**, 31–36.
- 14 (a) T. Dalton, T. Faber and F. Glorius, C–H Activation: Toward Sustainability and Applications, *ACS Cent. Sci.*, 2021, **7**, 245–261; (b) S. Santoro, A. Marrocchi, D. Lanari, L. Ackermann and L. Vaccaro, Towards Sustainable C–H Functionalization Reactions: The Emerging Role of Bio-Based Reaction Media, *Chem. – Eur. J.*, 2018, **24**, 13383–13390; (c) C. M. Alder, J. D. Hayler, R. K. Henderson, A. M. Redman, L. Shukla, L. E. Shuster and H. F. Sneddon, Updating and further expanding GSK's solvent sustainability guide, *Green Chem.*, 2016, **18**, 3879–3890; (d) C. Fischmeister and H. Doucet, Greener solvents for ruthenium and palladium-catalysed aromatic C–H bond functionalisation, *Green Chem.*, 2011, **13**, 741–753; (e) R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks and A. D. Curzons, Expanding GSK's solvent selection guide – embedding sustainability into solvent selection starting at medicinal chemistry, *Green Chem.*, 2011, **13**, 854–862; (f) D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehadeh and P. J. Dunn, CHEM21 selection guide of classical- and less classical-solvents, *Green Chem.*, 2016, **18**, 288–296; (g) J. H. Clark and S. J. Tavener, Alternative Solvents: Shades of Green, *Org. Process Res. Dev.*, 2007, **11**, 149–155; (h) L. J. Diorazio, D. R. J. Hose and N. K. Adlington, Toward a More Holistic Framework for Solvent Selection, *Org. Process Res. Dev.*, 2016, **20**, 760–773.
- 15 (a) F. G. Calvo-Flores, M. J. Monteagudo-Arrebola, J. A. Dobado and J. Isac-García, Green and Bio-Based Solvents, *Top. Curr. Chem.*, 2018, **376**, 18; (b) M. Sarmah, M. Mondal and U. Bora, Agro-Waste Extract Based Solvents: Emergence of Novel Green Solvent for the Design of Sustainable Processes in Catalysis and Organic Chemistry, *ChemistrySelect*, 2017, **2**, 5180–5188; (c) S. Santoro, F. Ferlin, L. Luciani, L. Ackermann and L. Vaccaro, Biomass-derived solvents as effective media for cross-coupling reactions and C–H functionalization processes, *Green Chem.*, 2017, **19**, 1601–1612; (d) G. C. Arlene, W. P. Márcio and S. S. Ricardo, Application of Bio-Based Solvents in Catalysis, *Curr. Org. Synth.*, 2015, **12**, 675–695; (e) Y. Gu and F. Jérôme, Bio-based solvents: an emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry, *Chem. Soc. Rev.*, 2013, **42**, 9550–9570.
- 16 P. Gandeepan, N. Kaplaneris, S. Santoro, L. Vaccaro and L. Ackermann, Biomass-Derived Solvents for Sustainable Transition Metal-Catalyzed C–H Activation, *ACS Sustainable Chem. Eng.*, 2019, **7**, 8023–8040.
- 17 (a) T. Kitanosono, K. Masuda, P. Xu and S. Kobayashi, Catalytic Organic Reactions in Water toward Sustainable Society, *Chem. Rev.*, 2018, **118**, 679–746; (b) B. Li and P. H. Dixneuf,  $sp^2$  C–H bond activation in water and catalytic cross-coupling reactions, *Chem. Soc. Rev.*, 2013, **42**, 5744–5767; (c) A. Chanda and V. V. Fokin, Organic Synthesis “On Water”, *Chem. Rev.*, 2009, **109**, 725–748; (d) C. I. Herrerías, X. Yao, Z. Li and C.-J. Li, Reactions of C–H Bonds in Water, *Chem. Rev.*, 2007, **107**, 2546–2562; (e) C.-J. Li, Organic Reactions in Aqueous Media with a Focus on Carbon–Carbon Bond Formations: A Decade Update, *Chem. Rev.*, 2005, **105**, 3095–3166.
- 18 (a) Y. Zhu, C. Romain and C. K. Williams, Sustainable polymers from renewable resources, *Nature*, 2016, **540**, 354–362; (b) B. Pereira, H. Zhang, M. De Mey, C. G. Lim, Z.-J. Li and G. Stephanopoulos, Engineering a novel biosynthetic pathway in *Escherichia coli* for production of renewable ethylene glycol, *Biotechnol. Bioeng.*, 2016, **113**, 376–383.
- 19 (a) M. Vafaezadeh and M. M. Hashemi, Polyethylene glycol (PEG) as a green solvent for carbon–carbon bond formation reactions, *J. Mol. Liq.*, 2015, **207**, 73–79; (b) E. Colacino, J. Martinez, F. Lamaty, L. S. Patrikeeva, L. L. Khemchyan, V. P. Ananikov and I. P. Beletskaya, PEG as an alternative reaction medium in metal-mediated transformations, *Coord. Chem. Rev.*, 2012, **256**, 2893–2920; (c) J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, Polyethylene glycol and solutions of polyethylene glycol as green reaction media, *Green Chem.*, 2005, **7**, 64–82.
- 20 L. Ackermann and R. Vicente, Catalytic Direct Arylations in Polyethylene Glycol (PEG): Recyclable Palladium(0) Catalyst for C–H Bond Cleavages in the Presence of Air, *Org. Lett.*, 2009, **11**, 4922–4925.
- 21 (a) L. Ackermann, A. Althammer and R. Born,  $[RuCl_3(H_2O)_n]$ -catalyzed direct arylations, *Tetrahedron*, 2008, **64**, 6115–6124; (b) L. Ackermann, A. Althammer and R. Born,  $[RuCl_3(H_2O)_n]$ -Catalyzed Direct Arylations with Bromides as Electrophiles, *Synlett*, 2007, 2833–2836.
- 22 L. Jian, H.-Y. He, J. Huang, Q.-H. Wu, M.-L. Yuan, H.-Y. Fu, X.-L. Zheng, H. Chen and R.-X. Li, Combination of  $RuCl_3 \cdot xH_2O$  with PEG – a simple and recyclable catalytic system for direct arylation of heteroarenes via C–H bond activation, *RSC Adv.*, 2017, **7**, 23515–23522.
- 23 S. I. Kozhushkov and L. Ackermann, Ruthenium-catalyzed direct oxidative alkenylation of arenes through twofold C–H bond functionalization, *Chem. Sci.*, 2013, **4**, 886–896.
- 24 N. Kavitha, G. Sukumar, V. P. Kumar, P. S. Mainkar and S. Chandrasekhar, Ruthenium-catalyzed benzimidazoquinoline synthesis via oxidative coupling of 2-arylbenzimidazoles with alkynes, *Tetrahedron Lett.*, 2013, **54**, 4198–4201.



- 25 (a) C. Kornhaaf, J. Li and L. Ackermann, Cationic Ruthenium Catalysts for Alkyne Annulations with Oximes by C–H/N–O Functionalizations, *J. Org. Chem.*, 2012, **77**, 9190–9198; (b) L. Ackermann and S. Fenner, Ruthenium-Catalyzed C–H/N–O Bond Functionalization: Green Isoquinolone Syntheses in Water, *Org. Lett.*, 2011, **13**, 6548–6551.
- 26 S. L. Yedage and B. M. Bhanage, Ru(II)/PEG-400 as a highly efficient and recyclable catalytic media for annulation and olefination reactions via C–H bond activation, *Green Chem.*, 2016, **18**, 5635–5642.
- 27 D. S. Deshmukh and B. M. Bhanage, N-Tosylhydrazone directed annulation via C–H/N–N bond activation in Ru(II)/PEG-400 as homogeneous recyclable catalytic system: a green synthesis of isoquinolines, *Org. Biomol. Chem.*, 2018, **16**, 4864–4873.
- 28 H. Zhao, T. Zhang, T. Yan and M. Cai, Recyclable and Reusable  $[\text{RuCl}_2(p\text{-cymene})]_2/\text{Cu}(\text{OAc})_2/\text{PEG-400}/\text{H}_2\text{O}$  System for Oxidative C–H Bond Alkenylations: Green Synthesis of Phthalides, *J. Org. Chem.*, 2015, **80**, 8849–8855.
- 29 M.-A. Hiebel, Y. Fall, M.-C. Scherrmann and S. Berteina-Raboin, Straightforward Synthesis of Various 2,3-Diarylimidazo[1,2-*a*]pyridines in PEG400 Medium through One-Pot Condensation and C–H Arylation, *Eur. J. Org. Chem.*, 2014, 4643–4650.
- 30 W. Ma and L. Ackermann, Cobalt(II)-Catalyzed Oxidative C–H Alkenylations: Regio- and Site-Selective Access to Isoindolin-1-one, *ACS Catal.*, 2015, **5**, 2822–2825.
- 31 C. Kuai, L. Wang, B. Li, Z. Yang and X. Cui, Cobalt-Catalyzed Selective Synthesis of Isoquinolines Using Picolinamide as a Traceless Directing Group, *Org. Lett.*, 2017, **19**, 2102–2105.
- 32 G. C. Reddy, P. Balasubramanyam, N. Salvanna and B. Das, Copper-Mediated C–H Activation of 1,3,4-Oxadiazoles with 1,1-Dibromo-1-alkenes Using PEG-400 as a Solvent Medium: Distinct Approach for the Alkynylation of 1,3,4-Oxadiazoles, *Eur. J. Org. Chem.*, 2012, 471–474.
- 33 I. T. Horváth, H. Mehdi, V. Fábos, L. Boda and L. T. Mika,  $\gamma$ -Valerolactone—a sustainable liquid for energy and carbon-based chemicals, *Green Chem.*, 2008, **10**, 238–242.
- 34 (a) Z. Zhang, Synthesis of  $\gamma$ -Valerolactone from Carbohydrates and its Applications, *ChemSusChem*, 2016, **9**, 156–171; (b) F. Liguori, C. Moreno-Marrodan and P. Barbaro, Environmentally Friendly Synthesis of  $\gamma$ -Valerolactone by Direct Catalytic Conversion of Renewable Sources, *ACS Catal.*, 2015, **5**, 1882–1894; (c) A. Farrán, C. Cai, M. Sandoval, Y. Xu, J. Liu, M. J. Hernáiz and R. J. Linhardt, Green Solvents in Carbohydrate Chemistry: From Raw Materials to Fine Chemicals, *Chem. Rev.*, 2015, **115**, 6811–6853; (d) D. M. Alonso, S. G. Wettstein and J. A. Dumesic, Gamma-valerolactone, a sustainable platform molecule derived from lignocellulosic biomass, *Green Chem.*, 2013, **15**, 584–595.
- 35 (a) G. Strappaveccia, L. Luciani, E. Bartollini, A. Marrocchi, F. Pizzo and L. Vaccaro,  $\gamma$ -Valerolactone as an alternative biomass-derived medium for the Sonogashira reaction, *Green Chem.*, 2015, **17**, 1071–1076; (b) G. Strappaveccia, E. Ismalaj, C. Petrucci, D. Lanari, A. Marrocchi, M. Drees, A. Facchetti and L. Vaccaro, A biomass-derived safe medium to replace toxic dipolar solvents and access cleaner Heck coupling reactions, *Green Chem.*, 2015, **17**, 365–372; (c) E. Ismalaj, G. Strappaveccia, E. Ballerini, F. Elisei, O. Piermatti, D. Gelman and L. Vaccaro,  $\gamma$ -Valerolactone as a Renewable Dipolar Aprotic Solvent Deriving from Biomass Degradation for the Hiyama Reaction, *ACS Sustainable Chem. Eng.*, 2014, **2**, 2461–2464.
- 36 (a) P. Pongrácz, B. Bartal, L. Kollár and L. T. Mika, Rhodium-catalyzed hydroformylation in  $\gamma$ -valerolactone as a biomass-derived solvent, *J. Organomet. Chem.*, 2017, **847**, 140–145; (b) P. Pongrácz, L. Kollár and L. T. Mika, A step towards hydroformylation under sustainable conditions: platinum-catalysed enantioselective hydroformylation of styrene in gamma-valerolactone, *Green Chem.*, 2016, **18**, 842–847.
- 37 D. Marosvölgyi-Haskó, B. Lengyel, J. M. Tukacs, L. Kollár and L. T. Mika, Application of  $\gamma$ -Valerolactone as an Alternative Biomass-Based Medium for Aminocarbonylation Reactions, *ChemPlusChem*, 2016, **81**, 1224–1229.
- 38 S. Tabasso, E. Calcio Gaudino, L. Rinaldi, A. Ledoux, P. Larini and G. Cravotto, Microwave-assisted, ligand-free, direct C–H arylation of thiophenes in biomass-derived  $\gamma$ -valerolactone, *New J. Chem.*, 2017, **41**, 9210–9215.
- 39 A. Bechtoldt, M. E. Baumert, L. Vaccaro and L. Ackermann, Ruthenium(II) oxidase catalysis for C–H alkenylations in biomass-derived  $\gamma$ -valerolactone, *Green Chem.*, 2018, **20**, 398–402.
- 40 Q. Bu, T. Rogge, V. Kotek and L. Ackermann, Distal Weak Coordination of Acetamides in Ruthenium(II)-Catalyzed C–H Activation Processes, *Angew. Chem., Int. Ed.*, 2018, **57**, 765–768.
- 41 Q. Bu, E. Gońka, K. Kuciński and L. Ackermann, Cobalt-Catalyzed Hiyama-Type C–H Activation with Arylsiloxanes: Versatile Access to Highly *ortho*-Decorated Biaryls, *Chem. – Eur. J.*, 2019, **25**, 2213–2216.
- 42 (a) R. Mariscal, P. Maireles-Torres, M. Ojeda, I. Sádaba and M. López Granados, Furfural: a renewable and versatile platform molecule for the synthesis of chemicals and fuels, *Energy Environ. Sci.*, 2016, **9**, 1144–1189; (b) C. M. Cai, T. Zhang, R. Kumar and C. E. Wyman, Integrated furfural production as a renewable fuel and chemical platform from lignocellulosic biomass, *J. Chem. Technol. Biotechnol.*, 2014, **89**, 2–10.
- 43 D. F. Aycock, Solvent Applications of 2-Methyltetrahydrofuran in Organometallic and Biphasic Reactions, *Org. Process Res. Dev.*, 2007, **11**, 156–159.
- 44 J. A. Leitch, P. B. Wilson, C. L. McMullin, M. F. Mahon, Y. Bhonoah, I. H. Williams and C. G. Frost, Ruthenium(II)-Catalyzed C–H Functionalization Using the Oxazolidinone Heterocycle as a Weakly Coordinating



- Directing Group: Experimental and Computational Insights, *ACS Catal.*, 2016, **6**, 5520–5529.
- 45 F. Fumagalli, S. Warratz, S.-K. Zhang, T. Rogge, C. Zhu, A. C. Stückl and L. Ackermann, Arene-Ligand-Free Ruthenium(II/III) Manifold for *meta*-C–H Alkylation: Remote Purine Diversification, *Chem. – Eur. J.*, 2018, **24**, 3984–3988.
- 46 R. Matsidik, A. Luzio, S. Hameury, H. Komber, C. R. McNeill, M. Caironi and M. Sommer, Effects of PNDIT2 end groups on aggregation, thin film structure, alignment and electron transport in field-effect transistors, *J. Mater. Chem. C*, 2016, **4**, 10371–10380.
- 47 T. Bura, S. Beaupré, O. A. Ibraikulov, M.-A. Légaré, J. Quinn, P. Lévêque, T. Heiser, Y. Li, N. Leclerc and M. Leclerc, New Fluorinated Dithienyldiketopyrrolopyrrole Monomers and Polymers for Organic Electronics, *Macromolecules*, 2017, **50**, 7080–7090.
- 48 (a) B. M. Monks, E. R. Fruchey and S. P. Cook, Iron-Catalyzed C(sp<sup>2</sup>)-H Alkylation of Carboxamides with Primary Electrophiles, *Angew. Chem., Int. Ed.*, 2014, **53**, 11065–11069; (b) E. R. Fruchey, B. M. Monks and S. P. Cook, A Unified Strategy for Iron-Catalyzed *ortho*-Alkylation of Carboxamides, *J. Am. Chem. Soc.*, 2014, **136**, 13130–13133.
- 49 (a) N. Krause, New surfactants for chemistry in water, *Curr. Opin. Green Sustainable Chem.*, 2017, **7**, 18–22; (b) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, “On Water”: Unique Reactivity of Organic Compounds in Aqueous Suspension, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275–3279; (c) J. E. Klijin and J. B. F. N. Engberts, Fast reactions ‘on water’, *Nature*, 2005, **435**, 746–747.
- 50 T. Nishikata, A. R. Abela and B. H. Lipshutz, Room Temperature C–H Activation and Cross-Coupling of Aryl Ureas in Water, *Angew. Chem., Int. Ed.*, 2010, **49**, 781–784.
- 51 F. Szabó, J. Daru, D. Simkó, T. Z. Nagy, A. Stirling and Z. Novák, Mild Palladium-Catalyzed Oxidative Direct *ortho*-C–H Acylation of Anilides under Aqueous Conditions, *Adv. Synth. Catal.*, 2013, **355**, 685–691.
- 52 S. R. Yetra, T. Rogge, S. Warratz, J. Struwe, W. Peng, P. Vana and L. Ackermann, Micellar Catalysis for Ruthenium(II)-Catalyzed C–H Arylation: Weak-Coordination-Enabled C–H Activation in H<sub>2</sub>O, *Angew. Chem., Int. Ed.*, 2019, **58**, 7490–7494.
- 53 (a) W. Liu, D. Wang, Y. Zhao, F. Yi and J. Chen, Palladium-Catalyzed Mono-Selective *ortho* C–H Arylation of Aryl Sulfonamides in Water: A Concise Access to Biaryl Sulfoamide Derivatives, *Adv. Synth. Catal.*, 2016, **358**, 1968–1974; (b) F. Chen, Q.-Q. Min and X. Zhang, Pd-Catalyzed Direct Arylation of Polyfluoroarenes on Water under Mild Conditions Using PPh<sub>3</sub> Ligand, *J. Org. Chem.*, 2012, **77**, 2992–2998; (c) L. Joucla, N. Batail and L. Djakovitch, “On Water” Direct and Site-Selective Pd-Catalyzed C–H Arylation of (NH)-Indoles, *Adv. Synth. Catal.*, 2010, **352**, 2929–2936; (d) S. A. Ohnmacht, P. Mamone, A. J. Culshaw and M. F. Greaney, Direct arylations on water: synthesis of 2,5-disubstituted oxazoles balsoxin and texaline, *Chem. Commun.*, 2008, 1241–1243; (e) G. L. Turner, J. A. Morris and M. F. Greaney, Direct Arylation of Thiazoles on Water, *Angew. Chem., Int. Ed.*, 2007, **46**, 7996–8000.
- 54 (a) S. Wu, X. Wu, C. Fu and S. Ma, Rhodium(III)-Catalyzed C–H Functionalization in Water for Isoindolin-1-one Synthesis, *Org. Lett.*, 2018, **20**, 2831–2834; (b) S. Kim, S. Han, J. Park, S. Sharma, N. K. Mishra, H. Oh, J. H. Kwak and I. S. Kim, Cp\*Rh(III)-catalyzed C(sp<sup>3</sup>)-H alkylation of 8-methylquinolines in aqueous media, *Chem. Commun.*, 2017, **53**, 3006–3009; (c) L. Shi and B. Wang, Tandem Rh(III)-Catalyzed C–H Amination/Annulation Reactions: Synthesis of Indoloquinoline Derivatives in Water, *Org. Lett.*, 2016, **18**, 2820–2823; (d) S. P. Midya, M. K. Sahoo, V. G. Landge, P. R. Rajamohan and E. Balaraman, Reversed reactivity of anilines with alkynes in the rhodium-catalysed C–H activation/carbonylation tandem, *Nat. Commun.*, 2015, **6**, 8591.
- 55 S. Debbarma, M. R. Sk, B. Modak and M. S. Maji, On-Water Cp\*Ir(III)-Catalyzed C–H Functionalization for the Synthesis of Chromones through Annulation of Salicylaldehydes with Diazo-Ketones, *J. Org. Chem.*, 2019, **84**, 6207–6216.
- 56 (a) W.-J. Han, F. Pu, C.-J. Li, Z.-W. Liu, J. Fan and X.-Y. Shi, Carboxyl-Directed Conjugate Addition of C–H Bonds to  $\alpha,\beta$ -Unsaturated Ketones in Air and Water, *Adv. Synth. Catal.*, 2018, **360**, 1358–1363; (b) L. Ackermann, L. Wang, R. Wolfram and A. V. Lygin, Ruthenium-Catalyzed Oxidative C–H Alkenylations of Anilides and Benzamides in Water, *Org. Lett.*, 2012, **14**, 728–731; (c) L. Ackermann and A. V. Lygin, Cationic Ruthenium(II) Catalysts for Oxidative C–H/N–H Bond Functionalizations of Anilines with Removable Directing Group: Synthesis of Indoles in Water, *Org. Lett.*, 2012, **14**, 764–767; (d) L. Ackermann and J. Pospech, Ruthenium-Catalyzed Oxidative C–H Bond Alkenylations in Water: Expedient Synthesis of Annulated Lactones, *Org. Lett.*, 2011, **13**, 4153–4155; (e) P. B. Arockiam, C. Fischmeister, C. Bruneau and P. H. Dixneuf, C–H Bond Functionalization in Water Catalyzed by Carboxylato Ruthenium(II) Systems, *Angew. Chem., Int. Ed.*, 2010, **49**, 6629–6632; (f) L. Ackermann, Phosphine Oxides as Preligands in Ruthenium-Catalyzed Arylations via C–H Bond Functionalization Using Aryl Chlorides, *Org. Lett.*, 2005, **7**, 3123–3125.
- 57 (a) J. Xu, L. Qiao, J. Shen, K. Chai, C. Shen and P. Zhang, Nickel(II)-Catalyzed Site-Selective C–H Bond Trifluoromethylation of Arylamine in Water through a Coordinating Activation Strategy, *Org. Lett.*, 2017, **19**, 5661–5664; (b) L.-Y. Xie, Y.-J. Li, J. Qu, Y. Duan, J. Hu, K.-J. Liu, Z. Cao and W.-M. He, A base-free, ultrasound accelerated one-pot synthesis of 2-sulfonylquinolines in water, *Green Chem.*, 2017, **19**, 5642–5646; (c) H. Qiao, S. Sun, F. Yang, Y. Zhu, J. Kang, Y. Wu and Y. Wu, Merging Photoredox Catalysis with Iron(III) Catalysis: C5-



- H Bromination and Iodination of 8-Aminoquinoline Amides in Water, *Adv. Synth. Catal.*, 2017, **359**, 1976–1980; (d) H. Fang, Y. Dou, J. Ge, M. Chhabra, H. Sun, P. Zhang, Y. Zheng and Q. Zhu, Regioselective and Direct Azidation of Anilines via Cu(II)-Catalyzed C–H Functionalization in Water, *J. Org. Chem.*, 2017, **82**, 11212–11217; (e) C.-J. Wu, J.-J. Zhong, Q.-Y. Meng, T. Lei, X.-W. Gao, C.-H. Tung and L.-Z. Wu, Cobalt-Catalyzed Cross-Dehydrogenative Coupling Reaction in Water by Visible Light, *Org. Lett.*, 2015, **17**, 884–887.
- 58 H. Wang, M. M. Lorion and L. Ackermann, Air-Stable Manganese(I)-Catalyzed C–H Activation for Decarboxylative C–H/C–O Cleavages in Water, *Angew. Chem., Int. Ed.*, 2017, **56**, 6339–6342.
- 59 H. Wang, I. Choi, T. Rogge, N. Kaplaneris and L. Ackermann, Versatile and robust C–C activation by chelation-assisted manganese catalysis, *Nat. Catal.*, 2018, **1**, 993–1001.
- 60 Q. Lu, F. J. R. Klauck and F. Glorius, Manganese-catalyzed allylation via sequential C–H and C–C/C–Het bond activation, *Chem. Sci.*, 2017, **8**, 3379–3383.
- 61 S. Santoro, S. I. Kozhushkov, L. Ackermann and L. Vaccaro, Heterogeneous catalytic approaches in C–H activation reactions, *Green Chem.*, 2016, **18**, 3471–3493.
- 62 A. A. Latimer, A. R. Kulkarni, H. Aljama, J. H. Montoya, J. S. Yoo, C. Tsai, F. Abild-Pedersen, F. Studt and J. K. Nørskov, Understanding trends in C–H bond activation in heterogeneous catalysis, *Nat. Mater.*, 2017, **16**, 225–229.
- 63 M. Parisien, D. Valette and K. Fagnou, Direct Arylation Reactions Catalyzed by Pd(OH)<sub>2</sub>/C: Evidence for a Soluble Palladium Catalyst, *J. Org. Chem.*, 2005, **70**, 7578–7584.
- 64 F. Jafarpour, S. Rahiminejadan and H. Hazrati, Triethanolamine-Mediated Palladium-Catalyzed Regioselective C-2 Direct Arylation of Free NH-Pyrroles, *J. Org. Chem.*, 2010, **75**, 3109–3112.
- 65 K. D. Collins, R. Honeker, S. Vásquez-Céspedes, D.-T. D. Tang and F. Glorius, C–H arylation of triphenylene, naphthalene and related arenes using Pd/C, *Chem. Sci.*, 2015, **6**, 1816–1824.
- 66 (a) Y.-B. Huang, M. Shen, X. Wang, P. Huang, R. Chen, Z.-J. Lin and R. Cao, Water-medium C–H activation over a hydrophobic perfluoroalkane-decorated metal-organic framework platform, *J. Catal.*, 2016, **333**, 1–7; (b) M. Cao, D. Wu, W. Su and R. Cao, Palladium nanocrystals stabilized by cucurbit[6]uril as efficient heterogeneous catalyst for direct C–H functionalization of polyfluoroarenes, *J. Catal.*, 2015, **321**, 62–69; (c) J. Malmgren, A. Nagendiran, C.-W. Tai, J.-E. Bäckvall and B. Olofsson, C-2 Selective Arylation of Indoles with Heterogeneous Nanopalladium and Diaryliodonium Salts, *Chem. – Eur. J.*, 2014, **20**, 13531–13535; (d) V. A. Zinovyeva, M. A. Vorotyntsev, I. Bezverkhyy, D. Chaumont and J.-C. Hierso, Highly Dispersed Palladium–Polypyrrole Nanocomposites: In-Water Synthesis and Application for Catalytic Arylation of Heteroaromatics by Direct C–H Bond Activation, *Adv. Funct. Mater.*, 2011, **21**, 1064–1075; (e) L. Wang, W.-b. Yi and C. Cai, Fluorous silica gel-supported perfluoro-tagged palladium nanoparticles: an efficient and reusable catalyst for direct C-2 arylation of indoles, *Chem. Commun.*, 2011, **47**, 806–808; (f) T.-H. Park, A. J. Hickman, K. Koh, S. Martin, A. G. Wong-Foy, M. S. Sanford and A. J. Matzger, Highly Dispersed Palladium(II) in a Defective Metal–Organic Framework: Application to C–H Activation and Functionalization, *J. Am. Chem. Soc.*, 2011, **133**, 20138–20141; (g) Y. Huang, Z. Lin and R. Cao, Palladium Nanoparticles Encapsulated in a Metal–Organic Framework as Efficient Heterogeneous Catalysts for Direct C2 Arylation of Indoles, *Chem. – Eur. J.*, 2011, **17**, 12706–12712; (h) S. Hernández, I. Moreno, R. SanMartin, G. Gómez, M. T. Herrero and E. Domínguez, Toward Safer Processes for C–C Biaryl Bond Construction: Catalytic Direct C–H Arylation and Tin-Free Radical Coupling in the Synthesis of Pyrazolophenanthridines, *J. Org. Chem.*, 2010, **75**, 434–441.
- 67 (a) S. Keshipour and A. Shaabani, Copper(I) and palladium nanoparticles supported on ethylenediamine-functionalized cellulose as an efficient catalyst for the 1,3-dipolar cycloaddition/direct arylation sequence, *Appl. Organomet. Chem.*, 2014, **28**, 116–119; (b) D.-T. D. Tang, K. D. Collins and F. Glorius, Completely Regioselective Direct C–H Functionalization of Benzo[b]thiophenes Using a Simple Heterogeneous Catalyst, *J. Am. Chem. Soc.*, 2013, **135**, 7450–7453.
- 68 E. Y. Lee and J. Park, Recyclable Copper Catalyst for meta-Selective C–H Bond Arylation, *ChemCatChem*, 2011, **3**, 1127–1129.
- 69 W. Zhang, Q. Zeng, X. Zhang, Y. Tian, Y. Yue, Y. Guo and Z. Wang, Ligand-Free CuO Nanospindle Catalyzed Arylation of Heterocycle C–H Bonds, *J. Org. Chem.*, 2011, **76**, 4741–4745.
- 70 (a) H. T. N. Le, T. T. Nguyen, P. H. L. Vu, T. Truong and N. T. S. Phan, Ligand-free direct C-arylation of heterocycles with aryl halides over a metal-organic framework Cu<sub>2</sub>(BPDC)<sub>2</sub>(BPY) as an efficient and robust heterogeneous catalyst, *J. Mol. Catal. A: Chem.*, 2014, **391**, 74–82; (b) F. Jeremias, D. Fröhlich, C. Janiak and S. K. Henninger, Advancement of sorption-based heat transformation by a metal coating of highly-stable, hydrophilic aluminium fumarate MOF, *RSC Adv.*, 2014, **4**, 24073–24082.
- 71 I. Choi, V. Müller, G. Lole, R. Köhler, V. Karius, W. Viöl, C. Jooss and L. Ackermann, Photoinduced Heterogeneous C–H Arylation by a Reusable Hybrid Copper Catalyst, *Chem. – Eur. J.*, 2020, **26**, 3509–3514.
- 72 H. Miura, K. Wada, S. Hosokawa and M. Inoue, Recyclable Solid Ruthenium Catalysts for the Direct Arylation of Aromatic C–H Bonds, *Chem. – Eur. J.*, 2010, **16**, 4186–4189.
- 73 (a) W. Liang, T. Zhang, Y. Liu, Y. Huang, Z. Liu, Y. Liu, B. Yang, X. Zhou and J. Zhang, Polydimethylsiloxane



- Sponge-Supported Nanometer Gold: Highly Efficient Recyclable Catalyst for Cross-Dehydrogenative Coupling in Water, *ChemSusChem*, 2018, **11**, 3586–3590; (b) Y. Zhang, Y. Zhao, Y. Luo, L. Xiao, Y. Huang, X. Li, Q. Peng, Y. Liu, B. Yang, C. Zhu, X. Zhou and J. Zhang, Directed Aromatic C–H Activation/Acetoxylation Catalyzed by Pd Nanoparticles Supported on Graphene Oxide, *Org. Lett.*, 2017, **19**, 6470–6473; (c) V. Panwar, P. Kumar, A. Bansal, S. S. Ray and S. L. Jain, PEGylated magnetic nanoparticles (PEG@Fe<sub>3</sub>O<sub>4</sub>) as cost effective alternative for oxidative cyanation of tertiary amines via CH activation, *Appl. Catal., A*, 2015, **498**, 25–31; (d) L. He, K. Natte, J. Rabeah, C. Taeschler, H. Neumann, A. Brückner and M. Beller, Heterogeneous Platinum-Catalyzed C–H Perfluoroalkylation of Arenes and Heteroarenes, *Angew. Chem., Int. Ed.*, 2015, **54**, 4320–4324; (e) H. Duan, M. Li, G. Zhang, J. R. Gallagher, Z. Huang, Y. Sun, Z. Luo, H. Chen, J. T. Miller, R. Zou, A. Lei and Y. Zhao, Single-Site Palladium(II) Catalyst for Oxidative Heck Reaction: Catalytic Performance and Kinetic Investigations, *ACS Catal.*, 2015, **5**, 3752–3759; (f) J. Chen, K. Natte and X.-F. Wu, Pd/C-catalyzed carbonylative C–H activation with DMF as the CO source, *Tetrahedron Lett.*, 2015, **56**, 6413–6416; (g) C. Bai, X. Yao and Y. Li, Easy Access to Amides through Aldehydic C–H Bond Functionalization Catalyzed by Heterogeneous Co-Based Catalysts, *ACS Catal.*, 2015, **5**, 884–891; (h) J. Chen, L. He, K. Natte, H. Neumann, M. Beller and X.-F. Wu, Palladium@Cerium(IV) Oxide-Catalyzed Oxidative Synthesis of N-(2-Pyridyl)indoles via C–H Activation Reaction, *Adv. Synth. Catal.*, 2014, **356**, 2955–2959; (i) R. Kishore, M. L. Kantam, J. Yadav, M. Sudhakar, S. Laha and A. Venugopal, Pd/Mg–La mixed oxide catalyzed oxidative sp<sup>2</sup> CH bond acylation with alcohols, *J. Mol. Catal. A: Chem.*, 2013, **379**, 213–218; (j) S. Verma, S. L. Jain and B. Sain, Starch Immobilized Ruthenium Trichloride Catalyzed Oxidative Cyanation of Tertiary Amines with Hydrogen Peroxide, *ChemCatChem*, 2011, **3**, 1329–1332; (k) L. L. Chng, J. Zhang, J. Yang, M. Amoura and J. Y. Ying, C–C Bond Formation via C–H Activation and C–N Bond Formation via Oxidative Amination Catalyzed by Palladium- Polyoxometalate Nanomaterials Using Dioxide as the Terminal Oxidant, *Adv. Synth. Catal.*, 2011, **353**, 2988–2998; (l) H. Miura, K. Wada, S. Hosokawa and M. Inoue, Catalytic Addition of Aromatic C–H Bonds to Vinylsilanes in the Presence of Ru/CeO<sub>2</sub>, *ChemCatChem*, 2010, **2**, 1223–1225; (m) S. Halder and S. Koner, Iron-Containing Mesoporous Aluminosilicate: A Highly Active and Reusable Heterogeneous Catalyst for Hydroarylation of Styrenes, *J. Org. Chem.*, 2010, **75**, 6005–6008.
- 74 D. Rasina, A. Kahler-Quesada, S. Ziarelli, S. Warratz, H. Cao, S. Santoro, L. Ackermann and L. Vaccaro, Heterogeneous palladium-catalysed Catellani reaction in biomass-derived  $\gamma$ -valerolactone, *Green Chem.*, 2016, **18**, 5025–5030.
- 75 X. Tian, F. Yang, D. Rasina, M. Bauer, S. Warratz, F. Ferlin, L. Vaccaro and L. Ackermann, C–H arylations of 1,2,3-triazoles by reusable heterogeneous palladium catalysts in biomass-derived  $\gamma$ -valerolactone, *Chem. Commun.*, 2016, **52**, 9777–9780.
- 76 F. Ferlin, L. Luciani, S. Santoro, A. Marrocchi, D. Lanari, A. Bechtoldt, L. Ackermann and L. Vaccaro, A continuous flow approach for the C–H functionalization of 1,2,3-triazoles in  $\gamma$ -valerolactone as a biomass-derived medium, *Green Chem.*, 2018, **20**, 2888–2893.
- 77 S. Vásquez-Céspedes, A. Ferry, L. Candish and F. Glorius, Heterogeneously Catalyzed Direct C–H Thiolation of Heteroarenes, *Angew. Chem., Int. Ed.*, 2015, **54**, 5772–5776.
- 78 R. Kishore, J. Yadav, B. Venu, A. Venugopal and M. Lakshmi Kantam, A Pd(II)/Mg–La mixed oxide catalyst for cyanation of aryl C–H bonds and tandem Suzuki–cyanation reactions, *New J. Chem.*, 2015, **39**, 5259–5264.
- 79 V. Pascanu, F. Carson, M. V. Solano, J. Su, X. Zou, M. J. Johansson and B. Martín-Matute, Selective Heterogeneous C–H Activation/Halogenation Reactions Catalyzed by Pd@MOF Nanocomposites, *Chem. – Eur. J.*, 2016, **22**, 3729–3737.
- 80 S. Warratz, D. J. Burns, C. Zhu, K. Korvorapun, T. Rogge, J. Scholz, C. Jooss, D. Gelman and L. Ackermann, *meta*-C–H Bromination on Purine Bases by Heterogeneous Ruthenium Catalysis, *Angew. Chem., Int. Ed.*, 2017, **56**, 1557–1560.
- 81 I. Choi, V. Müller, Y. Wang, K. Xue, R. Kuniyil, L. B. Andreas, V. Karius, J. G. Alauzun and L. Ackermann, Recyclable Ruthenium Catalyst for Distal *meta*-C–H Activation, *Chem. – Eur. J.*, 2020, **26**, 15290–15297.
- 82 H. Fei and S. M. Cohen, Metalation of a Thiocatechol-Functionalized Zr(IV)-Based Metal–Organic Framework for Selective C–H Functionalization, *J. Am. Chem. Soc.*, 2015, **137**, 2191–2194.
- 83 (a) F. Wu, Y. Feng and C. W. Jones, Recyclable Silica-Supported Iridium Bipyridine Catalyst for Aromatic C–H Borylation, *ACS Catal.*, 2014, **4**, 1365–1375; (b) R. Murakami, K. Tsunoda, T. Iwai and M. Sawamura, Stereoselective C–H Borylations of Cyclopropanes and Cyclobutanes with Silica-Supported Monophosphane–Ir Catalysts, *Chem. – Eur. J.*, 2014, **20**, 13127–13131; (c) T. Iwai, R. Murakami, T. Harada, S. Kawamorita and M. Sawamura, Silica-Supported Tripod Triarylphosphane: Application to Transition Metal-Catalyzed C(sp<sup>3</sup>)-H Borylations, *Adv. Synth. Catal.*, 2014, **356**, 1563–1570; (d) W. R. Grüning, G. Siddiqi, O. V. Safonova and C. Copéret, Bipyridine Periodic Mesoporous Organosilica: A Solid Ligand for the Iridium-Catalyzed Borylation of C–H Bonds, *Adv. Synth. Catal.*, 2014, **356**, 673–679; (e) S. Kawamorita, R. Murakami, T. Iwai and M. Sawamura, Synthesis of Primary and Secondary Alkylboronates through Site-Selective C(sp<sup>3</sup>)-H Activation with Silica-Supported Monophosphane–Ir Catalysts, *J. Am. Chem. Soc.*, 2013, **135**, 2947–2950; (f) T. Iwai, T. Harada, K. Hara and M. Sawamura, Threefold Cross-Linked



- Polystyrene–Triphenylphosphane Hybrids: Mono-P-Ligating Behavior and Catalytic Applications for Aryl Chloride Cross-Coupling and C(sp<sup>3</sup>)-H Borylation, *Angew. Chem., Int. Ed.*, 2013, **52**, 12322–12326; (g) S. Kawamorita, T. Miyazaki, T. Iwai, H. Ohmiya and M. Sawamura, Rh-Catalyzed Borylation of N-Adjacent C(sp<sup>3</sup>)-H Bonds with a Silica-Supported Triarylphosphine Ligand, *J. Am. Chem. Soc.*, 2012, **134**, 12924–12927; (h) S. Kawamorita, T. Miyazaki, H. Ohmiya, T. Iwai and M. Sawamura, Rh-Catalyzed Ortho-Selective C–H Borylation of N-Functionalized Arenes with Silica-Supported Bridgehead Monophosphine Ligands, *J. Am. Chem. Soc.*, 2011, **133**, 19310–19313; (i) K. Yamazaki, S. Kawamorita, H. Ohmiya and M. Sawamura, Directed *Ortho* Borylation of Phenol Derivatives Catalyzed by a Silica-Supported Iridium Complex, *Org. Lett.*, 2010, **12**, 3978–3981; (j) T. Tagata, M. Nishida and A. Nishida, Continuous-Flow C–H Borylation of Arene Derivatives, *Adv. Synth. Catal.*, 2010, **352**, 1662–1666; (k) S. Kawamorita, H. Ohmiya and M. Sawamura, Ester-Directed Regioselective Borylation of Heteroarenes Catalyzed by a Silica-Supported Iridium Complex, *J. Org. Chem.*, 2010, **75**, 3855–3858; (l) T. Tagata, M. Nishida and A. Nishida, Development of recyclable iridium catalyst for C–H borylation, *Tetrahedron Lett.*, 2009, **50**, 6176–6179; (m) S. Kawamorita, H. Ohmiya, K. Hara, A. Fukuoka and M. Sawamura, Directed *Ortho* Borylation of Functionalized Arenes Catalyzed by a Silica-Supported Compact Phosphine–Iridium System, *J. Am. Chem. Soc.*, 2009, **131**, 5058–5059; (n) Z. Yinghuai, K. Chenyan, A. T. Peng, A. Emi, W. Monalisa, L. Kui-Jin Louis, N. S. Hosmane and J. A. Maguire, Catalytic Phenylborylation Reaction by Iridium(0) Nanoparticles Produced from Hydrido-iridium Carborane, *Inorg. Chem.*, 2008, **47**, 5756–5761.
- 84 (a) G. E. M. Crisenza, D. Mazzarella and P. Melchiorre, Synthetic Methods Driven by the Photoactivity of Electron Donor–Acceptor Complexes, *J. Am. Chem. Soc.*, 2020, **142**, 5461–5476; (b) K. L. Skubi, T. R. Blum and T. P. Yoon, Dual Catalysis Strategies in Photochemical Synthesis, *Chem. Rev.*, 2016, **116**, 10035–10074; (c) M. H. Shaw, J. Twilton and D. W. C. MacMillan, Photoredox Catalysis in Organic Chemistry, *J. Org. Chem.*, 2016, **81**, 6898–6926; (d) D. Ravelli, S. Protti and M. Fagnoni, Carbon–Carbon Bond Forming Reactions via Photogenerated Intermediates, *Chem. Rev.*, 2016, **116**, 9850–9913; (e) S. Poplata, A. Tröster, Y.-Q. Zou and T. Bach, Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photocycloaddition Reactions, *Chem. Rev.*, 2016, **116**, 9748–9815; (f) E. C. Gentry and R. R. Knowles, Synthetic Applications of Proton-Coupled Electron Transfer, *Acc. Chem. Res.*, 2016, **49**, 1546–1556.
- 85 L. Guillemard and J. Wencel-Delord, When metal-catalyzed C–H functionalization meets visible-light photocatalysis, *Beilstein J. Org. Chem.*, 2020, **16**, 1754–1804.
- 86 (a) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans and D. W. C. MacMillan, The merger of transition metal and photocatalysis, *Nat. Rev. Chem.*, 2017, **1**, 52; (b) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle and D. W. C. MacMillan, Merging photoredox with nickel catalysis: Coupling of  $\alpha$ -carboxyl sp<sup>3</sup>-carbons with aryl halides, *Science*, 2014, **345**, 437–440; (c) J. C. Tellis, D. N. Primer and G. A. Molander, Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis, *Science*, 2014, **345**, 433–436; (d) M. Osawa, H. Nagai and M. Akita, Photo-activation of Pd-catalyzed Sonogashira coupling using a Ru/bipyridine complex as energy transfer agent, *Dalton Trans.*, 2007, 827–829.
- 87 (a) Y.-F. Liang, R. Steinbock, L. Yang and L. Ackermann, Continuous Visible-Light Photoflow Approach for a Manganese-Catalyzed (Het)Arene C–H Arylation, *Angew. Chem., Int. Ed.*, 2018, **57**, 10625–10629; (b) M. K. Sahoo, S. P. Midya, V. G. Landge and E. Balaraman, A unified strategy for silver-, base-, and oxidant-free direct arylation of C–H bonds, *Green Chem.*, 2017, **19**, 2111–2117; (c) H. P. L. Gemoets, I. Kalvet, A. V. Nyuchev, N. Erdmann, V. Hessel, F. Schoenebeck and T. Noël, Mild and selective base-free C–H arylation of heteroarenes: experiment and computation, *Chem. Sci.*, 2017, **8**, 1046–1055; (d) J. Zoller, D. C. Fabry and M. Rueping, Unexpected Dual Role of Titanium Dioxide in the Visible Light Heterogeneous Catalyzed C–H Arylation of Heteroarenes, *ACS Catal.*, 2015, **5**, 3900–3904; (e) D. Cantillo, C. Mateos, J. A. Rincon, O. de Frutos and C. O. Kappe, Light-Induced C–H Arylation of (Hetero)arenes by In Situ Generated Diazo Anhydrides, *Chem. – Eur. J.*, 2015, **21**, 12894–12898; (f) I. Ghosh, T. Ghosh, J. I. Bardagi and B. König, Reduction of aryl halides by consecutive visible light-induced electron transfer processes, *Science*, 2014, **346**, 725–728; (g) P. Schroll, D. P. Hari and B. König, Photocatalytic Arylation of Alkenes, Alkynes and Enones with Diazonium Salts, *ChemistryOpen*, 2012, **1**, 130–133; (h) D. P. Hari, P. Schroll and B. König, Metal-Free, Visible-Light-Mediated Direct C–H Arylation of Heteroarenes with Aryl Diazonium Salts, *J. Am. Chem. Soc.*, 2012, **134**, 2958–2961.
- 88 D. Kalyani, K. B. McMurtrey, S. R. Neufeldt and M. S. Sanford, Room-Temperature C–H Arylation: Merger of Pd-Catalyzed C–H Functionalization and Visible-Light Photocatalysis, *J. Am. Chem. Soc.*, 2011, **133**, 18566–18569.
- 89 G. Meng, N. Y. S. Lam, E. L. Lucas, T. G. Saint-Denis, P. Verma, N. Chekshin and J.-Q. Yu, Achieving Site-Selectivity for C–H Activation Processes Based on Distance and Geometry: A Carpenter’s Approach, *J. Am. Chem. Soc.*, 2020, **142**, 10571–10591.
- 90 (a) S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancharla, A. Maji, A. Hazra, M. Bera and D. Maiti, Remote para-C–H Functionalization of Arenes by a D-Shaped Biphenyl Template-Based Assembly, *J. Am. Chem. Soc.*, 2015, **137**, 11888–11891; (b) L. Wan, N. Dastbaravardeh, G. Li and J.-Q. Yu, Cross-Coupling of Remote meta-C–H Bonds Directed by a U-Shaped



- Template, *J. Am. Chem. Soc.*, 2013, **135**, 18056–18059;
- (c) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, Activation of remote meta-C–H bonds assisted by an end-on template, *Nature*, 2012, **486**, 518–522.
- 91 (a) H. J. Davis, M. T. Mihai and R. J. Phipps, Ion Pair-Directed Regiocontrol in Transition-Metal Catalysis: A Meta-Selective C–H Borylation of Aromatic Quaternary Ammonium Salts, *J. Am. Chem. Soc.*, 2016, **138**, 12759–12762; (b) Y. Kuninobu, H. Ida, M. Nishi and M. Kanai, A meta-selective C–H borylation directed by a secondary interaction between ligand and substrate, *Nat. Chem.*, 2015, **7**, 712–717.
- 92 (a) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle and J.-Q. Yu, Ligand-enabled meta-C–H activation using a transient mediator, *Nature*, 2015, **519**, 334–338; (b) Z. Dong, J. Wang and G. Dong, Simple Amine-Directed Meta-Selective C–H Arylation via Pd/Norbornene Catalysis, *J. Am. Chem. Soc.*, 2015, **137**, 5887–5890.
- 93 M. Catellani, E. Motti and N. Della Ca', Catalytic Sequential Reactions Involving Palladacycle-Directed Aryl Coupling Steps, *Acc. Chem. Res.*, 2008, **41**, 1512–1522.
- 94 (a) K. Korvorapun, R. Kuniyil and L. Ackermann, Late-Stage Diversification by Selectivity Switch in meta-C–H Activation: Evidence for Singlet Stabilization, *ACS Catal.*, 2020, **10**, 435–440; (b) K. Korvorapun, N. Kaplaneris, T. Rogge, S. Warratz, A. C. Stückl and L. Ackermann, Sequential meta-/ortho-C–H Functionalizations by One-Pot Ruthenium(II/III) Catalysis, *ACS Catal.*, 2018, **8**, 886–892; (c) J. Li, S. Warratz, D. Zell, S. De Sarkar, E. E. Ishikawa and L. Ackermann, N-Acyl Amino Acid Ligands for Ruthenium(II)-Catalyzed meta-C–H tert-Alkylation with Removable Auxiliaries, *J. Am. Chem. Soc.*, 2015, **137**, 13894–13901; (d) N. Hofmann and L. Ackermann, meta-Selective C–H Bond Alkylation with Secondary Alkyl Halides, *J. Am. Chem. Soc.*, 2013, **135**, 5877–5884; (e) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey and C. G. Frost, Ruthenium-Catalyzed Meta Sulfonation of 2-Phenylpyridines, *J. Am. Chem. Soc.*, 2011, **133**, 19298–19301.
- 95 P. Gandeepan, J. Koeller, K. Korvorapun, J. Mohr and L. Ackermann, Visible-Light-Enabled Ruthenium-Catalyzed meta-C–H Alkylation at Room Temperature, *Angew. Chem., Int. Ed.*, 2019, **58**, 9820–9825.
- 96 A. Sagadevan and M. F. Greaney, meta-Selective C–H Activation of Arenes at Room Temperature Using Visible Light: Dual-Function Ruthenium Catalysis, *Angew. Chem., Int. Ed.*, 2019, **58**, 9826–9830.
- 97 K. Korvorapun, J. Struwe, R. Kuniyil, A. Zangarelli, A. Casnati, M. Waeterschoot and L. Ackermann, Photo-Induced Ruthenium-Catalyzed C–H Arylations at Ambient Temperature, *Angew. Chem.*, 2020, **59**, 18103–18109.
- 98 I. V. Seregin and V. Gevorgyan, Direct transition metal-catalyzed functionalization of heteroaromatic compounds, *Chem. Soc. Rev.*, 2007, **36**, 1173–1193.
- 99 F. Yang, J. Koeller and L. Ackermann, Photoinduced Copper-Catalyzed C–H Arylation at Room Temperature, *Angew. Chem., Int. Ed.*, 2016, **55**, 4759–4762.
- 100 (a) G. Shan, J. Flegel, H. Li, C. Merten, S. Ziegler, A. P. Antonchick and H. Waldmann, C–H Bond Activation for the Synthesis of Heterocyclic Atropisomers Yields Hedgehog Pathway Inhibitors, *Angew. Chem., Int. Ed.*, 2018, **57**, 14250–14254; (b) T. Piou and T. Rovis, Electronic and Steric Tuning of a Prototypical Piano Stool Complex: Rh(III) Catalysis for C–H Functionalization, *Acc. Chem. Res.*, 2018, **51**, 170–180; (c) N. Guimond and K. Fagnou, Isoquinoline Synthesis via Rhodium-Catalyzed Oxidative Cross-Coupling/Cyclization of Aryl Aldimines and Alkynes, *J. Am. Chem. Soc.*, 2009, **131**, 12050–12051.
- 101 (a) F. W. Patureau and F. Glorius, Rh Catalyzed Olefination and Vinylation of Unactivated Acetanilides, *J. Am. Chem. Soc.*, 2010, **132**, 9982–9983; (b) N. Umeda, K. Hirano, T. Satoh and M. Miura, Rhodium-Catalyzed Mono- and Divinylation of 1-Phenylpyrazoles and Related Compounds via Regioselective C–H Bond Cleavage, *J. Org. Chem.*, 2009, **74**, 7094–7099; (c) K. Ueura, T. Satoh and M. Miura, An Efficient Waste-Free Oxidative Coupling via Regioselective C–H Bond Cleavage: Rh/Cu-Catalyzed Reaction of Benzoic Acids with Alkynes and Acrylates under Air, *Org. Lett.*, 2007, **9**, 1407–1409.
- 102 D. C. Fabry, J. Zoller, S. Raja and M. Rueping, Combining Rhodium and Photoredox Catalysis for C–H Functionalizations of Arenes: Oxidative Heck Reactions with Visible Light, *Angew. Chem., Int. Ed.*, 2014, **53**, 10228–10231.
- 103 (a) D. C. Fabry and M. Rueping, Merging Visible Light Photoredox Catalysis with Metal Catalyzed C–H Activations: On the Role of Oxygen and Superoxide Ions as Oxidants, *Acc. Chem. Res.*, 2016, **49**, 1969–1979; (b) D. C. Fabry, M. A. Ronge, J. Zoller and M. Rueping, C–H Functionalization of Phenols Using Combined Ruthenium and Photoredox Catalysis: In Situ Generation of the Oxidant, *Angew. Chem., Int. Ed.*, 2015, **54**, 2801–2805.
- 104 D. Kalsi, N. Barsu, S. Chakrabarti, P. Dahiya, M. Rueping and B. Sundararaju, C–H and N–H bond annulation of aryl amides with unactivated olefins by merging cobalt (III) and photoredox catalysis, *Chem. Commun.*, 2019, **55**, 11626–11629.
- 105 (a) S. Govaerts, A. Nyuchev and T. Noel, Pushing the boundaries of C–H bond functionalization chemistry using flow technology, *J. Flow Chem.*, 2020, **10**, 13–71; (b) S. Santoro, F. Ferlin, L. Ackermann and L. Vaccaro, C–H functionalization reactions under flow conditions, *Chem. Soc. Rev.*, 2019, **48**, 2767–2782; (c) M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, The Hitchhiker's Guide to Flow Chemistry, *Chem. Rev.*, 2017, **117**, 11796–11893; (d) J. Britton and T. F. Jamison, A Unified Continuous Flow Assembly-Line Synthesis of Highly Substituted Pyrazoles and Pyrazolines, *Angew. Chem., Int. Ed.*, 2017, **56**, 8823–8827; (e) D. Cambié,





- C. Bottecchia, N. J. W. Straathof, V. Hessel and T. Noël, Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment, *Chem. Rev.*, 2016, **116**, 10276–10341.
- 106 J. Zakrzewski, A. P. Smalley, M. A. Kabeshov, M. J. Gaunt and A. A. Lapkin, Continuous-Flow Synthesis and Derivatization of Aziridines through Palladium-Catalyzed C(sp<sup>3</sup>)-H Activation, *Angew. Chem., Int. Ed.*, 2016, **55**, 8878–8883.
- 107 A. P. Smalley and M. J. Gaunt, Mechanistic Insights into the Palladium-Catalyzed Aziridination of Aliphatic Amines by C-H Activation, *J. Am. Chem. Soc.*, 2015, **137**, 10632–10641.
- 108 F. Ferlin, S. Santoro, L. Ackermann and L. Vaccaro, Heterogeneous C-H alkenylations in continuous-flow: oxidative palladium-catalysis in a biomass-derived reaction medium, *Green Chem.*, 2017, **19**, 2510–2514.
- 109 U. K. Sharma, H. P. L. Gemoets, F. Schröder, T. Noël and E. V. Van der Eycken, Merger of Visible-Light Photoredox Catalysis and C-H Activation for the Room-Temperature C-2 Acylation of Indoles in Batch and Flow, *ACS Catal.*, 2017, **7**, 3818–3823.
- 110 A. Bacalini, S. Vergura, P. Dolui, G. Zanoni and D. Maiti, Recent advances in cobalt-catalysed C-H functionalizations, *Org. Biomol. Chem.*, 2019, **17**, 10119–10141.
- 111 H. Wang, F. Pesciaoli, J. C. A. Oliveira, S. Warratz and L. Ackermann, Synergistic Manganese(I) C-H Activation Catalysis in Continuous Flow: Chemoselective Hydroarylation, *Angew. Chem., Int. Ed.*, 2017, **56**, 15063–15067.
- 112 C. Zhu, J. C. A. Oliveira, Z. Shen, H. Huang and L. Ackermann, Manganese(II/III/I)-Catalyzed C-H Arylations in Continuous Flow, *ACS Catal.*, 2018, **8**, 4402–4407.
- 113 T. H. Meyer, L. H. Finger, P. Gandeepan and L. Ackermann, Resource Economy by Metallalectrocatalysis: Merging Electrochemistry and C-H Activation, *Trends Chem.*, 2019, **1**, 63–76.
- 114 (a) S. Warratz, C. Kornhaas, A. Cajaraville, B. Niepötter, D. Stalke and L. Ackermann, Ruthenium(II)-Catalyzed C-H Activation/Alkyne Annulation by Weak Coordination with O<sub>2</sub> as the Sole Oxidant, *Angew. Chem., Int. Ed.*, 2015, **54**, 5513–5517; (b) J. Piera and J.-E. Bäckvall, Catalytic Oxidation of Organic Substrates by Molecular Oxygen and Hydrogen Peroxide by Multistep Electron Transfer—A Biomimetic Approach, *Angew. Chem., Int. Ed.*, 2008, **47**, 3506–3523; (c) S. S. Stahl, Palladium Oxidase Catalysis: Selective Oxidation of Organic Chemicals by Direct Dioxygen-Coupled Turnover, *Angew. Chem., Int. Ed.*, 2004, **43**, 3400–3420; (d) R. Mei, H. Wang, S. Warratz, S. A. Macgregor and L. Ackermann, Cobalt-Catalyzed Oxidase C-H/N-H Alkyne Annulation: Mechanistic Insights and Access to Anticancer Agents, *Chem. – Eur. J.*, 2016, **22**, 6759–6763.
- 115 P. M. Osterberg, J. K. Niemeier, C. J. Welch, J. M. Hawkins, J. R. Martinelli, T. E. Johnson, T. W. Root and S. S. Stahl, Experimental Limiting Oxygen Concentrations for Nine Organic Solvents at Temperatures and Pressures Relevant to Aerobic Oxidations in the Pharmaceutical Industry, *Org. Process Res. Dev.*, 2015, **19**, 1537–1543.
- 116 (a) H. Kolbe and E. Lautemann, Ueber die Constitution und Basicität der Salicylsäure, *Justus Liebigs Ann. Chem.*, 1860, **115**, 157–206; (b) M. Faraday, XX. On new compounds of carbon and hydrogen, and on certain other products obtained during the decomposition of oil by heat, *Philos. Trans. R. Soc. London*, 1825, **115**, 440–466.
- 117 T. Shono, Electroorganic chemistry in organic synthesis, *Tetrahedron*, 1984, **40**, 811–850.
- 118 (a) D. Pollok and S. R. Waldvogel, Electro-organic synthesis – a 21st century technique, *Chem. Sci.*, 2020, **11**, 12386–12400; (b) J. Liu, L. Lu, D. Wood and S. Lin, New Redox Strategies in Organic Synthesis by Means of Electrochemistry and Photochemistry, *ACS Cent. Sci.*, 2020, **6**, 1317–1340; (c) R. D. Little, A Perspective on Organic Electrochemistry, *J. Org. Chem.*, 2020, **85**, 13375–13390; (d) K.-J. Jiao, Y.-K. Xing, Q.-L. Yang, H. Qiu and T.-S. Mei, Site-Selective C-H Functionalization via Synergistic Use of Electrochemistry and Transition Metal Catalysis, *Acc. Chem. Res.*, 2020, **53**, 300–310; (e) P. Xiong and H.-C. Xu, Chemistry with Electrochemically Generated N-Centered Radicals, *Acc. Chem. Res.*, 2019, **52**, 3339–3350; (f) S. Tang, Y. Liu and A. Lei, Electrochemical Oxidative Cross-coupling with Hydrogen Evolution: A Green and Sustainable Way for Bond Formation, *Chem*, 2018, **4**, 27–45; (g) K. D. Moeller, Using Physical Organic Chemistry To Shape the Course of Electrochemical Reactions, *Chem. Rev.*, 2018, **118**, 4817–4833; (h) M. Yan, Y. Kawamata and P. S. Baran, Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance, *Chem. Rev.*, 2017, **117**, 13230–13319; (i) A. Jutand, Contribution of Electrochemistry to Organometallic Catalysis, *Chem. Rev.*, 2008, **108**, 2300–2347; (j) H. Kolbe, Untersuchungen über die Elektrolyse organischer Verbindungen, *Justus Liebigs Ann. Chem.*, 1849, **69**, 257–294; (k) M. Faraday, Sechste Reihe von Experimental-Untersuchungen über Elektrizität, *Ann. Phys.*, 1834, **109**, 149–189.
- 119 (a) R. C. Samanta, T. H. Meyer, I. Siewert and L. Ackermann, Renewable resources for sustainable metallalectro-catalysed C-H activation, *Chem. Sci.*, 2020, **11**, 8657–8670; (b) L. Ackermann, Metalla-electrocatalyzed C-H Activation by Earth-Abundant 3d Metals and Beyond, *Acc. Chem. Res.*, 2020, **53**, 84–104; (c) Q.-L. Yang, P. Fang and T.-S. Mei, Recent Advances in Organic Electrochemical C-H Functionalization, *Chin. J. Chem.*, 2018, **36**, 338–352; (d) N. Sauermann, T. H. Meyer, Y. Qiu and L. Ackermann, Electrocatalytic C-H Activation, *ACS Catal.*, 2018, **8**, 7086–7103; (e) C. Ma, P. Fang and T.-S. Mei, Recent Advances in C-H Functionalization Using Electrochemical Transition Metal Catalysis, *ACS Catal.*, 2018, **8**, 7179–7189.



- 120 C. Amatore, C. Cammoun and A. Jutand, Electrochemical Recycling of Benzoquinone in the Pd/Benzoquinone-Catalyzed Heck-Type Reactions from Arenes, *Adv. Synth. Catal.*, 2007, **349**, 292–296.
- 121 F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, S. Urano, M. Sato, S. Nishiyama and T. Tanabe, Palladium-Catalyzed Aromatic C–H Halogenation with Hydrogen Halides by Means of Electrochemical Oxidation, *J. Am. Chem. Soc.*, 2009, **131**, 11310–11311.
- 122 Y. B. Dudkina, D. Y. Mikhaylov, T. V. Gryaznova, A. I. Tufatullin, O. N. Kataeva, D. A. Vicic and Y. H. Budnikova, Electrochemical Ortho Functionalization of 2-Phenylpyridine with Perfluorocarboxylic Acids Catalyzed by Palladium in Higher Oxidation States, *Organometallics*, 2013, **32**, 4785–4792.
- 123 M. Konishi, K. Tsuchida, K. Sano, T. Kochi and F. Kakiuchi, Palladium-Catalyzed *ortho*-Selective C–H Chlorination of Benzamide Derivatives under Anodic Oxidation Conditions, *J. Org. Chem.*, 2017, **82**, 8716–8724.
- 124 Q.-L. Yang, Y.-Q. Li, C. Ma, P. Fang, X.-J. Zhang and T.-S. Mei, Palladium-Catalyzed C(sp<sup>3</sup>)-H Oxygenation via Electrochemical Oxidation, *J. Am. Chem. Soc.*, 2017, **139**, 3293–3298.
- 125 (a) Q.-L. Yang, C.-Z. Li, L.-W. Zhang, Y.-Y. Li, X. Tong, X.-Y. Wu and T.-S. Mei, Palladium-Catalyzed Electrochemical C–H Alkylation of Arenes, *Organometallics*, 2019, **38**, 1208–1212; (b) C. Ma, C.-Q. Zhao, Y.-Q. Li, L.-P. Zhang, X.-T. Xu, K. Zhang and T.-S. Mei, Palladium-catalyzed C–H activation/C–C cross-coupling reactions via electrochemistry, *Chem. Commun.*, 2017, **53**, 12189–12192.
- 126 (a) L. Yang, R. Steinbock, A. Scheremetjew, R. Kuniyil, L. H. Finger, A. M. Messinis and L. Ackermann, Azaruthena(II)-bicyclo[3.2.0]heptadiene: Key Intermediate for Ruthenaelectro(II/III/I)-catalyzed Alkyne Annulations, *Angew. Chem.*, 2020, **59**, 11130–11135; (b) X. Tan, X. Hou, T. Rogge and L. Ackermann, Ruthenaelectro-Catalyzed Domino Three-Component Alkyne Annulation Expedient Isoquinoline Assembly, *Angew. Chem.*, 2020, **60**, 4619–4624; (c) L. Massignan, X. Tan, T. H. Meyer, R. Kuniyil, A. M. Messinis and L. Ackermann, C–H Oxygenation Reactions Enabled by Dual Catalysis with Electrogenerated Hypervalent Iodine Species and Ruthenium Complexes, *Angew. Chem.*, 2020, **59**, 3184–3189; (d) Z.-Q. Wang, C. Hou, Y.-F. Zhong, Y.-X. Lu, Z.-Y. Mo, Y.-M. Pan and H.-T. Tang, Electrochemically Enabled Double C–H Activation of Amides: Chemoselective Synthesis of Polycyclic Isoquinolinones, *Org. Lett.*, 2019, **21**, 9841–9845; (e) M.-J. Luo, T.-T. Zhang, F.-J. Cai, J.-H. Li and D.-L. He, Decarboxylative [4 + 2] annulation of arylglyoxylic acids with internal alkynes using the anodic ruthenium catalysis, *Chem. Commun.*, 2019, **55**, 7251–7254; (f) M.-J. Luo, M. Hu, R.-J. Song, D.-L. He and J.-H. Li, Ruthenium(II)-catalyzed electrooxidative [4 + 2] annulation of benzylic alcohols with internal alkynes: entry to isocoumarins, *Chem. Commun.*, 2019, **55**, 1124–1127; (g) F. Xu, Y.-J. Li, C. Huang and H.-C. Xu, Ruthenium-Catalyzed Electrochemical Dehydrogenative Alkyne Annulation, *ACS Catal.*, 2018, **8**, 3820–3824; (h) Y. Qiu, C. Tian, L. Massignan, T. Rogge and L. Ackermann, Electrooxidative Ruthenium-Catalyzed C–H/O–H Annulation by Weak O-Coordination, *Angew. Chem., Int. Ed.*, 2018, **57**, 5818–5822; (i) R. Mei, J. Koeller and L. Ackermann, Electrochemical ruthenium-catalyzed alkyne annulations by C–H/Het–H activation of aryl carbamates or phenols in protic media, *Chem. Commun.*, 2018, **54**, 12879–12882.
- 127 (a) W.-J. Kong, Z. Shen, L. H. Finger and L. Ackermann, Electrochemical Access to Aza-Polycyclic Aromatic Hydrocarbons: Rhoda-Electrocatalyzed Domino Alkyne Annulations, *Angew. Chem.*, 2020, **59**, 5551–5556; (b) Z.-J. Wu, F. Su, W. Lin, J. Song, T.-B. Wen, H.-J. Zhang and H.-C. Xu, Scalable Rhodium(III)-Catalyzed Aryl C–H Phosphorylation Enabled by Anodic Oxidation Induced Reductive Elimination, *Angew. Chem., Int. Ed.*, 2019, **58**, 16770–16774; (c) W.-J. Kong, L. H. Finger, J. C. A. Oliveira and L. Ackermann, Rhodaelectrocatalysis for Annulative C–H Activation: Polycyclic Aromatic Hydrocarbons through Versatile Double Electrocatalysis, *Angew. Chem., Int. Ed.*, 2019, **58**, 6342–6346; (d) W.-J. Kong, L. H. Finger, A. M. Messinis, R. Kuniyil, J. C. A. Oliveira and L. Ackermann, Flow Rhodaelectro-Catalyzed Alkyne Annulations by Versatile C–H Activation: Mechanistic Support for Rhodium(III/IV), *J. Am. Chem. Soc.*, 2019, **141**, 17198–17206; (e) Y. Qiu, A. Scheremetjew and L. Ackermann, Electro-Oxidative C–C Alkenylation by Rhodium(III) Catalysis, *J. Am. Chem. Soc.*, 2019, **141**, 2731–2738; (f) Y. Qiu, W.-J. Kong, J. Struwe, N. Sauermann, T. Rogge, A. Scheremetjew and L. Ackermann, Electrooxidative Rhodium-Catalyzed C–H/C–H Activation: Electricity as Oxidant for Cross-Dehydrogenative Alkenylation, *Angew. Chem., Int. Ed.*, 2018, **57**, 5828–5832.
- 128 (a) Q.-L. Yang, Y.-K. Xing, X.-Y. Wang, H.-X. Ma, X.-J. Weng, X. Yang, H.-M. Guo and T.-S. Mei, Electrochemistry-Enabled Ir-Catalyzed Vinylic C–H Functionalization, *J. Am. Chem. Soc.*, 2019, **141**, 18970–18976; (b) Y. Qiu, M. Stangier, T. H. Meyer, J. C. A. Oliveira and L. Ackermann, Iridium-Catalyzed Electrooxidative C–H Activation by Chemoselective Redox-Catalyst Cooperation, *Angew. Chem., Int. Ed.*, 2018, **57**, 14179–14183.
- 129 L. Ackermann, J. Pospesch, K. Graczyk and K. Rauch, Versatile Synthesis of Isocoumarins and  $\alpha$ -Pyrone by Ruthenium-Catalyzed Oxidative C–H/O–H Bond Cleavages, *Org. Lett.*, 2012, **14**, 930–933.
- 130 R. Mandal and B. Sundararaju, Cp\*Co(III)-Catalyzed Annulation of Carboxylic Acids with Alkynes, *Org. Lett.*, 2017, **19**, 2544–2547.
- 131 P. Gandeepan, L. H. Finger, T. H. Meyer and L. Ackermann, 3d metallaelectrocatalysis for resource



- economical syntheses, *Chem. Soc. Rev.*, 2020, **49**, 4254–4272.
- 132 N. Sauermann, T. H. Meyer, C. Tian and L. Ackermann, Electrochemical Cobalt-Catalyzed C–H Oxygenation at Room Temperature, *J. Am. Chem. Soc.*, 2017, **139**, 18452–18455.
- 133 L.-B. Zhang, X.-Q. Hao, S.-K. Zhang, Z.-J. Liu, X.-X. Zheng, J.-F. Gong, J.-L. Niu and M.-P. Song, Cobalt-Catalyzed C(sp<sup>2</sup>)–H Alkoxylation of Aromatic and Olefinic Carboxamides, *Angew. Chem., Int. Ed.*, 2015, **54**, 272–275.
- 134 (a) R. Mei, U. Dhawa, R. C. Samanta, W. Ma, J. Wencel-Delord and L. Ackermann, Cobalt-Catalyzed Oxidative C–H Activation: Strategies and Concepts, *ChemSusChem*, 2020, **13**, 3306–3356; (b) N. Sauermann, T. H. Meyer and L. Ackermann, Electrochemical Cobalt-Catalyzed C–H Activation, *Chem. – Eur. J.*, 2018, **24**, 16209–16217.
- 135 N. Sauermann, R. Mei and L. Ackermann, Electrochemical C–H Amination by Cobalt Catalysis in a Renewable Solvent, *Angew. Chem., Int. Ed.*, 2018, **57**, 5090–5094.
- 136 L.-B. Zhang, S.-K. Zhang, D. Wei, X. Zhu, X.-Q. Hao, J.-H. Su, J.-L. Niu and M.-P. Song, Cobalt(II)-Catalyzed C–H Amination of Arenes with Simple Alkylamines, *Org. Lett.*, 2016, **18**, 1318–1321.
- 137 X. Gao, P. Wang, L. Zeng, S. Tang and A. Lei, Cobalt(II)-Catalyzed Electrooxidative C–H Amination of Arenes with Alkylamines, *J. Am. Chem. Soc.*, 2018, **140**, 4195–4199.
- 138 C. Tian, L. Massignan, T. H. Meyer and L. Ackermann, Electrochemical C–H/N–H Activation by Water-Tolerant Cobalt Catalysis at Room Temperature, *Angew. Chem., Int. Ed.*, 2018, **57**, 2383–2387.
- 139 S. Tang, D. Wang, Y. Liu, L. Zeng and A. Lei, Cobalt-catalyzed electrooxidative C–H/N–H [4 + 2] annulation with ethylene or ethyne, *Nat. Commun.*, 2018, **9**, 798.
- 140 R. Mei, N. Sauermann, J. C. A. Oliveira and L. Ackermann, Electroremovable Traceless Hydrazides for Cobalt-Catalyzed Electro-Oxidative C–H/N–H Activation with Internal Alkynes, *J. Am. Chem. Soc.*, 2018, **140**, 7913–7921.
- 141 (a) R. Mei, X. Fang, L. He, J. Sun, L. Zou, W. Ma and L. Ackermann, Cobalt-electrocatalyzed oxidative allene annulation by electro-removable hydrazides, *Chem. Commun.*, 2020, **56**, 1393–1396; (b) T. H. Meyer, J. C. A. Oliveira, S. C. Sau, N. W. J. Ang and L. Ackermann, Electrooxidative Allene Annulations by Mild Cobalt-Catalyzed C–H Activation, *ACS Catal.*, 2018, **8**, 9140–9147.
- 142 S. C. Sau, R. Mei, J. Struwe and L. Ackermann, Cobalt-electrocatalyzed C–H Activation with Carbon Monoxide or Isocyanides, *ChemSusChem*, 2019, **12**, 3023–3027.
- 143 R. Mei, W. Ma, Y. Zhang, X. Guo and L. Ackermann, Cobalt-electrocatalyzed Oxidative C–H/N–H Activation with 1,3-Diynes by Electro-Removable Hydrazides, *Org. Lett.*, 2019, **21**, 6534–6538.
- 144 U. Dhawa, C. Tian, W. Li and L. Ackermann, Cobalt-Electrocatalyzed C–H Allylation with Unactivated Alkenes, *ACS Catal.*, 2020, **10**, 6457–6462.
- 145 (a) T. Yamaguchi, Y. Kommagalla, Y. Aihara and N. Chatani, Cobalt-catalyzed chelation assisted C–H allylation of aromatic amides with unactivated olefins, *Chem. Commun.*, 2016, **52**, 10129–10132; (b) R. Manoharan, G. Sivakumar and M. Jeganmohan, Cobalt-catalyzed C–H olefination of aromatics with unactivated alkenes, *Chem. Commun.*, 2016, **52**, 10533–10536; (c) S. Maity, R. Kancharla, U. Dhawa, E. Hoque, S. Pimparkar and D. Maiti, Switch to Allylic Selectivity in Cobalt-Catalyzed Dehydrogenative Heck Reactions with Unbiased Aliphatic Olefins, *ACS Catal.*, 2016, **6**, 5493–5499.
- 146 T. H. Meyer, G. A. Chesnokov and L. Ackermann, Cobalt-Electrocatalyzed C–H Activation in Biomass-Derived Glycerol: Powered by Renewable Wind and Solar Energy, *ChemSusChem*, 2020, **13**, 668–671.
- 147 S.-K. Zhang, R. C. Samanta, A. Del Vecchio and L. Ackermann, Evolution of High-Valent Nickel-Electrocatalyzed C–H Activation: From Cross (-Electrophile)-Couplings to Electrooxidative C–H Transformations, *Chem. – Eur. J.*, 2020, **26**, 10936–10947.
- 148 S.-K. Zhang, R. C. Samanta, N. Sauermann and L. Ackermann, Nickel-Catalyzed Electrooxidative C–H Amination: Support for Nickel(IV), *Chem. – Eur. J.*, 2018, **24**, 19166–19170.
- 149 S.-K. Zhang, J. Struwe, L. Hu and L. Ackermann, Nickel-electrocatalyzed C–H Alkoxylation with Secondary Alcohols: Oxidation-Induced Reductive Elimination at Nickel(III), *Angew. Chem.*, 2020, **59**, 3178–3183.
- 150 R. C. Samanta, J. Struwe and L. Ackermann, Nickel-electrocatalyzed Mild C–H Alkylations at Room Temperature, *Angew. Chem.*, 2020, **59**, 14154–14159.
- 151 (a) Y. Aihara, M. Tobisu, Y. Fukumoto and N. Chatani, Ni(II)-Catalyzed Oxidative Coupling between C(sp<sup>2</sup>)–H in Benzamides and C(sp<sup>3</sup>)–H in Toluene Derivatives, *J. Am. Chem. Soc.*, 2014, **136**, 15509–15512; (b) Z. Ruan, S. Lackner and L. Ackermann, A General Strategy for the Nickel-Catalyzed C–H Alkylation of Anilines, *Angew. Chem., Int. Ed.*, 2016, **55**, 3153–3157; (c) T. Uemura, M. Yamaguchi and N. Chatani, Phenyltrimethylammonium Salts as Methylation Reagents in the Nickel-Catalyzed Methylation of C–H Bonds, *Angew. Chem., Int. Ed.*, 2016, **55**, 3162–3165.
- 152 Q.-L. Yang, X.-Y. Wang, J.-Y. Lu, L.-P. Zhang, P. Fang and T.-S. Mei, Copper-Catalyzed Electrochemical C–H Amination of Arenes with Secondary Amines, *J. Am. Chem. Soc.*, 2018, **140**, 11487–11494.
- 153 S. Kathiravan, S. Suriyanarayanan and I. A. Nicholls, Electrooxidative Amination of sp<sup>2</sup> C–H Bonds: Coupling of Amines with Aryl Amides via Copper Catalysis, *Org. Lett.*, 2019, **21**, 1968–1972.
- 154 C. Tian, U. Dhawa, A. Scheremetjew and L. Ackermann, Cupraelectrocatalyzed Alkyne Annulation: Evidence for Distinct C–H Alkynylation and Decarboxylative C–H/C–C Manifolds, *ACS Catal.*, 2019, **9**, 7690–7696.
- 155 (a) A. Fürstner, Iron Catalysis in Organic Synthesis: A Critical Assessment of What It Takes To Make This Base



- Metal a Multitasking Champion, *ACS Cent. Sci.*, 2016, **2**, 778–789; (b) I. Bauer and H.-J. Knölker, Iron Catalysis in Organic Synthesis, *Chem. Rev.*, 2015, **115**, 3170–3387; (c) S. Enthaler, K. Junge and M. Beller, Sustainable Metal Catalysis with Iron: From Rust to a Rising Star?, *Angew. Chem., Int. Ed.*, 2008, **47**, 3317–3321; (d) A. Correa, O. García Mancheño and C. Bolm, Iron-catalysed carbon–heteroatom and heteroatom–heteroatom bond forming processes, *Chem. Soc. Rev.*, 2008, **37**, 1108–1117.
- 156 R. Shang, L. Ilies and E. Nakamura, Iron-Catalyzed C–H Bond Activation, *Chem. Rev.*, 2017, **117**, 9086–9139.
- 157 C. Zhu, M. Stangier, J. C. A. Oliveira, L. Massignan and L. Ackermann, Iron-Electrocatalyzed C–H Arylations: Mechanistic Insights into Oxidation-Induced Reductive Elimination for Ferraelectrocatalysis, *Chem. – Eur. J.*, 2019, **25**, 16382–16389.
- 158 (a) K. E. Poremba, S. E. Dibrell and S. E. Reisman, Nickel-Catalyzed Enantioselective Reductive Cross-Coupling Reactions, *ACS Catal.*, 2020, **10**, 8237–8246; (b) X. Chang, Q. Zhang and C. Guo, Asymmetric Electrochemical Transformations, *Angew. Chem.*, 2020, **59**, 12612–12622; (c) Q. Lin, L. Li and S. Luo, Asymmetric Electrochemical Catalysis, *Chem. – Eur. J.*, 2019, **25**, 10033–10044; (d) M. Ghosh, V. S. Shinde and M. Rueping, A review of asymmetric synthetic organic electrochemistry and electrocatalysis: concepts, applications, recent developments and future directions, *Beilstein J. Org. Chem.*, 2019, **15**, 2710–2746.
- 159 U. Dhawa, C. Tian, T. Wdowik, J. C. A. Oliveira, J. Hao and L. Ackermann, Enantioselective Pallada-Electrocatalyzed C–H Activation by Transient Directing Groups: Expedient Access to Helicenes, *Angew. Chem., Int. Ed.*, 2020, **59**, 13451–13457.

