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MINI REVIEW

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Rhodaelectro-Catalyzed C–H and C–C Activation

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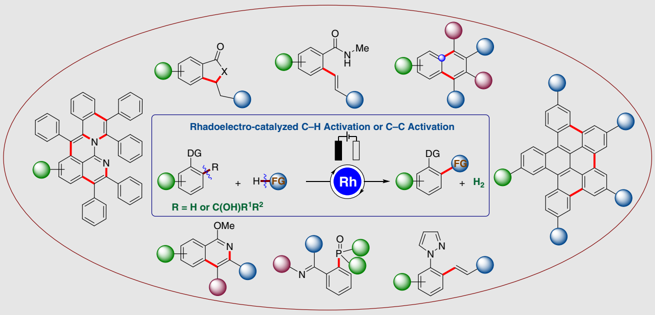
Rhodium(III) catalysis has set the stage for a plethora of oxidative C–H functionalizations over the last decade, which have predominantly employed stoichiometric amounts of toxic and expensive metal oxidants, such as silver(I) salts. In the meantime, electrosynthesis has emerged as an increasingly viable alternative for expensive and toxic oxidants. Recently, significant momentum has been achieved with the merger of electrocatalysis with organometallic C–H activation. However, user-friendly and robust rhodaelectro-catalysis has until very recently proven elusive for oxidative C–H activations. This minireview highlights the current knowledge and recent advances of electrooxidation in rhodium-catalyzed C–H or C–C activations, with a topical focus on contributions from the Ackermann group through July 2020.



Keywords: **electrosynthesis, rhodium catalysis, C–H activation, C–C activation, mechanistic in-sights, rhodaelectro-catalysis**

Introduction

Organometallic C–H activation has emerged as one of the most efficient tools for molecular synthesis.[1–10] Particularly, rhodium(III) catalysis has received notable attention for the development of oxidative C–H functionalizations.[11–16] Despite considerable advances, rhodium(III)-catalyzed oxidative C–H activations heavily rely on stoichiometric amounts of toxic and/or expensive copper(II) and silver(I) salts as sacrificial oxidants.[17–21] In the meantime, electrocatalysis has been identified as an increasingly viable strategy for organometallic C–H activations over the last decade.[22–36] While general reviews and reports on metallaelectro-catalysis have appeared,[37–59] a focus on state-of-the-art rhodaelectro-catalyzed transformations is not yet available,[60,61] despite its unique potential for molecular syntheses, pharmaceutical industries, and material sciences.[62–65] Herein, we discuss recent developments of rhodaelectro-catalyzed transformations with specific interests on mechanistic aspects. Thus, we specifically summarize our findings on rhodaelectro-catalyzed C–H and C–C activations, which provide a number of useful molecular structures and, more importantly, reveal new synthetic disconnections. Overall, rhodaelectro-catalyzed C–H/C–C activations have set the stage for molecular syntheses with unique levels of resource economy.[66]

Rhodaelectro-Catalyzed C–H Alkenylation

In 2018, a key breakthrough in rhodaelectro-catalyzed C–H activation was established by the Ackermann group (Göttingen, Germany) (Scheme 1).[67] Hence, cross-dehydrogenative C–H/C–H alkenylation was

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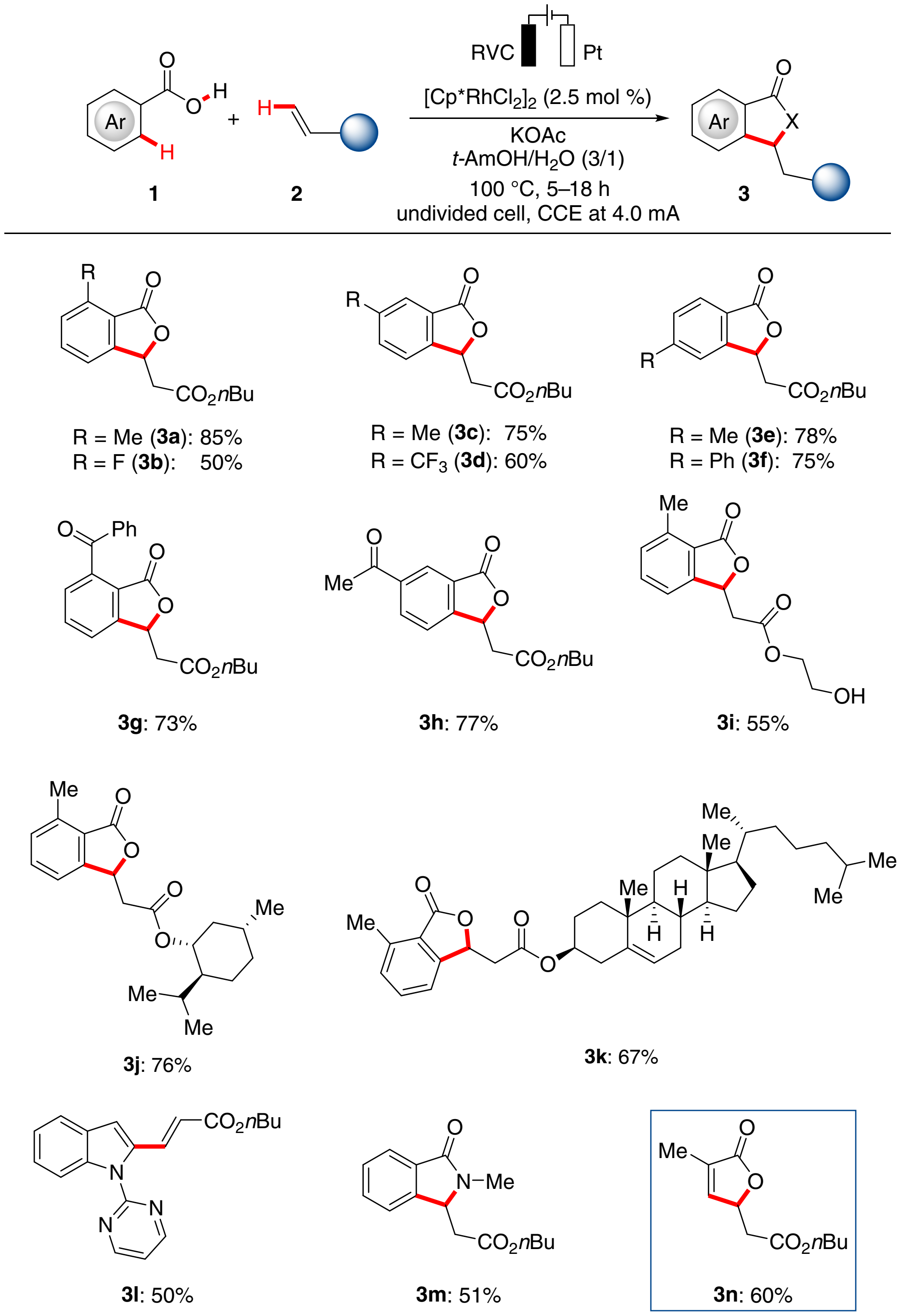
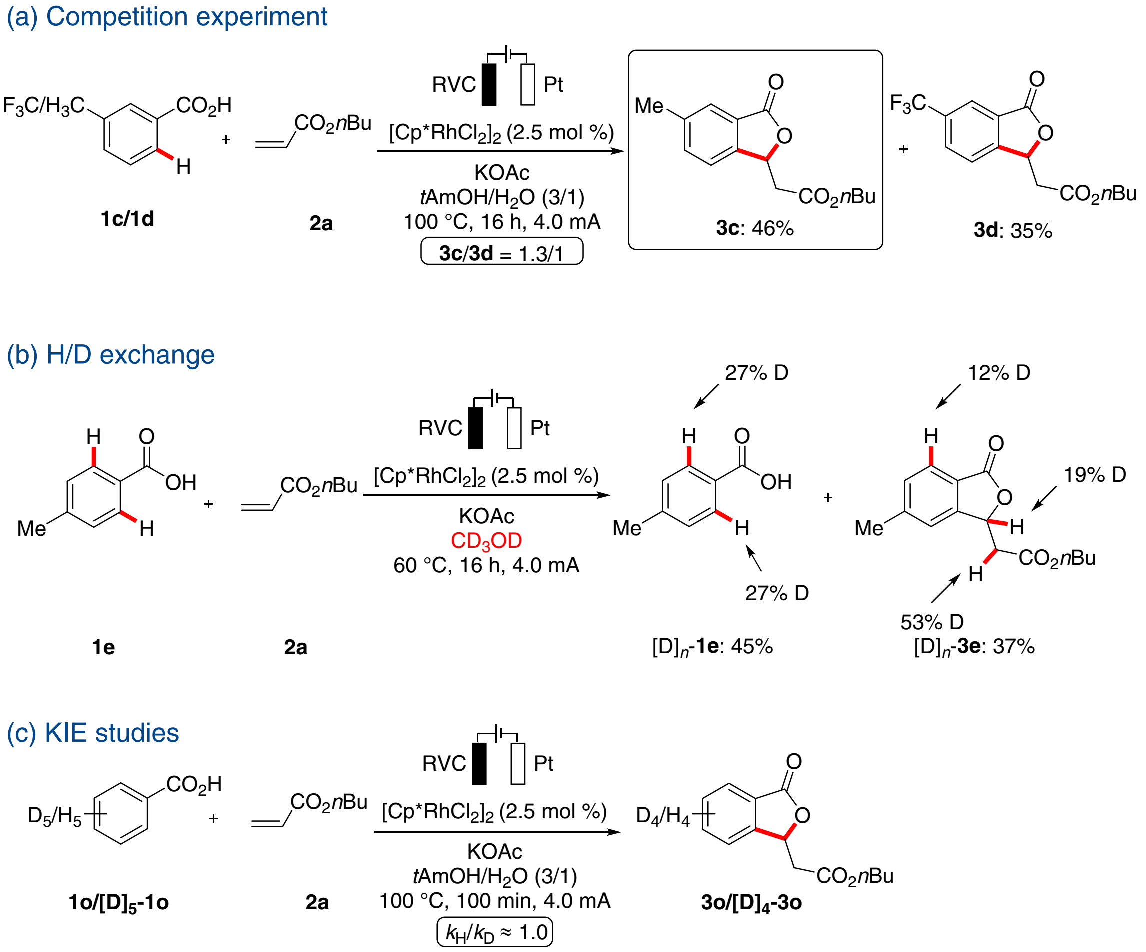


Scheme 1 | *Rhodaelectro-catalyzed C–H alkenylation.*

achieved with weakly *O*-coordinating[68] benzoic acids **1** and alkenes **2**, serving as a proof of concept for the first rhodium electrocatalyzed C–H activation. The optimized reaction conditions were characterized by using Potassium acetate (KOAc) as the additive and a mixture of *t*-AmOH and H_2O as the effective solvent system, delivering the desired products **3** in a user-friendly undivided cell setup. Initially, various substituents in the *ortho*-, *meta*-, and *para*-positions of benzoic acids were employed to probe the robustness of the electrocatalyzed C–H transformation, proceeding with excellent levels of positional, diastereo-, and chemoselectivities. Notably, a variety of valuable electrophilic functional groups, including sensitive esters and ketones, were fully tolerated in this electrooxidative rhodium-catalyzed C–H alkenylations. Likewise, variously substituted acrylates **2** proved to be amenable, including an oxidation-sensitive aliphatic hydroxy group. Furthermore, the procedure proved to be applicable to amides and indoles. Specifically, endogenous steroid pregnenolone **2k** could be efficiently converted to the desired products **3k** without racemization of the stereogenic centers. It is worth



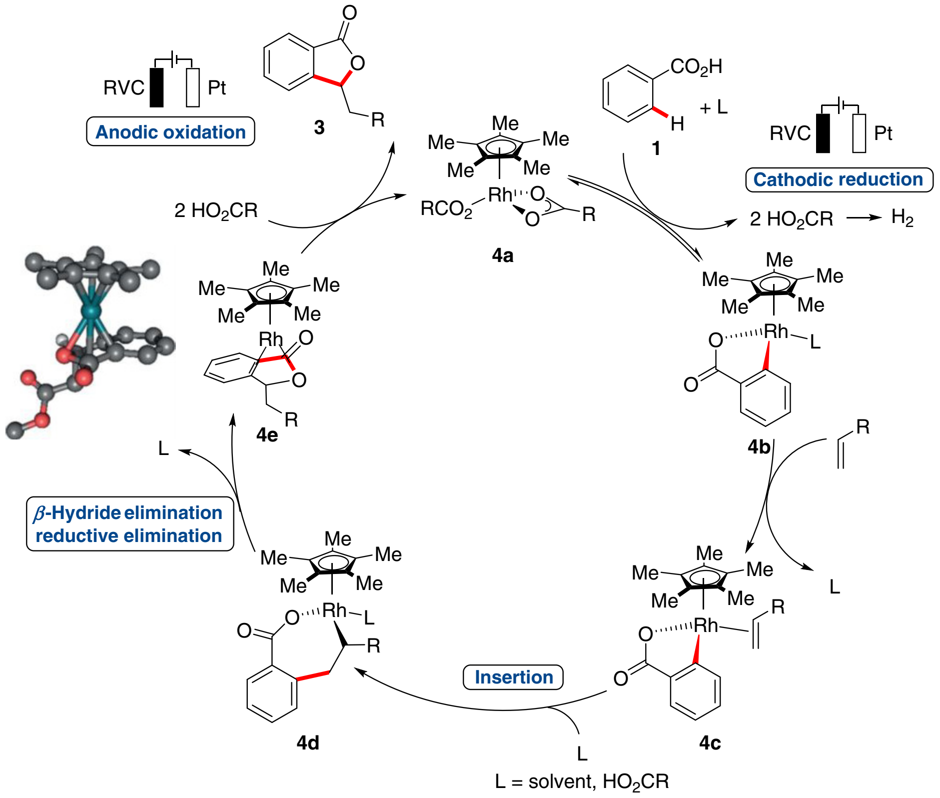
Scheme 2 | *(a–c) Summary of key mechanistic findings.*

noting that electrochemical vinyl C–H activation was initially realized in this study, as well.[69,70]

Competitive experiments showed a clear preference in favor of the more electron-rich benzoic acids **1**. The experiment was conducted by an analysis of the initial rates for electron-rich and electron-deficient benzoic acids **1c** and **1d** in independent reactions (Scheme 2a). This observation is in good agreement with a base-assisted intramolecular electrophilic-type substitution (BIES)[71–78] C–H activation manifold. Furthermore, deuteration studies using CD_3OD as the cosolvent suggested a facile and reversible C–H activation event, while highlighting an organometallic C–H activation mechanism (Scheme 2b). A minor kinetic isotopic effect illustrated that C–H rhodanation is not the rate-determining step, providing an additional support for fast C–H scission (Scheme 2c).

On the basis of the mechanistic findings, a catalytic cycle depicted in Scheme 3 has been proposed. Initially, carboxylate-assisted BIES C–H activation delivers cyclometalated intermediate **4b**. Next, migratory alkene insertion generates the catalytically competent rhodium(III) species **4d**. Thereafter, β-hydride elimination and reductive elimination deliver the desired products **3**. Finally, the key anodic oxidation of the reduced rhodium(I) intermediate **4e** regenerates the catalytically active rhodium(III) species **4a** via an anodic single-electron transfer (SET) event.

In contrast to the alkenylation of α,β-unsaturated carbonyl compounds under rhodaelectro-catalysis, Ackermann recently reported an intriguing alkenylation reaction using unactivated alkenes **6** with weakly coordinating benzamides (Scheme 4).[79] Here, the dehydrogenative alkenylation products **7** were obtained by using NaOPiv instead of the previously reported KOAc additive. The rhodaelectro-catalyzed C–H alkenylation was shown to proceed with ample substrate scope, including heterocycles and valuable electrophilic functional group, such as chloro, bromo, and nitrile. Likewise, various alkenes **6** proved to be amenable, including oxidation-sensitive hydroxyl substituents. A gram-scale reaction highlighted the synthetic utility of the rhodaelectro-catalyzed C–H activation.



Scheme 3 | *Plausible catalytic cycle for alkenylation.*

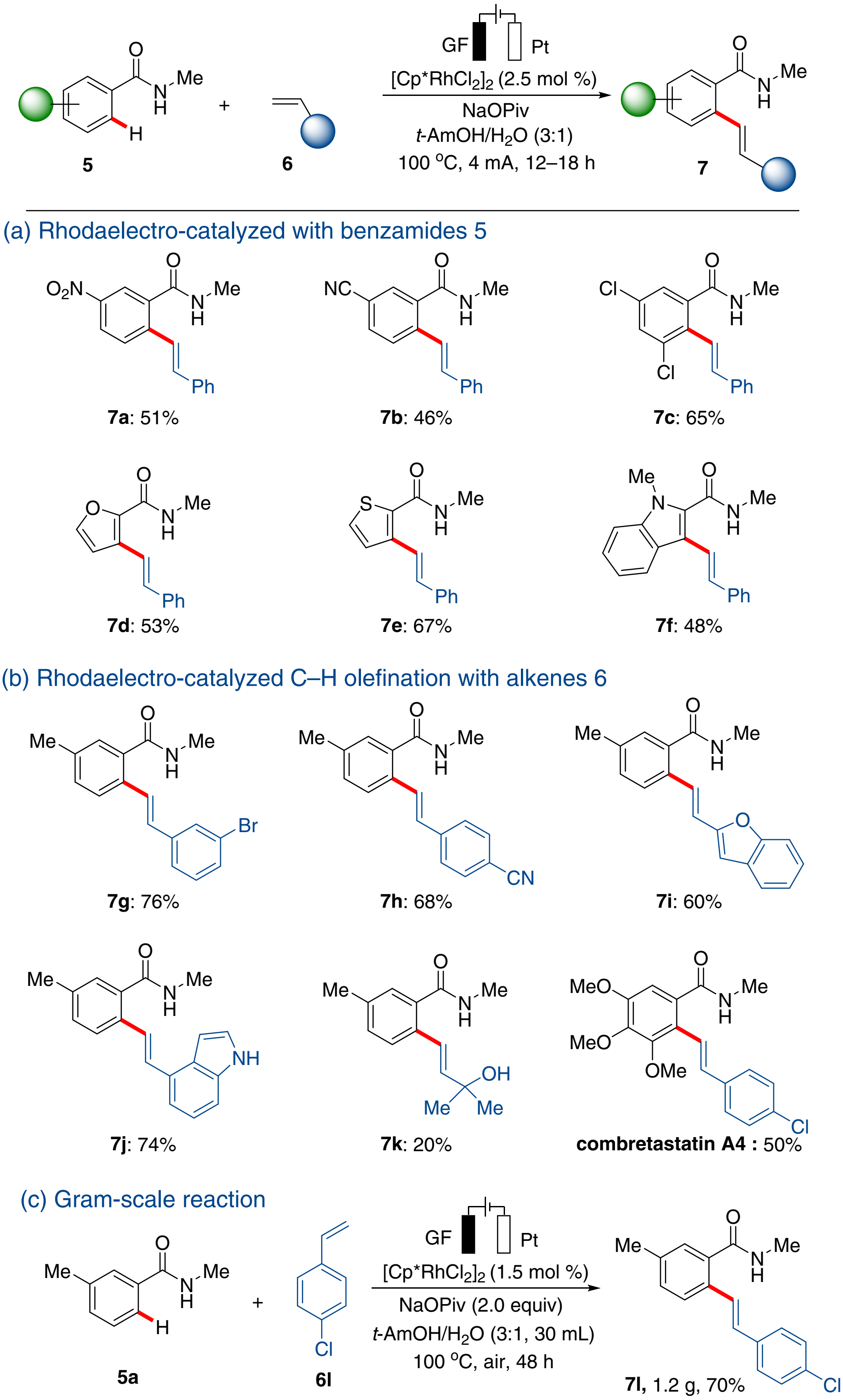
Rhodaelectro-Catalyzed C–H Alkynylation

The strategy of rhodaelectro-catalytic C–H activation proved to be broadly applicable and gave access to synthetically useful polycyclic aromatic hydrocarbons (PAHs)[80–84] through a two-step sequential dehydrogenative annulation electrocatalysis (Scheme 5a).[85] Thus, electrooxidative C–B/C–H [2 + 2 + 2] cyclization was realized with a variety of boronic acids featuring versatile rhodium catalysis. The C–B/C–H annulation was efficiently established with ample scope and remarkable levels of functional group tolerance, such as chloro, ester, and cyano substituents, in a user-friendly undivided cell setup. Notably, the chemoselectivity of the conversion of sensitive iodo-substituted boronic acids could be significantly improved as compared with transformations with typical chemical oxidants, AgOAc and $Cu(OAc)_2$ (Scheme 5b).

Further transformation of substituted tetraphenyl naphthalenes into π-conjugation PAHs proved viable in the presence of 20 mol % of 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a divided electrochemical cell at room temperature (Scheme 6).[86,87] Thereby, a set of useful late-stage diversification reactions provided access to important PAHs derivatives. The unambiguous structure of cyclodehydrogenated product **11** was confirmed by X-ray diffraction analysis, revealing a structurally nonplanar PAH. In addition, the conducted photoabsorption and cyclic voltammetry (CV) measurements reflected the new optoelectronic properties of the electrochemically generated PAHs (Scheme 7).[88,89]

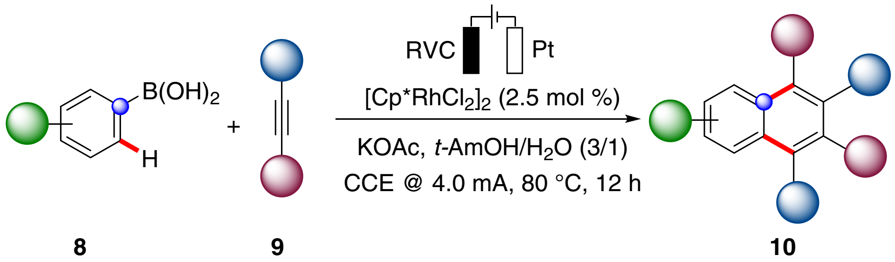
Importantly, Ackermann also established robust flow rhodaelectro-catalyzed alkyne annulations using aryl imidates **12** as the substrates (Scheme 8).[90] It is particularly noteworthy that C–H/N–H alkyne annulations were amenable to electroflow technology using a slightly modified IKA setup.[91–98] This strategy represents a user-friendly tool for the efficient upscaling of a reaction with significantly improved control of heat and mass transfer. The scope for this challenging flow rhodaelectro-catalyzed alkyne annulation gave access to isoquinolines, as well as azo-tetracycles, by an intramolecular reaction.

In-depth mechanistic studies were performed to probe the catalyst's modus operandi (Scheme 8). Thus, the stoichiometric synthesis of the two novel cyclometalated rhodium(III) complexes **17a** and **17b** from imidates **12a** was accomplished (Scheme 9a). The well-defined rhodium(III) complexes were found to be competent in the catalytic C–H annulation (Scheme 9b). Notably, the formation of well-characterized rhodium(III)-heptacycle **18** was observed when treating complex **17b** with alkyne **13a**, whereas alkyne **13a** underwent an insertion reaction (Scheme 9c). The formation of product **14a** was observed

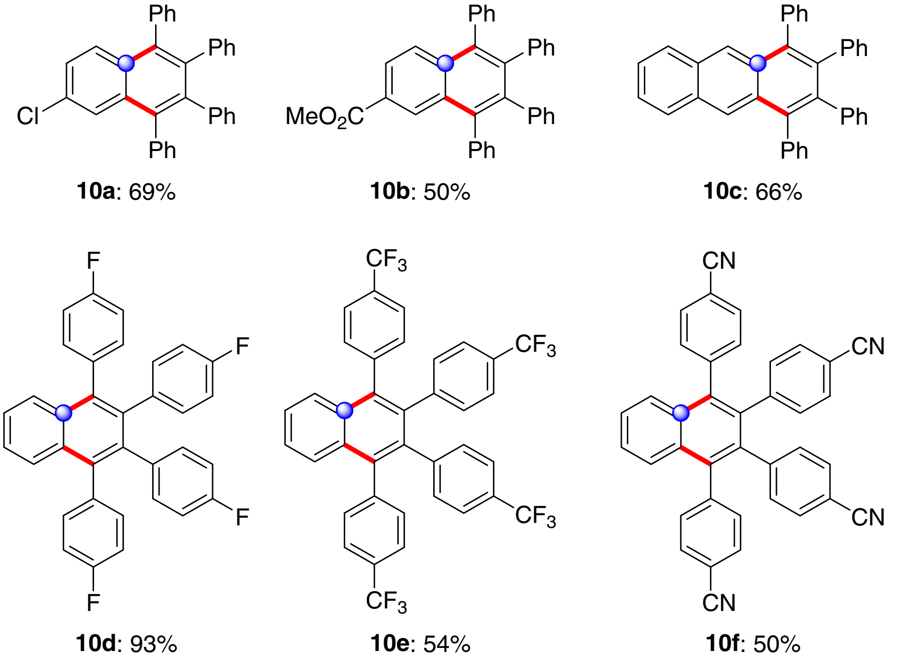


Scheme 4 | *(a–c) Rhodaelectro-catalyzed C–H alkenylation and gram-scale reaction.*

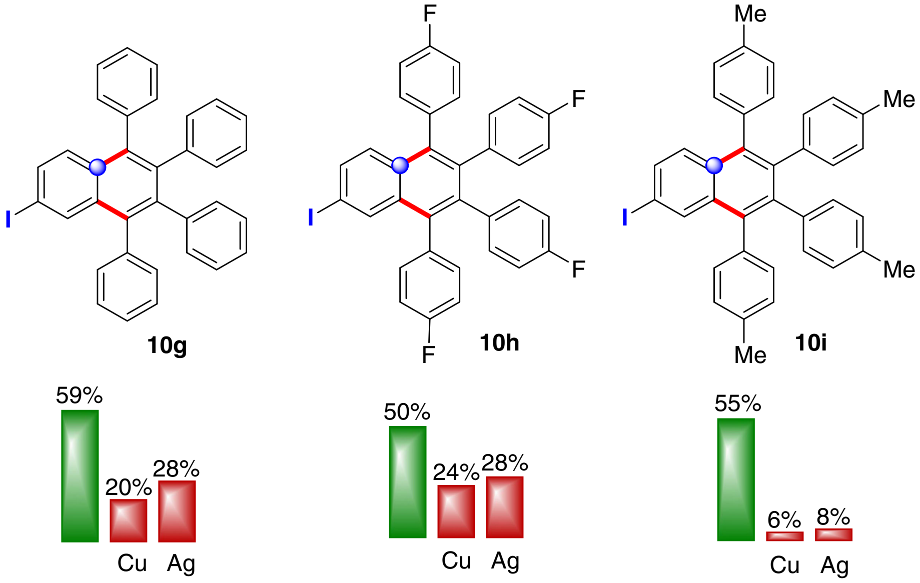
when electricity was applied, thus providing support for an oxidation-induced reductive elimination within a unusual rhodium(III/IV/II) regime (Scheme 9d).[99,100] In addition, the Ackermann group conducted CV experiments to gain further insights into the role of sodium salt. These studies indicated that the additive, NaOPiv, accelerated the product formation from rhodacycle **18** upon electrolysis.



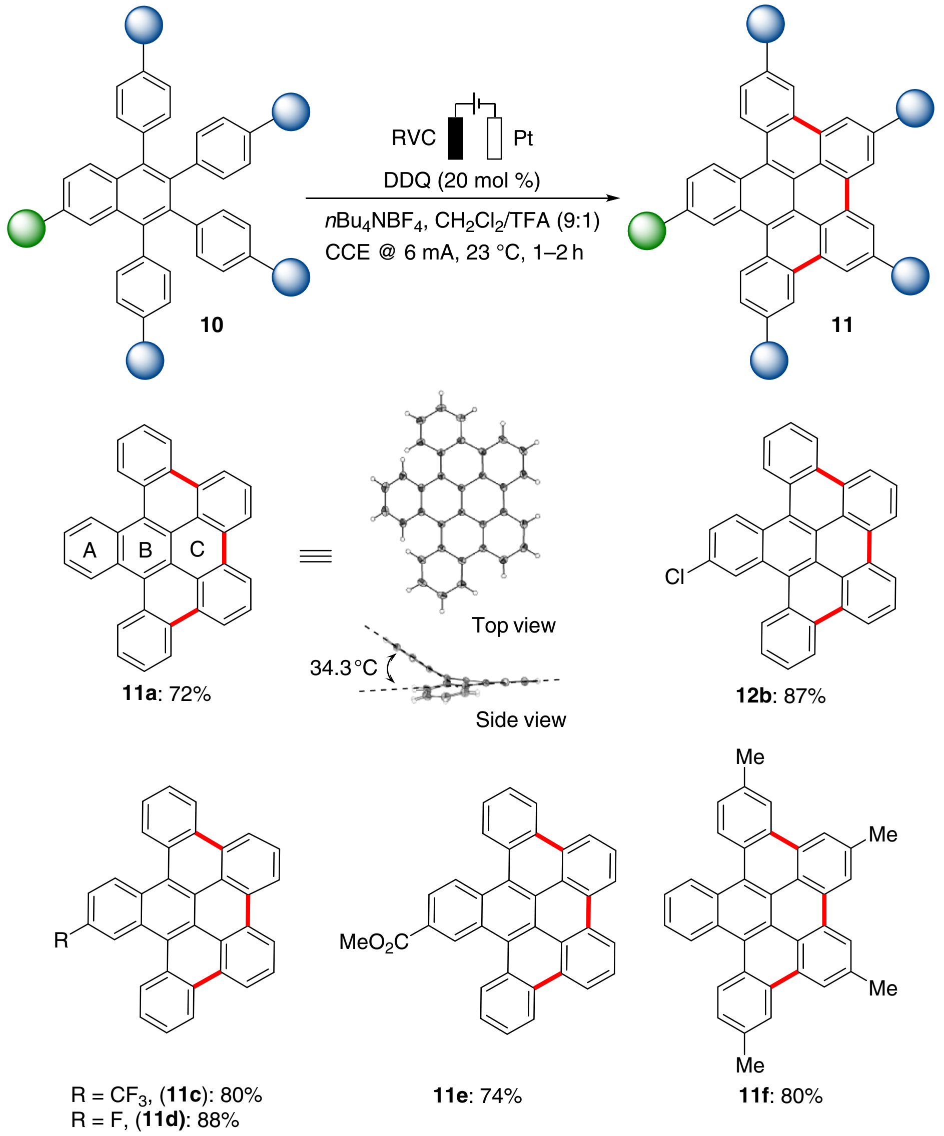
(a) Rhodaelectro-catalyzed [2 + 2 + 2] cyclization



(b) Electrocatalysis for improved chemoselectivity



Scheme 5 | *(a and b) Rhodaelectro-catalyzed C–B/C–H [2 + 2 + 2] annulation.*



Scheme 6 | *Late-stage diversification by DDQ-catalyzed electrochemical cyclodehydrogenation.*

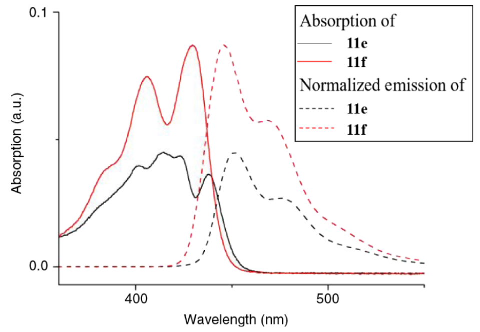
In addition, computational studies rationalized a favorable Rh(III/IV/II) manifold with an activation barrier of 15.2 kcal mol^{-1} for the oxidatively induced reductive elimination step (Figure 1). These computational studies were in good agreement with the experimental findings.

On the basis of these mechanistic studies, a plausible catalytic cycle was proposed to feature carboxylate-assisted C–H rhodanation to deliver the cyclometallated rhodium complex **17** (Scheme 10). Thereafter, migratory insertion and anodic SET generated rhodium(IV) complex **C** to subsequently undergo oxidatively induced reductive elimination from intermediate **C**. Thereby, product **14** is released, while the catalytically competent species **A** was regenerated.

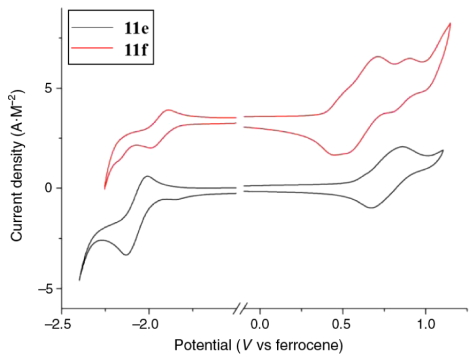
Electrooxidative alkyne annulation was recently merged with a multiple C–H domino strategy (Scheme 11).[101] In contrast to the previous transformation,[85] the use of easily accessible imidamides **19** enabled the challenging formation of various aza-PAHs. The rhodaelectro-catalyzed cascade C–H activations were efficiently realized with ample scope and remarkable functional group tolerance.

Having demonstrated the versatility of the rhodaelectro-catalyzed C–H annulation, Ackermann was encouraged to investigate its mechanism (Scheme 12). It is noteworthy that the electrosynthesis occurred in the presence of well-defined rhodacycles **21** and **22** as the catalysts. These findings provide support for the order of the three subsequent C–H activation events. An additional application for a unique dendrimer **23** through electrooxidative assembly of protected d-lactone **24** was accomplished (Scheme 13).

(a) Photoabsorption and normalized emission spectra of 11e and 11f



(b) Cyclic voltammograms



Scheme 7 | *(a) Photoabsorption and (b) CV of* ***11e*** *and* ***11f****.*

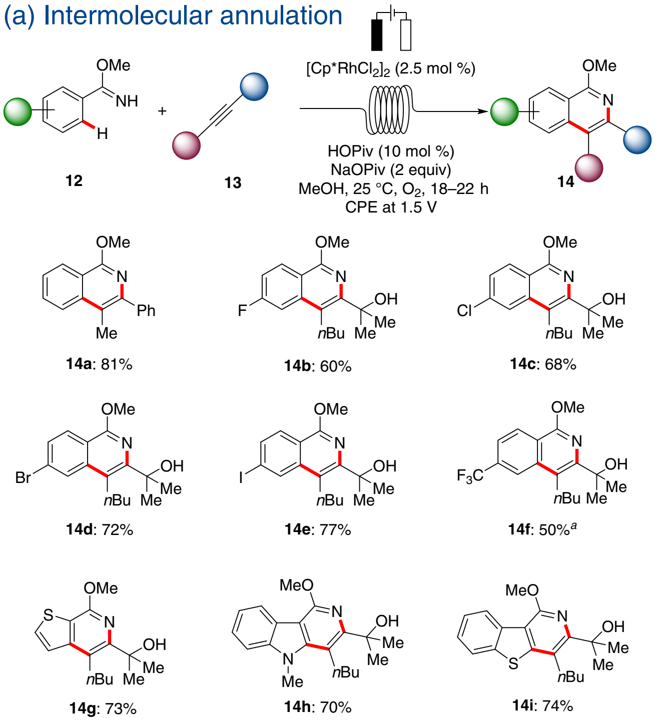
Rhodaelectro-Catalyzed C–H Phosphorylation

Recently, the Xu group[102] concurrently disclosed a mechanistically related phosphorylation using a *N*-coordinating directing group (Scheme 14). The broadly applicable concept of rhodaelectro-catalysis was further utilized for effective C–H phosphorylation using diphenylphosphines **26**. To prove scalability, a decagram scale reaction was successfully performed, illustrating the potential for future industrial applications.

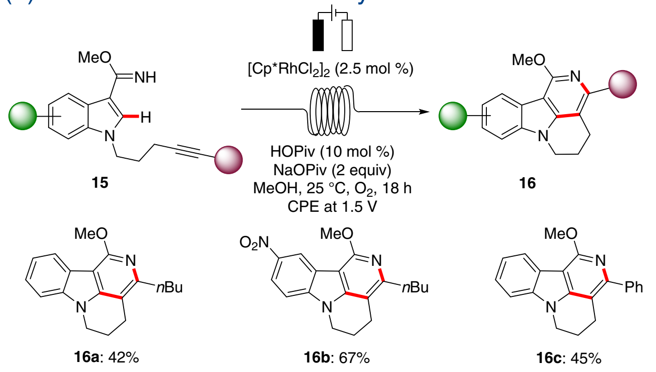
The catalyst's modus operandi was interrogated by detailed mechanistic studies. Specifically, two well-defined rhodium(III) complexes **28** and **29** were prepared. Both complexes **28** and **29** proved to be catalytically active in catalytic settings (Scheme 15a). Thus, the rhodium(III) complex **28** undergoes ligand exchange to form the more oxidizable key intermediate **29**, which is followed by oxidation-induced reductive elimination to generate the desired product **27** (Scheme 15b).

Notably, electrochemistry is an ideal platform for mechanistic studies. In a proof-of-concept study, the Chang group[103] recently probed the viability of cyclometallated rhodium complexes for oxidatively induced reductive elimination steps studies. First, two fully characterized stable cyclometallated rhodium complexes **33** and **35a** were successfully prepared and their electrochemical properties investigated by CV studies (Scheme 16a). An irreversible oxidation potential for **35a** was observed at $E_{pa} = 0.331$ V versus Fc/Fc$^+$ in tetrahydrofuran (THF), which can be further oxidized by silver salt to generate a putative high-valence rhodium

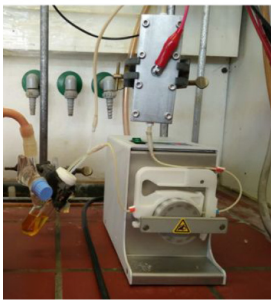
(a) Intermolecular annulation



(b) Intramolecular electrocatalysis

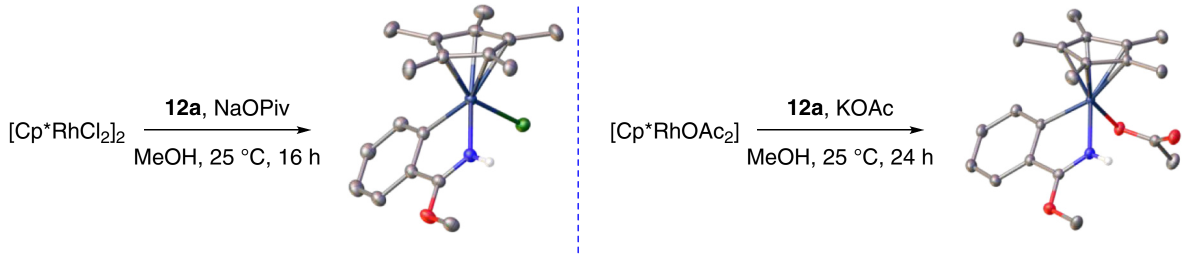


(c) Flow electrochemistry equipment



Scheme 8 | *(a–c) Flow-rhodaelectro-catalyzed alkyne annulations.*[a] *[Cp*Rh(CH$_3$CN)$_3$](SbF$_6$)$_2$ (5.0 mol %) as the catalyst, 50 °C, 10 h, batch reaction.*

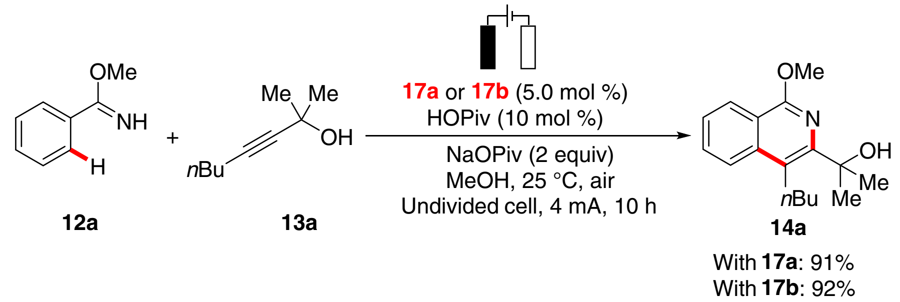
(a) Synthesis of rhodacycles 17a and 17b



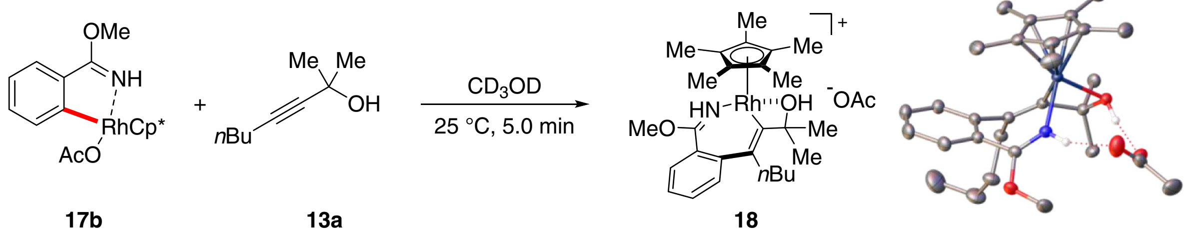
17a (CCDC 1919760)

17b (CCDC 1919761)

(b) Catalytic reaction with 17a and 17b

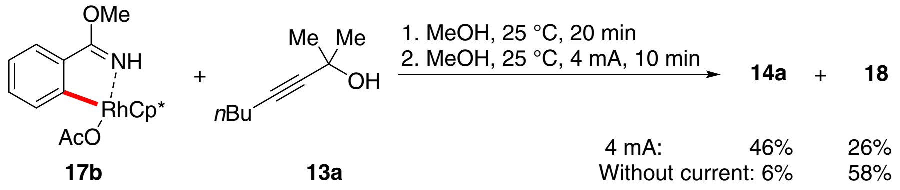


(c) Rhodacycle 18 formation



18 (CCDC 1939864)

(d) Oxidatively induced reductive elimination



Scheme 9 | *(a–d) Synthesis of rhodacyles* ***17a, 17b, 18,*** *and applications to C–H activation catalysis.*

species according to the known oxidation potential of Ag^I ($E_{1/2} = 0.41$ V vs Fc/Fc^+ in THF). Indeed, the desired arylated and methylated products **37a** and **37b** were obtained, while reductive elimination did not take place even at 80 °C under oxidant-free conditions. These findings confirm that reductive elimination was induced by single-electron oxidation (Schemes 16b and 16c).

Rhodaelectro-Catalyzed C–C Alkenylation

The versatile electrochemical rhodium catalysis manifold is not limited to C–H transformations. Hence, Ackermann disclosed a rhodaelectro-catalyzed C–C alkenylation, representing the proof-of-concept for organometallic C–C functionalization[104] by electrocatalysis.[105] Within the organometallic C–C activation manifold, electrochemical chelation-assisted C–C functionalizations were demonstrated to proceed with ample substrate scope and outstanding levels of chemo- and position-based selectivities (Scheme 17a). In addition, competition experiments between the C–C and C–H functionalizations revealed a preferential reactivity of the C–C activation manifold, thus position selectively furnishing densely decorated 1,2,3-substituted arenes, not accessible by more common C–H activation strategies (Scheme 17b).

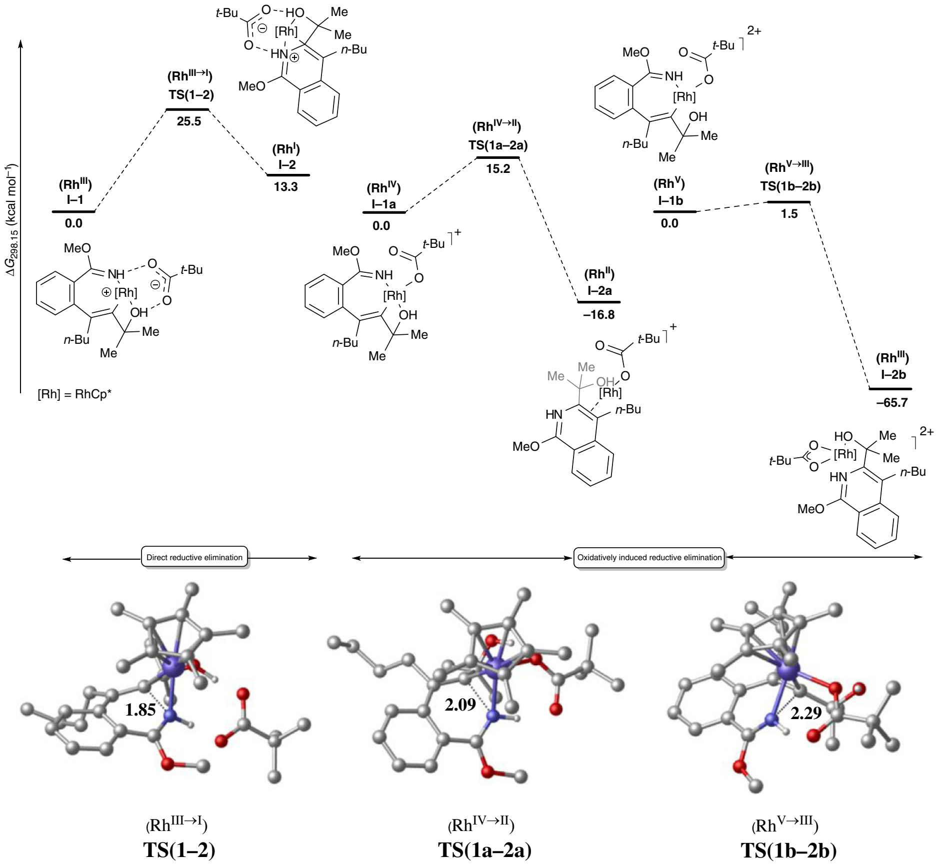
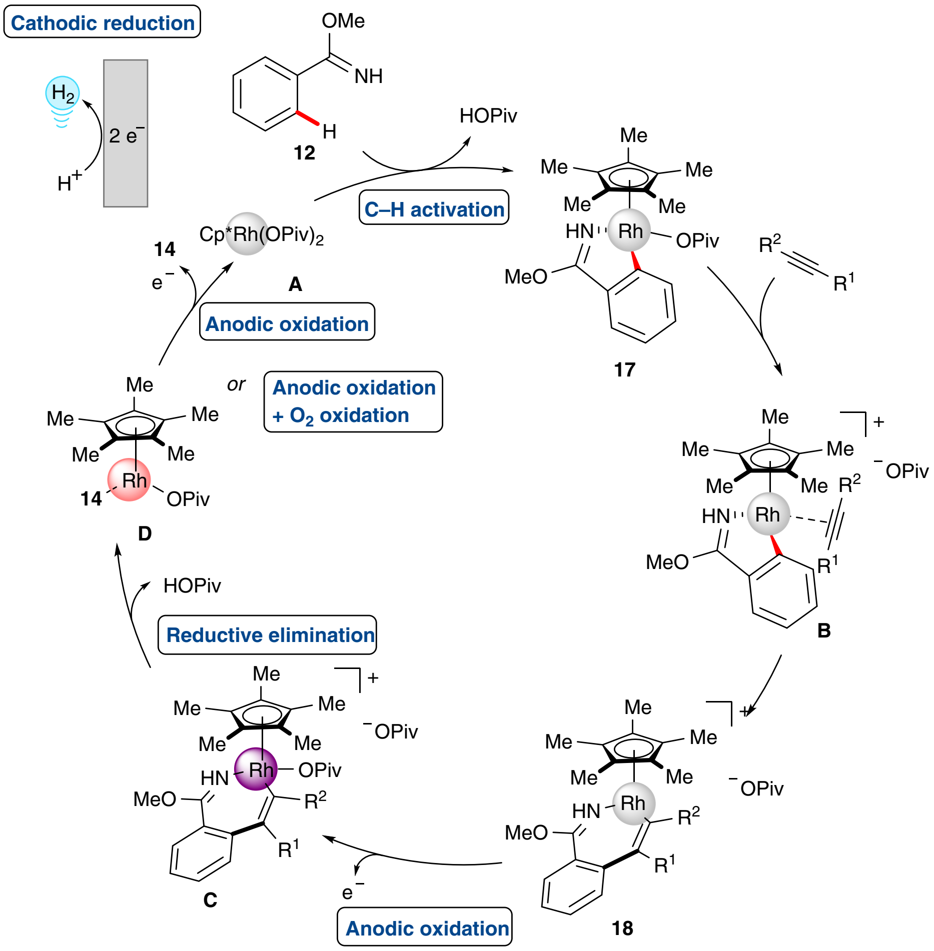


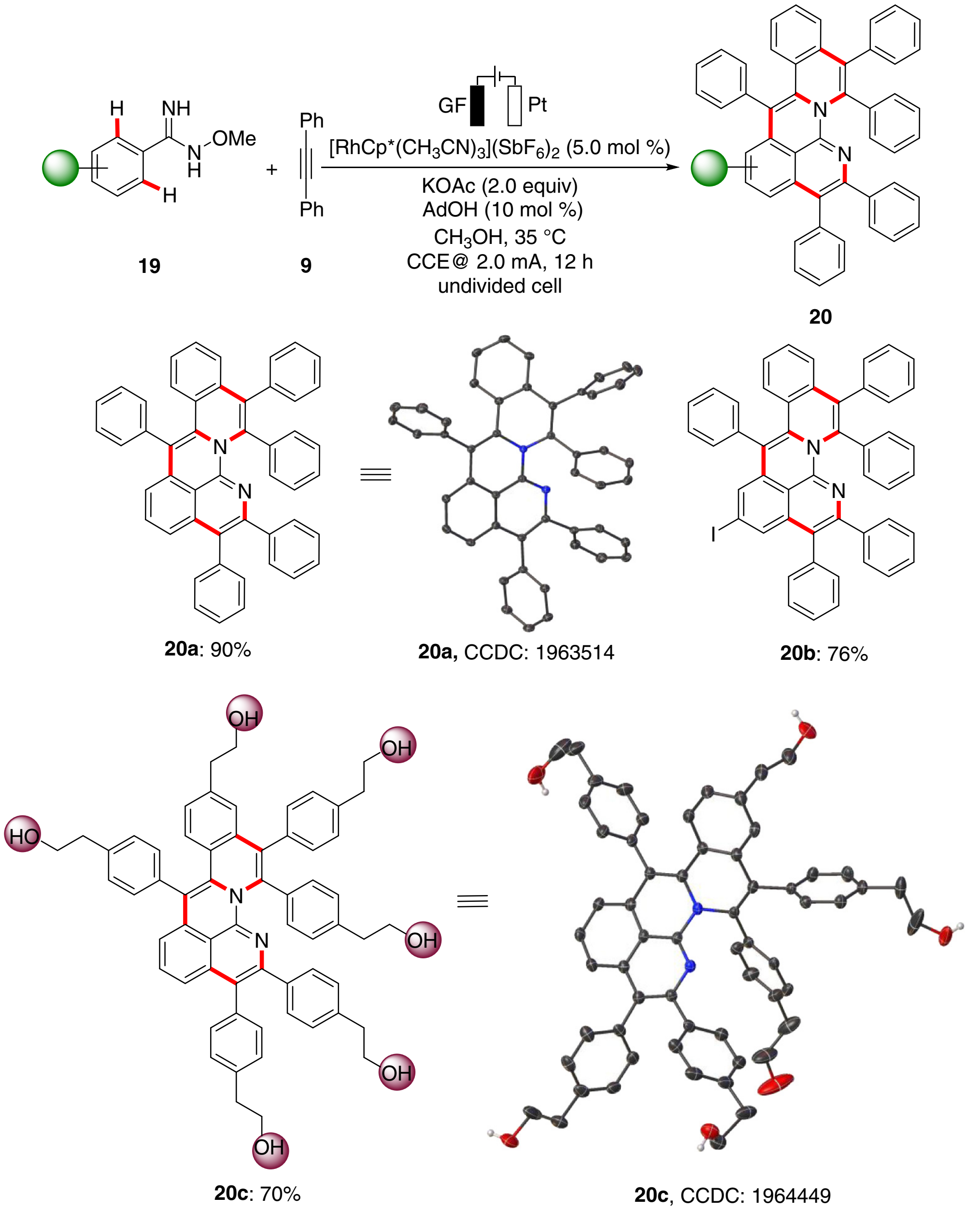
Figure 1 | *Gibbs free-energy profile (in kcal mol^{-1}) comparing the direct reductive elimination and oxidatively induced reductive elimination at the B3LYP-D3(BJ)/6-311++G*(d,p)*,SDD(Rh)+SMD(methanol)//B3LYP-D3(BJ)/6-31G*(d,p)*, SDD(Rh) level of theory. Nonparticipating hydrogen atoms were omitted for clarity.*

The catalyst's mode of action was investigated by detailed mechanistic studies (Scheme 18). Competition experiments showed that electron-rich arenes and olefins were preferentially converted (Scheme 18a). The C–C and C–H functionalization competition experiment showed that the C–C activation occurred faster than the C–H activation (Scheme 18b). The use of isotopically labeled [D]$_1$-*t*AmOD and D_2O did not lead to a significant deuteration in the unreacted starting material or the obtained product. These findings are indicative of a slow C–C scission (Scheme 18c). The formation of hydrogen as the sole byproduct of cathodic proton reduction was confirmed by headspace gas chromatographic analysis (Scheme 18d). Notably, the two well-defined rhodium complexes **42a** and **42b** proved to be competent catalysts for the organometallic nature of the electrooxidative C–C alkenylation (Scheme 18e).

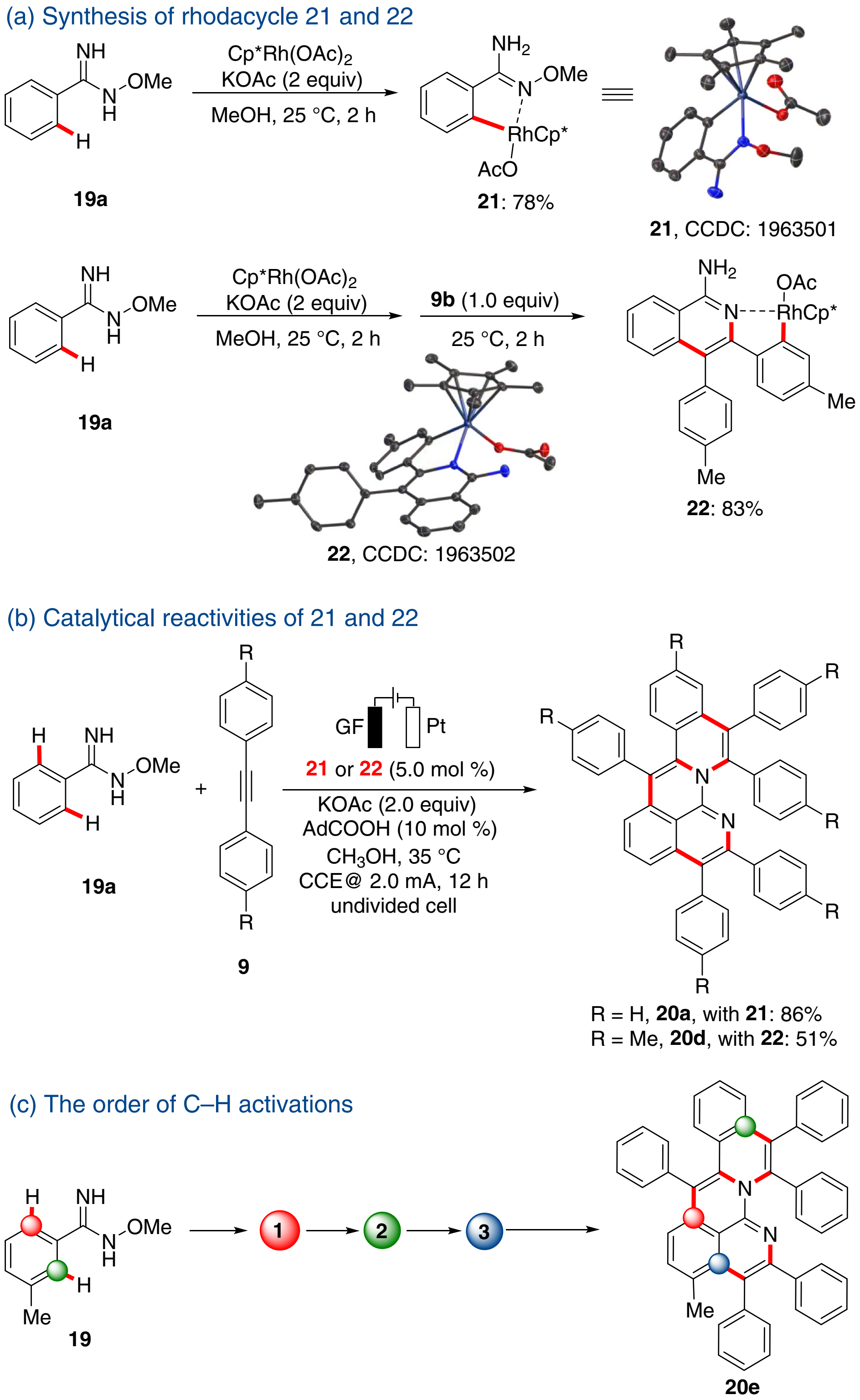
Their findings were rationalized by a plausible catalytic cycle depicted in Scheme 19. Initiated by the formation of active catalyst **4a**, the seven-membered rhodacycle **43** was formed upon chelating with the nitrogen and oxygen of substrate **38** with the rhodium(III) catalyst. Thereafter, migratory alkene insertion occurred to form the key seven-membered intermediate **46**. Finally, reductive elimination furnished the desired product **40,** and the active catalyst **4a** was regenerated upon anodic oxidation of the rhodium(I) intermediate **47**.



Scheme 10 | *Proposed catalytic cycle for flow-rhodaelectro-catalyzed alkyne annulation.*



Scheme 11 | *Rhodaelectro-catalyzed domino annulation.*

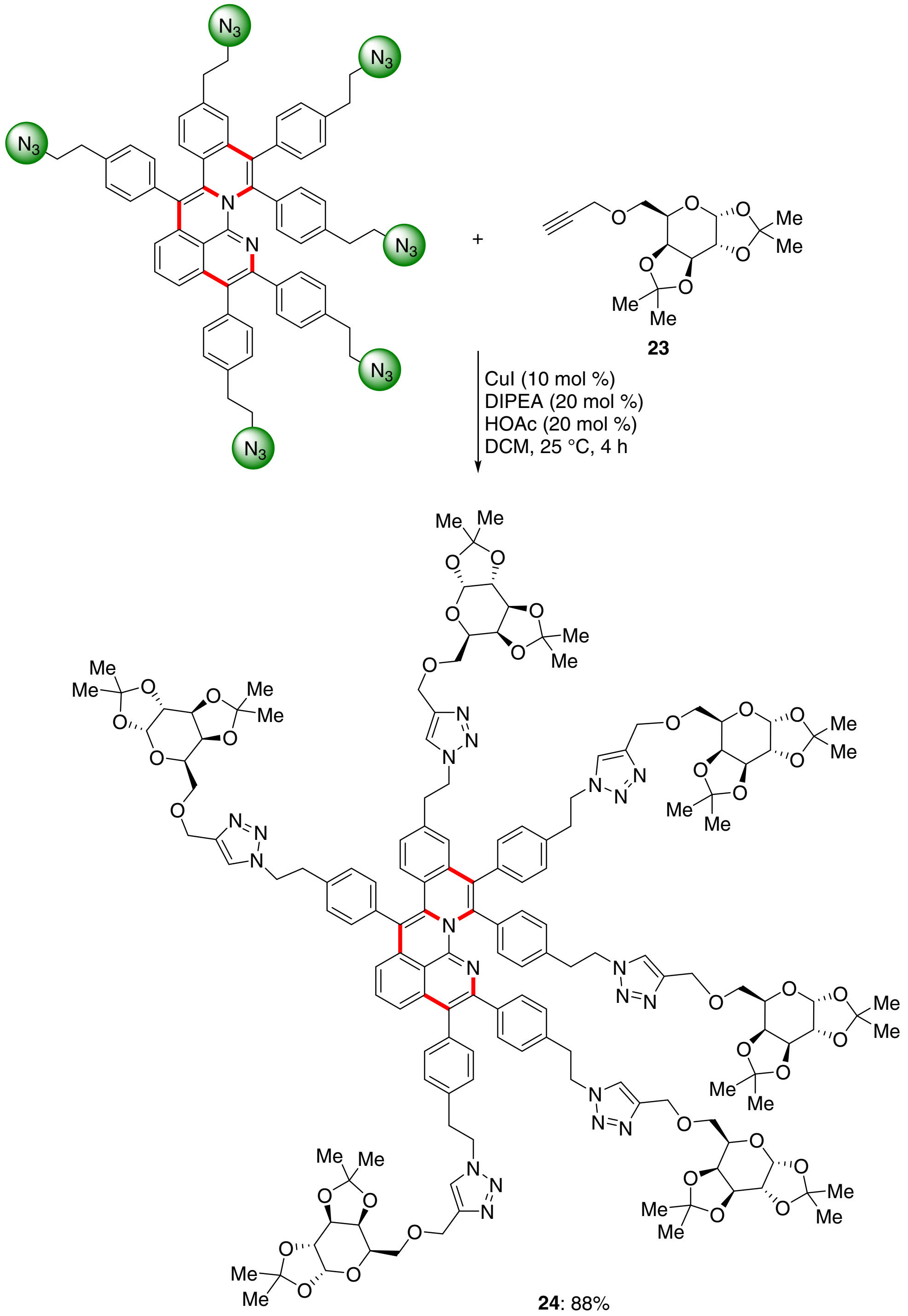


(a) Synthesis of rhodacycle 21 and 22

(b) Catalytical reactivities of 21 and 22

(c) The order of C–H activations

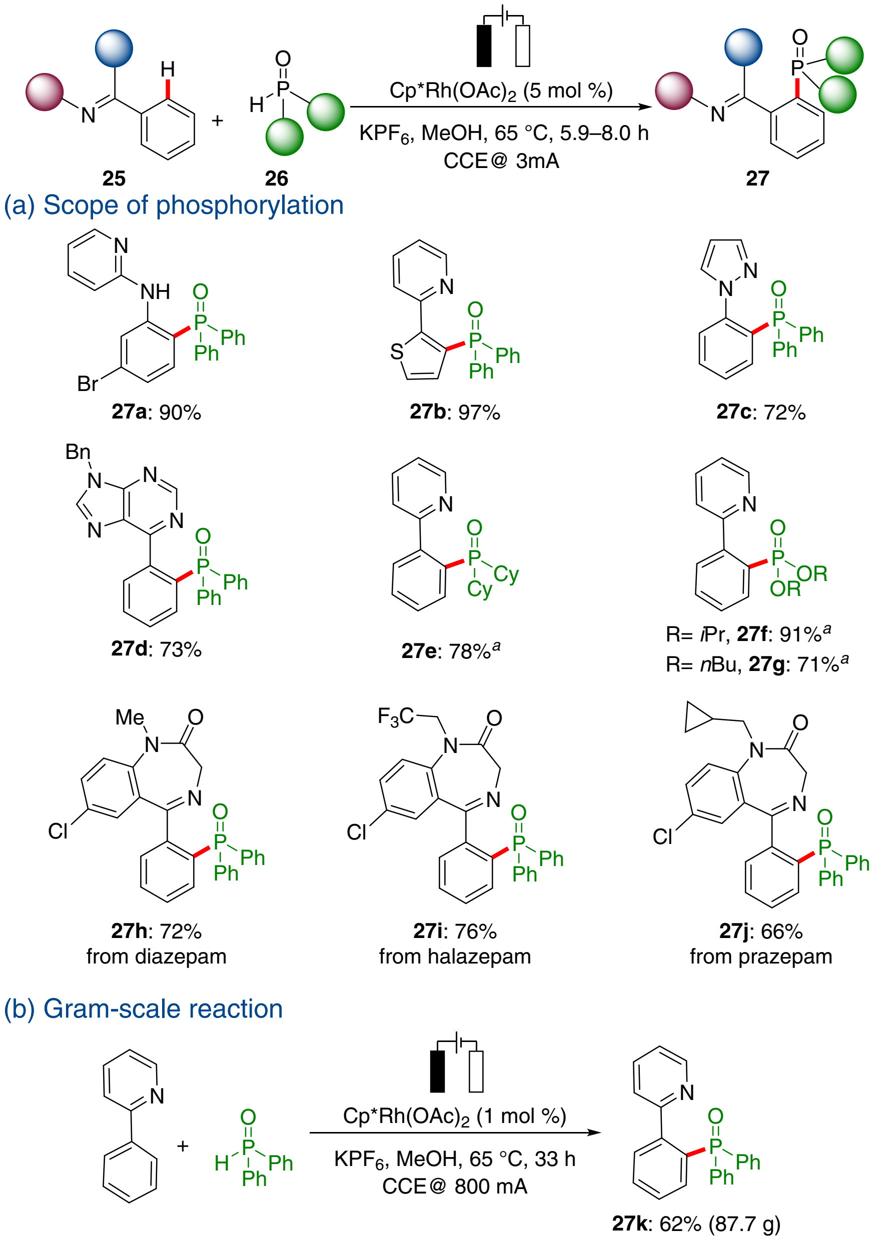
Scheme 12 | *(a–c) Key mechanistic findings.*



23

24: 88%

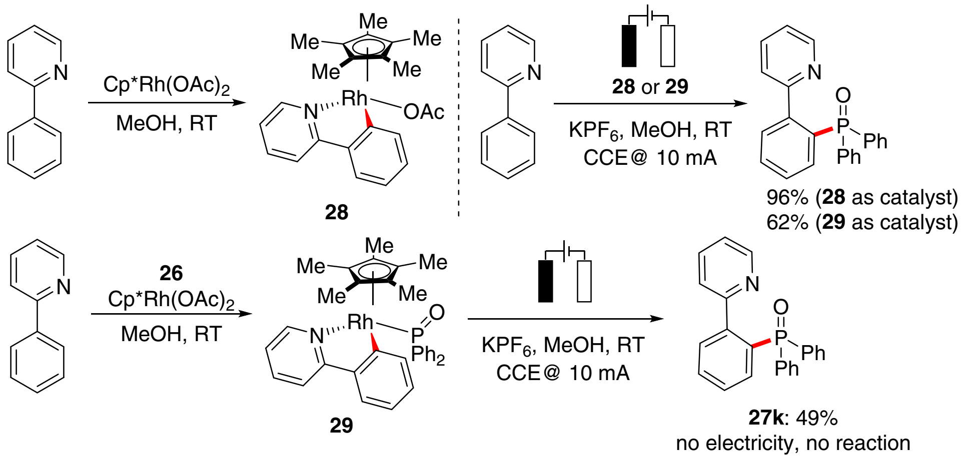
Scheme 13 | *Late-stage functionalization of aza-PAHs.*



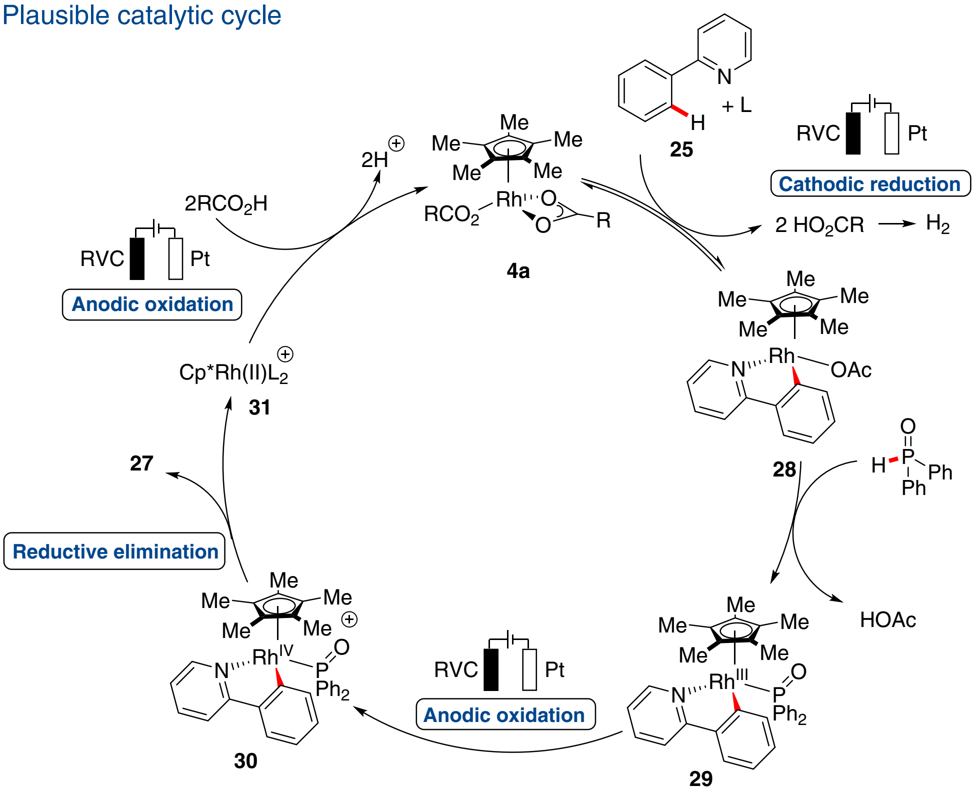
[a]Under 10 mA.

Scheme 14 | *(a and b) Rhodaelectro-catalyzed C–H phosphorylation.*

(a) Rh-complexs and anodic oxidation induced reductive elimination



(b) Plausible catalytic cycle



Scheme 15 | *(a and b) Key mechanistic findings and plausible catalytic cycle for rhodaelectro-catalyzed C–H phosphorylation.*

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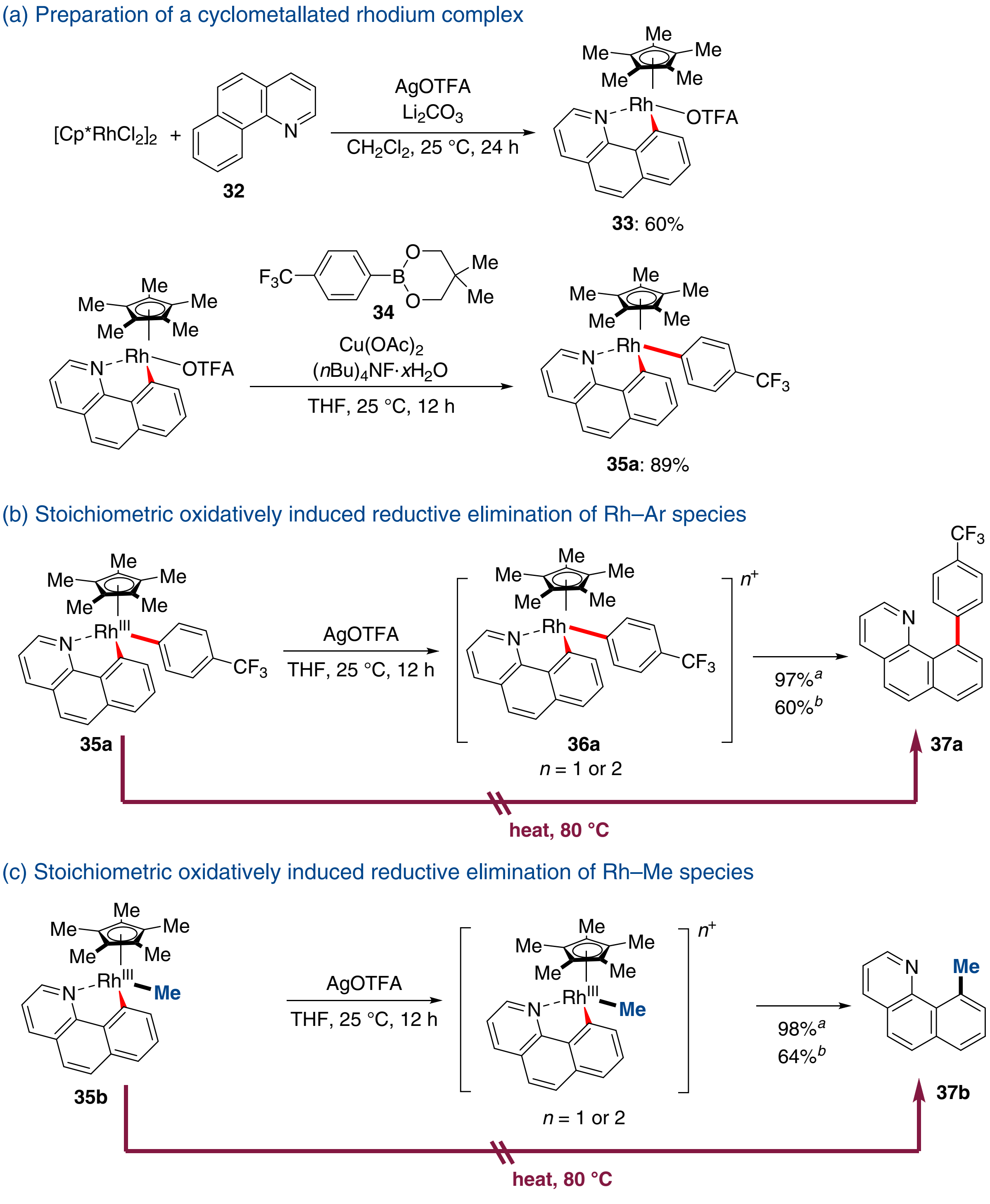
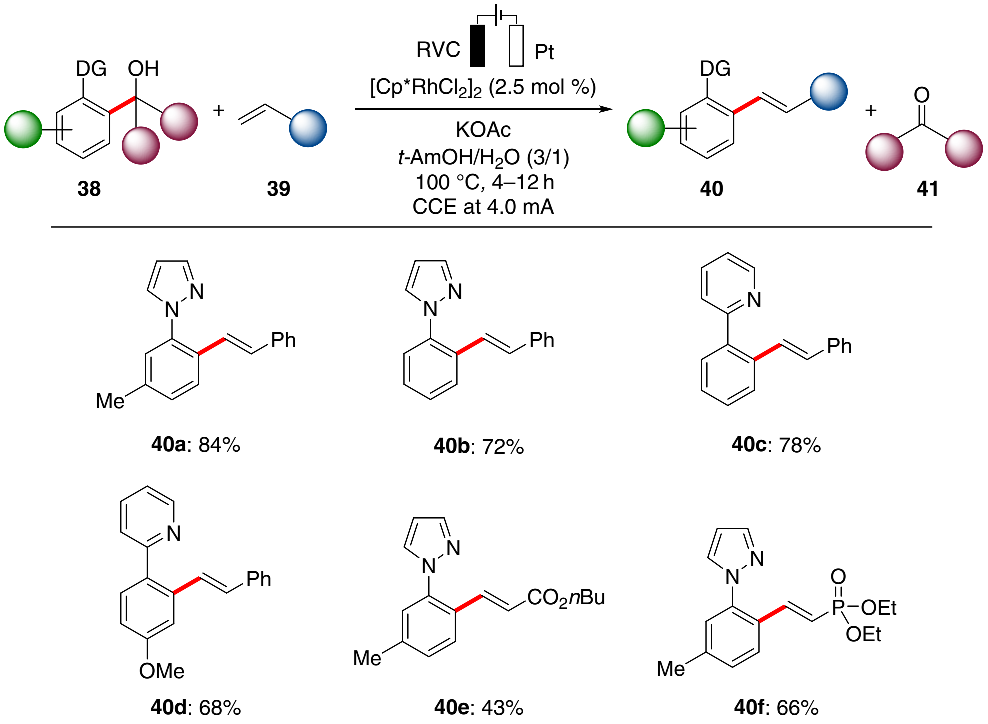


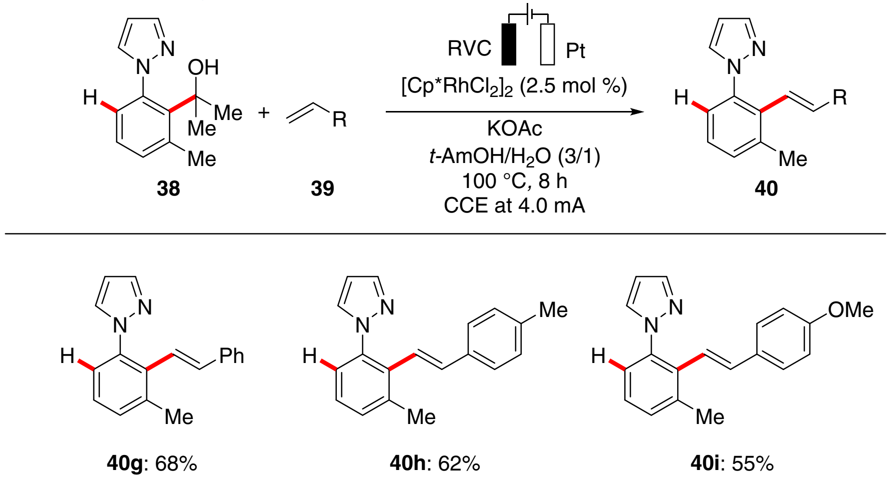
[a] 2.2 equiv AgOTFA; [b] 1.0 equiv AgOTFA

Scheme 16 | *(a–c) Oxidatively induced reductive elimination of rhodium complexes.*

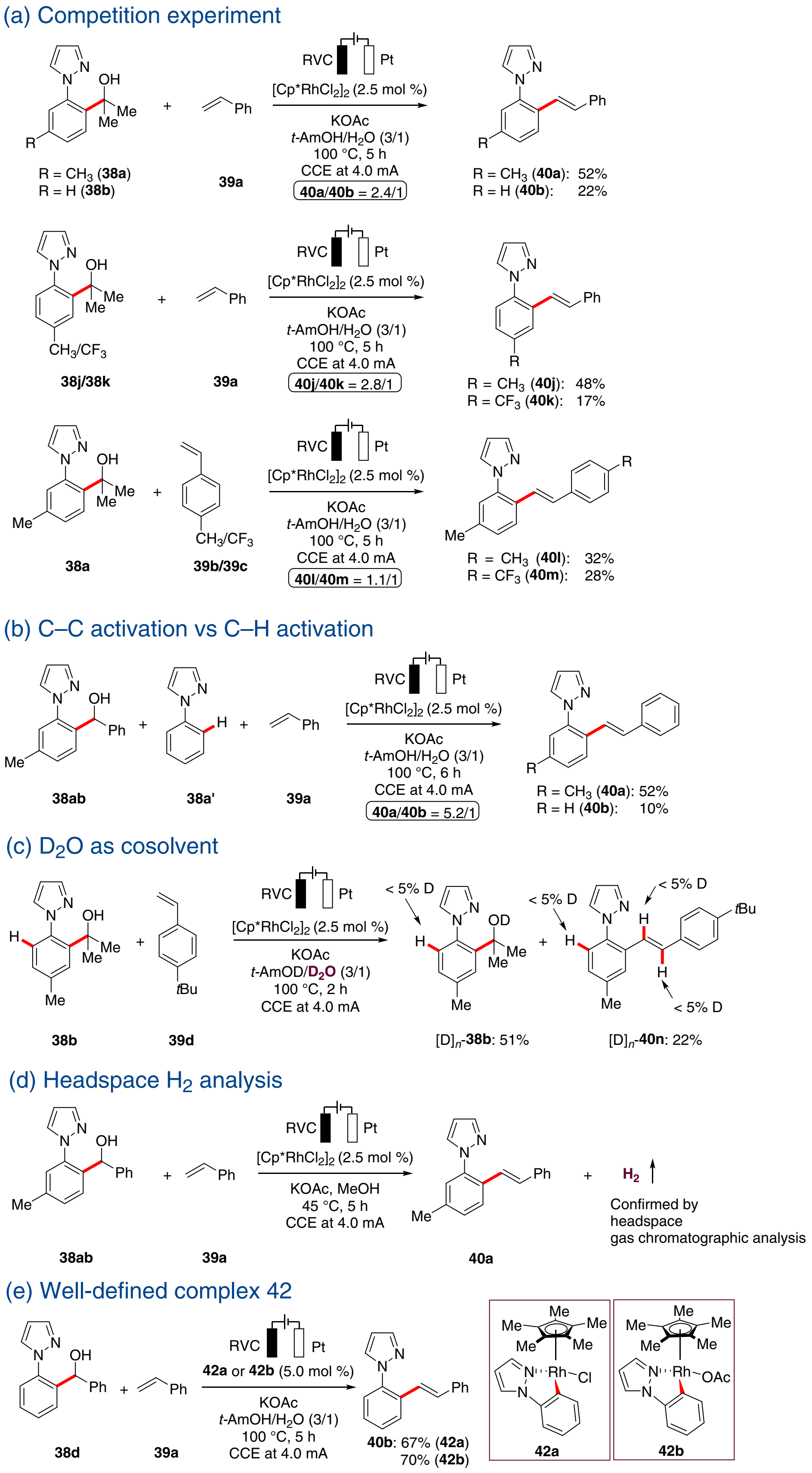
(a) Scope of rhodaelectro-catalyzed C–C alkenylation



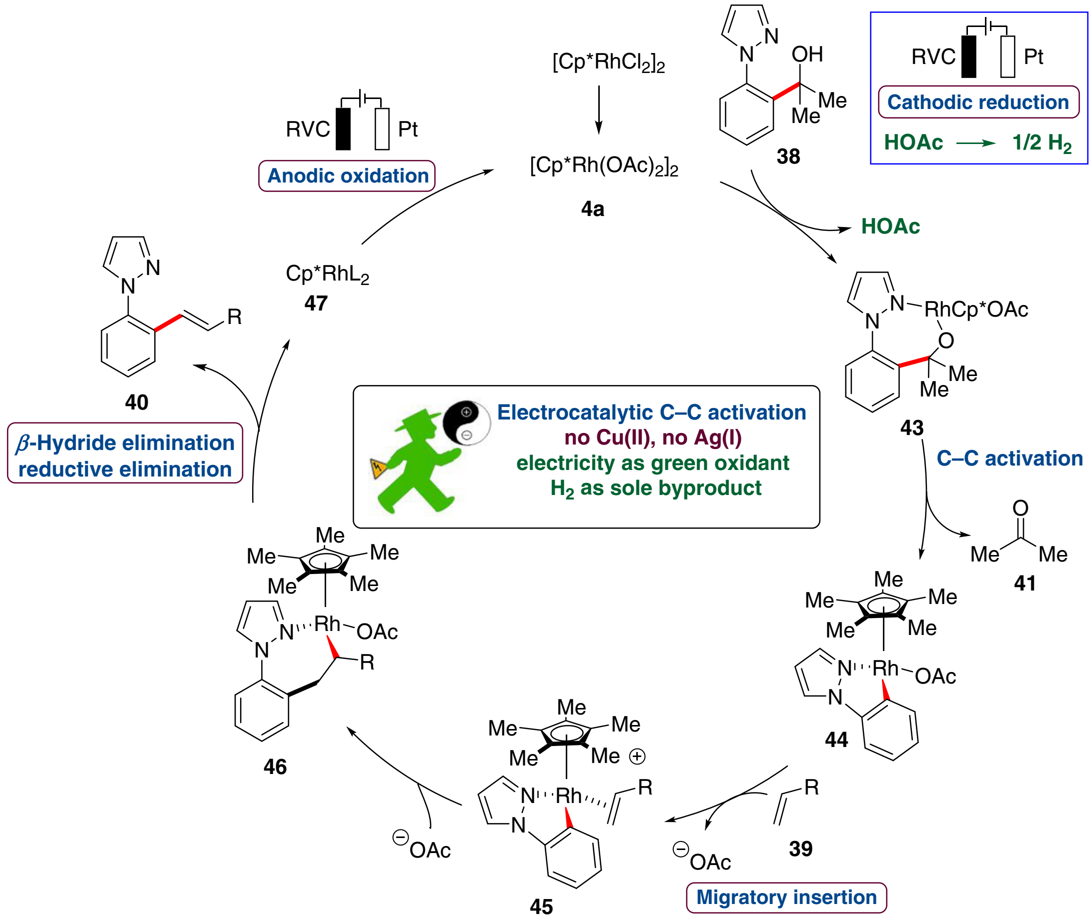
(b) Position-selectivity



Scheme 17 | *(a and b) Rhodaelectro-catalyzed C–C alkenylation and position selectivity.*



Scheme 18 | *(a–e) Key mechanistic findings of rhodaelectro-catalyzed C–C alkenylation.*



Scheme 19 | *Plausible catalytic cycle of rhodaelectro-catalyzed C–C alkenylation.*

Conclusions

In recent years, rhodaelectro-catalyzed C–H activation has emerged as a powerful platform for molecular synthesis, employing sustainable electricity as the terminal oxidant and avoiding the use of stoichiometric amounts of sacrificial chemical oxidants. Since the first example of rhodaelectro-catalyzed C–H activation with weakly *O*-coordinating benzoic acids was described by the Ackermann group, numerous elegant transformations applying rhodaelectro-catalyzed C–H or C–C activations have been established. Key breakthroughs in the understanding of the catalytic mode of action and overall catalysis have been achieved by among others headspace gas chromatographic analyses, CV, and computation, prominently featuring oxidation-induced reductive elimination pathways. A flow metallaelectro-catalyzed C–H activation was realized in terms of robust rhodaelectro-catalyzed alkyne annulations. In addition, the electrochemical assembly of PAHs was proved viable via rhodaelectro-catalyzed cascade C–H annulations. Furthermore, electrochemical C–C activations were accomplished by expedient oxidative rhodium(III) catalysis. Given the sustainable nature of metallaelectro-catalyzed C–H activation reaction, exciting future advances are expected in this rapidly evolving research area, which should address enantioselective metallaelectro-catalysis,[106] photoelectrochemical transformations,[107–112] and organic materials electrochemical syntheses.

Conflict of Interest

The authors declare no conflict of interest.

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References

1. Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247–9301.

2. Gandeepan, P.; Ackermann, L. Transient Directing Groups for Transformative C–H Activation by Synergistic Metal Catalysis. *Chem* **2018**, *4*, 199–222.
3. Piou, T.; Rovis, T. Electronic and Steric Tuning of a Prototypical Piano Stool Complex: Rh(III) Catalysis for C–H Functionalization. *Acc. Chem. Res.* **2018**, *51*, 170–180.
4. Wei, Y.; Hu, P.; Zhang, M.; Su, W. Metal-Catalyzed Decarboxylative C–H Functionalization. *Chem. Rev.* **2017**, *117*, 8864–8907.
5. He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C–H Bonds. *Chem. Rev.* **2017**, *117*, 8754–8786.
6. Wencel-Delord, J.; Glorius, F. C–H Bond Activation Enables the Rapid Construction and Late-Stage Diversification of Functional Molecules. *Nat. Chem.* **2013**, *5*, 369–375.
7. Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium (II)-Catalyzed C–H Bond Activation and Functionalization. *Chem. Rev.* **2012**, *112*, 5879–5918.
8. Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C–H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315–1345.
9. Davies, H. M. L.; Manning, J. R. Catalytic C–H Functionalization by Metal Carbenoid and Nitrenoid Insertion. *Nature* **2008**, *451*, 417–424.
10. Bergman, R. G. C–H Activation. *Nature* **2007**, *446*, 391–393.
11. Shin, K.; Kim, H.; Chang, S. Transition-Metal-Catalyzed C–N Bond Forming Reactions Using Organic Azides as the Nitrogen Source: A Journey for the Mild and Versatile C–H Amination. *Acc. Chem. Res.* **2015**, *48*, 1040–1052.
12. Sperger, T.; Sanhueza, I. A.; Kalvet, I.; Schoenebeck, F. Computational Studies of Synthetically Relevant Homogeneous Organometallic Catalysis Involving Ni, Pd, Ir, and Rh: An Overview of Commonly Employed DFT Methods and Mechanistic Insights. *Chem. Rev.* **2015**, *115*, 9532–9586.
13. Kuhl, N.; Schroeder, N.; Glorius, F. Formal SN-Type Reactions in Rhodium(III)-Catalyzed C–H Bond Activation. *Adv. Synth. Catal.* **2014**, *356*, 1443–1460.
14. Song, G.; Wang, F.; Li, X. C–C, C–O and C–N Bond Formation via Rhodium(III)-Catalyzed Oxidative C–H Activation. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678.
15. Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C–C Bond Formation via Heteroatom-Directed C–H Bond Activation. *Chem. Rev.* **2010**, *110*, 624–655.
16. Satoh, T.; Miura, M. Oxidative Coupling of Aromatic Substrates with Alkynes and Alkenes Under Rhodium Catalysis. *Chem. Eur. J.* **2010**, *16*, 11212–11222.
17. Liu, Y.; Yang, Y.; Shi, Y.; Wang, X.; Zhang, L.; Cheng, Y.; You, J. Rhodium-Catalyzed Oxidative Coupling of Benzoic Acids with Terminal Alkynes: An Efficient Access to 3-Ylidenephthalides. *Organometallics* **2016**, *35*, 1350–1353.
18. Kudo, E.; Shibata, Y.; Yamazaki, M.; Masutomi, K.; Miyauchi, Y.; Fukui, M.; Sugiyama, H.; Uekusa, H.; Satoh, T.; Miura, M. Oxidative Annulation of Arenecarboxylic and Acrylic Acids with Alkynes Under Ambient Conditions Catalyzed by an Electron-Deficient Rhodium(III) Complex. *Chem. Eur. J.* **2016**, *22*, 14190–14194.
19. Gandeepan, P.; Rajamalli, P.; Cheng, C. H. Rhodium(III)-Catalyzed [4+1] Annulation of Aromatic and Vinylic Carboxylic Acids with Allenes: An Efficient Method Towards Vinyl-Substituted Phthalides and 2-Furanones. *Chem. Eur. J.* **2015**, *21*, 9198–9203.
20. Zhang, G.; Yang, L.; Wang, Y.; Xie, Y.; Huang, H. An Efficient Rh/O2 Catalytic System for Oxidative C–H Activation/Annulation: Evidence for Rh(I) to Rh(III) Oxidation by Molecular Oxygen. *J. Am. Chem. Soc.* **2013**, *135*, 8850–8853.
21. Ueura, K.; Satoh, T.; Miura, M. 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.
22. Zhu, C.; Stangier, M.; Oliveira, J. C. A.; Massignan, L.; Ackermann, L. Iron-Electrocatalyzed C–H Arylations: Mechanistic Insights into Oxidation-Induced Reductive Elimination for Ferraelectrocatalysis. *Chem. Eur. J.* **2019**, *25*, 16382–16389.
23. Xiong, P.; Xu, H.-C. Chemistry with Electrochemically Generated N-Centered Radicals. *Acc. Chem. Res.* **2019**, *52*, 3339–3350.
24. Parry, J. B.; Fu, N.; Lin, S. Electrocatalytic Difunctionalization of Olefins as a General Approach to the Synthesis of Vicinal Diamines. *Synlett* **2018**, *29*, 257–265.
25. Möhle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R. Modern ElectroChemical Aspects for the Synthesis of Value-Added Organic Products. *Angew. Chem. Int. Ed.* **2018**, *57*, 6018–6041.
26. Sauermann, N.; Meyer, T. H.; Qiu, Y.; Ackermann, L. Electrocatalytic C–H Activation. *ACS Catal.* **2018**, *8*, 7086–7103.
27. Tang, S.; Liu, Y.; Lei, A. Electrochemical Oxidative Cross-Coupling with Hydrogen Evolution: A Green and Sustainable Way for Bond Formation. *Chem* **2018**, *4*, 27–45.
28. Feng, R.; Smith, J. A.; Moeller, K. D. Anodic Cyclization Reactions and the Mechanistic Strategies that Enable Optimization. *Acc. Chem. Res.* **2017**, *50*, 2346–2352.
29. Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230–13319.
30. Hou, Z.-W.; Mao, Z.-Y.; Xu, H.-C. Recent Progress on the Synthesis of (aza) Indoles Through Oxidative Alkyne Annulation Reactions. *Synlett* **2017**, *28*, 1867–1872.
31. Jiao, K.-J.; Zhao, C.-Q.; Fang, P.; Mei, T.-S. Palladium Catalyzed CH Functionalization with Electrochemical Oxidation. *Tetrahedron Lett.* **2017**, *58*, 797–802.
32. Horn, E. J.; Rosen, B. R.; Baran, P. S. Synthetic Organic Electrochemistry: An Enabling and Innately Sustainable Method. *ACS Cent. Sci.* **2016**, *2*, 302–308.
33. Francke, R.; Little, R. D. Redox Catalysis in Organic Electrosynthesis: Basic Principles and Recent Developments. *Chem. Soc. Rev.* **2014**, *43*, 2492–2521.
34. Waldvogel, S. R.; Janza, B. Renaissance of Electrosynthetic Methods for the Construction of Complex Molecules. *Angew. Chem. Int. Ed.* **2014**, *53*, 7122–7123.
35. Jutand, A. Contribution of Electrochemistry to Organometallic Catalysis. *Chem. Rev.* **2008**, *108*, 2300–2347.

36. Yoshida, J.-i.; Kataoka, K.; Horcajada, R.; Nagaki, A. Modern Strategies in Electroorganic Synthesis. *Chem. Rev.* **2008**, *108*, 2265–2299.
37. Ackermann, L. Metalla-Electrocatalyzed C–H Activation by Earth-Abundant 3d Metals and Beyond. *Acc. Chem. Res.* **2020**, *53*, 84–104.
38. Qiu, Y.; Scheremetjew, A.; Finger, L. H.; Ackermann, L. Electrophotocatalytic Undirected C–H Trifluoromethylations of (Het)Arenes. *Chem. Eur. J.* **2020**, *26*, 3241–3246.
39. Shrestha, A.; Lee, M.; Dunn, A. L.; Sanford, M. S. Palladium-Catalyzed C–H Bond Acetoxylation via Electrochemical Oxidation. *Org. Lett.* **2018**, *20*, 204–207.
40. Xu, F.; Li, Y.-J.; Huang, C.; Xu, H.-C. Ruthenium-Catalyzed Electrochemical Dehydrogenative Alkyne Annulation. *ACS Catal.* **2018**, *8*, 3820–3824.
41. Qiu, Y.; Tian, C.; Massignan, L.; Rogge, T.; Ackermann, L. Electrooxidative Ruthenium-Catalyzed C–H/O–H Annulation by Weak O-Coordination. *Angew. Chem. Int. Ed.* **2018**, *57*, 5818–5822.
42. Meyer, T. H.; Oliveira, J. C. A.; Sau, S. C.; Ang, N. W. J.; Ackermann, L. Electrooxidative Allene Annulations by Mild Cobalt-Catalyzed C–H Activation. *ACS Catal.* **2018**, *8*, 9140–9147.
43. Tian, C.; Massignan, L.; Meyer, T. H.; Ackermann, L. Electrochemical C–H/N–H Activation by Water-Tolerant Cobalt Catalysis at Room Temperature. *Angew. Chem. Int. Ed.* **2018**, *57*, 2383–2387.
44. Mei, R.; Sauermann, N.; Oliveira, J. C. A.; Ackermann, L. Electroremovable Traceless Hydrazides for Cobalt-Catalyzed Electro-Oxidative C–H/N–H Activation with Internal Alkynes. *J. Am. Chem. Soc.* **2018**, *140*, 7913–7921.
45. Ye, K.-Y.; Pombar, G.; Fu, N.; Sauer, G. S.; Keresztes, I.; Lin, S. Anodically Coupled Electrolysis for the Heterodifunctionalization of Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 2438–2441.
46. Gao, X.; Wang, P.; Zeng, L.; Tang, S.; Lei, A. Cobalt (II)-Catalyzed Electrooxidative C–H Amination of Arenes with Alkylamines. *J. Am. Chem. Soc.* **2018**, *140*, 4195–4199.
47. Tang, S.; Wang, D.; Liu, Y.; Zeng, L.; Lei, A. Cobalt-Catalyzed Electrooxidative C–H/N–H [4+2] Annulation with Ethylene or Ethyne. *Nat. Commun.* **2018**, *9*, 798.
48. Qiu, Y.; Struwe, J.; Meyer, T. H.; Oliveira, J. C. A.; Ackermann, L. Catalyst- and Reagent-Free Electrochemical Azole C–H Amination. *Chem. Eur. J.* **2018**, *24*, 12784–12789.
49. Yang, Q.-L.; Li, Y.-Q.; Ma, C.; Fang, P.; Zhang, X.-J.; Mei, T.-S. Palladium-Catalyzed C(sp^3)–H Oxygenation via Electrochemical Oxidation. *J. Am. Chem. Soc.* **2017**, *139*, 3293–3298.
50. Ma, C.; Zhao, C.-Q.; Li, Y.-Q.; Zhang, L.-P.; Xu, X.-T.; Zhang, K.; Mei, T.-S. Palladium-Catalyzed C–H Activation/C–C Cross-Coupling Reactions via Electrochemistry. *Chem. Comm.* **2017**, *53*, 12189–12192.
51. Wiebe, A.; Lips, S.; Schollmeyer, D.; Franke, R.; Waldvogel, S. R. Single and Twofold Metal- and Reagent-Free Anodic C–C Cross-Coupling of Phenols with Thiophenes. *Angew. Chem. Int. Ed.* **2017**, *56*, 14727–14731.
52. Konishi, M.; Tsuchida, K.; Sano, K.; Kochi, T.; Kakiuchi, F. Palladium-Catalyzed Ortho-Selective C–H Chlorination of Benzamide Derivatives Under Anodic Oxidation Conditions. *J. Org. Chem.* **2017**, *82*, 8716–8724.
53. Li, Y.-Q.; Yang, Q.-L.; Fang, P.; Mei, T.-S.; Zhang, D. Palladium-Catalyzed C(sp^2)–H Acetoxylation via Electrochemical Oxidation. *Org. Lett.* **2017**, *19*, 2905–2908.
54. Fu, N.; Sauer, G. S.; Saha, A.; Loo, A.; Lin, S. Metal-Catalyzed Electrochemical Diazidation of Alkenes. *Science* **2017**, *357*, 575–579.
55. Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D.-H.; Chen, J.; Starr, J. T.; Baran, P. S. Scalable, Electrochemical Oxidation of Unactivated C–H Bonds. *J. Am. Chem. Soc.* **2017**, *139*, 7448–7451.
56. Horn, E. J.; Rosen, B. R.; Chen, Y.; Tang, J.; Chen, K.; Eastgate, M. D.; Baran, P. S. Scalable and Sustainable Electrochemical Allylic C–H Oxidation. *Nature* **2016**, *533*, 77–81.
57. Saito, F.; Aiso, H.; Kochi, T.; Kakiuchi, F. Palladium-Catalyzed Regioselective Homocoupling of Arenes Using Anodic Oxidation: Formal Electrolysis of Aromatic Carbon-Hydrogen Bonds. *Organometallics* **2014**, *33*, 6704–6707.
58. Aiso, H.; Kochi, T.; Mutsutani, H.; Tanabe, T.; Nishiyama, S.; Kakiuchi, F. Catalytic Electrochemical C–H Iodination and One-Pot Arylation by ON/OFF Switching of Electric Current. *J. Org. Chem.* **2012**, *77*, 7718–7724.
59. Amatore, C.; Cammoun, C.; Jutand, A. Electrochemical Recycling of Benzoquinone in the Pd/Benzoquinone-Catalyzed Heck-Type Reactions from Arenes. *Adv. Synth. Catal.* **2007**, *349*, 292–296.
60. Wienkamp, R.; Steckhan, E. Indirect Electrochemical Regeneration of NADH by a Bipyridinerhodium(I) Complex as Electron-Transfer Agent. *Angew. Chem. Int. Ed.* **1982**, *21*, 782–783.
61. Levitin, I.; Sigan, A. L.; Vol'pin, M. E. Electrochemical Generation and Reactivity of Organo-Cobalt(IV) and -Rhodium(IV) Chelates. *Chem. Comm.* **1975**, 469–470.
62. Pouliot, J.-R. m.; Grenier, F. o.; Blaskovits, J. T.; Beaupré, S.; Leclerc, M. Direct (Hetero)Arylation Polymerization: Simplicity for Conjugated Polymer Synthesis. *Chem. Rev.* **2016**, *116*, 14225–14274.
63. Park, Y.; Jee, S.; Kim, J. G.; Chang, S. Study of Sustainability and Scalability in the Cp*Rh (III)-Catalyzed Direct C–H Amidation with 1,4,2-Dioxazol-5-Ones. *Org. Process. Res. Dev.* **2015**, *19*, 1024–1029.
64. Ackermann, L. 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.
65. Lapointe, D.; Fagnou, K. Overview of the Mechanistic Work on the Concerted Metallation-Deprotonation Pathway. *Chem. Lett.* **2010**, *39*, 1118–1126.
66. Meyer, T. H.; Finger, L. H.; Gandeepan, P.; Ackermann, L. Resource Economy by Metallaelectrocatalysis: Merging Electrochemistry and C H Activation. *Trends Chem.* **2019**, *1*, 63–76.
67. Qiu, Y.; Kong, W.-J.; Struwe, J.; Sauermann, N.; Rogge, T.; Scheremetjew, A.; Ackermann, L. Electrooxidative Rhodium-Catalyzed C–H/C–H Activation: Electricity as Oxidant for

Cross-Dehydrogenative Alkenylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 5828–5832.

68. Qiu, Y.; Struwe, J.; Ackermann, L. Metallaelectro-Catalyzed C–H Activation by Weak Coordination. *Synlett* **2019**, *30*, 1164–1173.

69. Yang, Q.-L.; Xing, Y.-K.; Wang, X.-Y.; Ma, H.-X.; Weng, X.-J.; Yang, X.; Guo, H.-M.; Mei, T.-S. Electrochemistry-Enabled Ir-Catalyzed Vinylic C–H Functionalization. *J. Am. Chem. Soc.* **2019**, *141*, 18970–18976.

70. Qiu, Y.; Stangier, M.; Meyer, T. H.; Oliveira, J. C. A.; Ackermann, L. Iridium-Catalyzed Electrooxidative C–H Activation by Chemoselective Redox-Catalyst Cooperation. *Angew. Chem. Int. Ed.* **2018**, *57*, 14179–14183.

71. Wang, L.; Carrow, B. P. Oligothiophene Synthesis by a General C–H Activation Mechanism: Electrophilic Concerted Metalation-Deprotonation (eCMD). *ACS Catal.* **2019**, *9*, 6821–6836.

72. Naksomboon, K.; Poater, J.; Bickelhaupt, F. M.; Fernández-Ibáñez, M. Á. Para-Selective C–H Olefination of Aniline Derivatives via Pd/S, O-Ligand Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 6719–6725.

73. Tan, E.; Quinonero, O.; Elena de Orbe, M.; Echavarren, A. M. Broad-Scope Rh-Catalyzed Inverse-Sonogashira Reaction Directed by Weakly Coordinating Groups. *ACS Catal.* **2018**, *8*, 2166–2172.

74. Zell, D.; Bursch, M.; Müller, V.; Grimme, S.; Ackermann, L. Full Selectivity Control in Cobalt(III)-Catalyzed C–H Alkylations by Switching of the C–H Activation Mechanism. *Angew. Chem. Int. Ed.* **2017**, *56*, 10378–10382.

75. Mei, R.; Loup, J.; Ackermann, L. Oxazolinyl-Assisted C–H Amidation by Cobalt(III) Catalysis. *ACS Catal.* **2016**, *6*, 793–797.

76. Wang, H.; Moselage, M.; González, M. J.; Ackermann, L. Selective Synthesis of Indoles by Cobalt(III)-Catalyzed C–H/N–O Functionalization with Nitrones. *ACS Catal.* **2016**, *6*, 2705–2709.

77. Ma, W.; Mei, R.; Tenti, G.; Ackermann, L. Ruthenium(II)-Catalyzed Oxidative C–H Alkenylations of Sulfonic Acids, Sulfonyl Chlorides and Sulfonamides. *Chem. Eur. J.* **2014**, *20*, 15248–15251.

78. O'Ferrall, R. M. Relationships Between E2 and E1cB Mechanisms of β-Elimination.*J. Chem. Soc. B* **1970**, 274–277.

79. Zhang, Y.; Struwe, J.; Ackermann, L. Rhodium-Catalyzed Electrooxidative C–H Olefination of Benzamides. *Angew. Chem. Int. Ed.* **2020**, *59*, 15076–15080.

80. Brasholz, M. "Super-Reducing" Photocatalysis: Consecutive Energy and Electron Transfers with Polycyclic Aromatic Hydrocarbons. *Angew. Chem. Int. Ed.* **2017**, *56*, 10280–10281.

81. Ye, Q.; Chi, C. Recent Highlights and Perspectives on Acene Based Molecules and Materials. *Chem. Mater.* **2014**, *26*, 4046–4056.

82. Ponomarenko, L. A.; Schedin, F.; Katsnelson, M. I.; Yang, R.; Hill, E. W.; Novoselov, K. S.; Geim, A. K. Chaotic Dirac Billiard in Graphene Quantum Dots. *Science* **2008**, *320*, 356–358.

83. Wu, J.; Pisula, W.; Müllen, K. Graphenes as Potential Material for Electronics. *Chem. Rev.* **2007**, *107*, 718–747.

84. Anthony, J. E. Functionalized Acenes and Heteroacenes for Organic Electronics. *Chem. Rev.* **2006**, *106*, 5028–5048.

85. Kong, W.-J.; Finger, L. H.; Oliveira, J. C. A.; Ackermann, L. Rhodaelectrocatalysis for Annulative C–H Activation: Polycyclic Aromatic Hydrocarbons Through Versatile Double Electrocatalysis. *Angew. Chem. Int. Ed.* **2019**, *58*, 6342–6346.

86. Röse, P.; Emge, S.; König, C. A.; Hilt, G. Efficient Oxidative Coupling of Arenes via Electrochemical Regeneration of 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) Under Mild Reaction Conditions. *Adv. Synth. Catal.* **2017**, *359*, 1359–1372.

87. Grzybowski, M.; Skonieczny, K.; Butenschön, H.; Gryko, D. T. Comparison of Oxidative Aromatic Coupling and the Scholl Reaction. *Angew. Chem. Int. Ed.* **2013**, *52*, 9900–9930.

88. Wu, Y.-T.; Wu, T.-C.; Chen, M.-K.; Hsin, H.-J. Synthetic and Structural Considerations on Highly Curved Bowl-Shaped Fragments of Fullerenes. *Pure Appl. Chem.* **2014**, *86*, 539–544.

89. Wu, Y.-T.; Siegel, J. S. Aromatic Molecular-Bowl Hydrocarbons: Synthetic Derivatives, Their Structures, and Physical Properties. *Chem. Rev.* **2006**, *106*, 4843–4867.

90. Kong, W.-J.; Finger, L. H.; Messinis, A. M.; Kuniyil, R.; Oliveira, J. C. A.; Ackermann, L. Flow Rhodaelectro-Catalyzed Alkyne Annulations by Versatile C–H Activation: Mechanistic Support for Rhodium(III/IV). *J. Am. Chem. Soc.* **2019**, *141*, 17198–17206.

91. Santoro, S.; Ferlin, F.; Ackermann, L.; Vaccaro, L. C–H Functionalization Reactions Under Flow Conditions. *Chem. Soc. Rev.* **2019**, *48*, 2767–2782.

92. Beil, S. B.; Uecker, I.; Franzmann, P.; Müller, T.; Waldvogel, S. R. Mild, Fast, and Easy to Conduct $MoCl_5$-Mediated Dehydrogenative Coupling Reactions in Flow. *Org. Lett.* **2018**, *20*, 4107–4110.

93. Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The Hitchhiker's Guide to Flow Chemistry. *Chem. Rev.* **2017**, *117*, 11796–11893.

94. Folgueiras-Amador, A. A.; Wirth, T. Perspectives in Flow Electrochemistry. *J. Flow Chem.* **2017**, *7*, 94–95.

95. Wang, H.; Pesciaioli, F.; Oliveira, J. C. A.; Warratz, S.; Ackermann, L. Synergistic Manganese(I) C–H Activation Catalysis in Continuous Flow: Chemoselective Hydroarylation. *Angew. Chem. Int. Ed.* **2017**, *56*, 15063–15067.

96. Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. Taming Hazardous Chemistry by Continuous Flow Technology. *Chem. Soc. Rev.* **2016**, *45*, 4892–4928.

97. Gemoets, H. P. L.; Su, Y.; Shang, M.; Hessel, V.; Luque, R.; Noël, T. Liquid Phase Oxidation Chemistry in Continuous-flow Microreactors. *Chem. Soc. Rev.* **2016**, *45*, 83–117.

98. Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. Visible-Light Photoredox Catalysis in Flow. *Angew. Chem. Int. Ed.* **2012**, *51*, 4144–4147.

99. Shin, K.; Park, Y.; Baik, M.-H.; Chang, S. Iridium-Catalysed Arylation of C–H Bonds Enabled by Oxidatively Induced Reductive Elimination. *Nat. Chem.* **2018**, *10*, 218–224.

100. Li, L.; Brennessel, W. W.; Jones, W. D. An Efficient Low-Temperature Route to Polycyclic Isoquinoline Salt

Synthesis via C–H Activation with [Cp*MCl_2]$_2$ (M = Rh, Ir). *J. Am. Chem. Soc.* **2008**, *130*, 12414–12419.

101. Kong, W.-J.; Shen, Z.; Finger, L. H.; Ackermann, L. Electrochemical Access to Aza-Polycyclic Aromatic Hydrocarbons: Rhoda-Electrocatalyzed Domino Alkyne Annulations. *Angew. Chem. Int. Ed.* **2020**, *59*, 5551–5556.

102. Wu, Z.-J.; Su, F.; Lin, W.; Song, J.; Wen, T.-B.; Zhang, H.-J.; Xu, H.-C. Scalable Rhodium(III)-Catalyzed Aryl C–H Phosphorylation Enabled by Anodic Oxidation Induced Reductive Elimination. *Angew. Chem. Int. Ed.* **2019**, *58*, 16770–16774.

103. Kim, J.; Shin, K.; Jin, S.; Kim, D.; Chang, S. Oxidatively Induced Reductive Elimination: Exploring the Scope and Catalyst Systems with Ir, Rh, and Ru Complexes. *J. Am. Chem. Soc.* **2019**, *141*, 4137–4146.

104. Chen, F.; Wang, T.; Jiao, N. Recent Advances in Transition-Metal-Catalyzed Functionalization of Unstrained Carbon–Carbon Bonds. *Chem. Rev.* **2014**, *114*, 8613–8661.

105. Qiu, Y.; Scheremetjew, A.; Ackermann, L. Electro-Oxidative C–C Alkenylation by Rhodium(III) Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 2731–2738.

106. Dhawa, U.; Tian, C.; Wdowik, T.; Oliveira, J. C. A.; Hao, J.; Ackermann, L. Enantioselective Pallada-Electrocatalyzed C–H Activation by Transient Directing Groups: Expedient Access to Helicenes. *Angew. Chem. Int.* **2020**, *59*, 13451–13457.

107. Lai, X. L.; Shu, X. M.; Song, J.; Xu, H. C. Electrophotocatalytic Decarboxylative C–H Functionalization of Heteroarenes. *Angew. Chem. Int. Ed.* **2020**, *59*, 10626–10632.

108. Xu, P.; Chen, P.-Y.; Xu, H.-C. Scalable Photoelectrochemical Dehydrogenative Cross-Coupling of Heteroarenes with Aliphatic C–H Bonds. *Angew. Chem. Int. Ed.* **2020**, *59*, 14275–14280.

109. Huang, H.; Strater, Z. M.; Rauch, M.; Shee, J.; Sisto, T. J.; Nuckolls, C.; Lambert, T. H. Electrophotocatalysis with a Trisaminocyclopropenium Radical Dication. *Angew. Chem. Int. Ed.* **2019**, *58*, 13318–13322.

110. Yan, H.; Hou, Z.-W.; Xu, H.-C. Photoelectrochemical C–H Alkylation of Heteroarenes with Organotrifluoroborates. *Angew. Chem. Int. Ed.* **2019**, *58*, 4592–4595.

111. Zhang, L.; Liardet, L.; Luo, J.; Ren, D.; Grätzel, M.; Hu, X. Photoelectrocatalytic Arene C–H Amination. *Nat. Catal.* **2019**, *2*, 366–373.

112. Barham, J. P.; König, B. Synthetic Photoelectrochemistry. *Angew. Chem. Int. Ed.* **2020**, *59*, 11732–11747.