ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, **57**, 3668

Received 14th December 2020,
Accepted 10th March 2021

DOI: 10.1039/d0cc08123j

rsc.li/chemcomm

Rhodaelectro-catalyzed chemo-divergent C–H activations with alkylidenecyclopropanes for selective cyclopropylations†

Zhigao Shen, Isaac Maksso, Rositha Kuniyil, Torben Rogge and Lutz Ackermann *

Herein, we report on selectivity control in C–H activations with alkylidenecyclopropanes (ACPs) for the chemo-selective assembly of cyclopropanes or dienes. Thus, unprecedented rhodaelectro-catalyzed C–H activations were realized with diversely decorated ACPs with a wide substrate scope and electricity as the sole oxidant.

Throughout the last decade, C–H activation has emerged as an increasingly powerful tool in molecular syntheses.[1] In sharp contrast, strategies for transition metal-catalyzed C–C activation remain comparably underdeveloped.[2] In recent years, major advances, in particular in ring-strain release-promoted C–C cleavages, have been achieved by *Dong*,[3] *Bower*,[4] and *Marek*,[5] among others.[6] Alkylidenecyclopropanes[7] (ACPs) have previously been recognized as a versatile platform for C–H/C–C functionalizations. However, their application within a bifurcated mechanistic manifold for the selective introduction of cyclopropane[8] or 1,3-dienes[9] motifs has thus far proven elusive, although they represent crucial structural scaffolds in a variety of pharmaceuticals, biologically active molecules and natural products. While a single example of rhodium-catalyzed dienylation was realized with chemical oxidants,[10] cyclopropylations are as of yet not available.

The use of electricity to drive chemical reactions has recently witnessed a remarkable renaissance.[11] Significant momentum was particularly gained by the merger of metallaelectrocatalysis and QJ;C–H activation to avoid often toxic and expensive oxidants.[1b,12] With our continued interest in rhodaelectro-catalyzed C–H activation,[13] we have now developed a bifurcated C–H activation with alkylidenecyclopropanes that can be conducted under sustainable and operationally-simple electrochemical conditions. Salient features of our strategy include (a) full control of selectivity within a bifurcated manifold for C–H cyclopropylations *versus* dienylations *via* β-H over β-C elimination, (b) detailed mechanistic insights by means of experiment and computation, (c) absence of external chemical oxidants, (d) water as the reaction medium, and (e) a user-friendly undivided cell setup without additional electrolyte (Fig. 1).

We initiated our studies with indole **1a** and ACP **2a** to evaluate C–H dienylations and cyclopropylations in a user-friendly undivided cell setup with a graphite felt (GF) anode and a platinum cathode (Table 1). The dienylated product **3aa** was obtained in 72% yield in the presence of 2.5 mol% $[Cp^*RhCl_2]_2$, using 1,4-dioxane/H_2O (1 : 1) as the solvent. After examination of different bases, NaO_2CAd led to the best result, delivering diene **3aa** in 85% yield with an *Z*/*E* ratio of 4.5/1 (entries 1–5). The indispensable roles of electricity and the rhodium catalyst were further confirmed by control experiments (entries 6 and 7). A variation of the current did not result in an improved performance (entries 8 and 9). We also tested different acids and found that cyclopentanecarboxylic acid proved beneficial (entries 10 and 11). With an increased amount of NaO_2CAd, the product was obtained in a higher *Z*/*E* ratio, albeit with a small decrease in efficiency (entry 12).

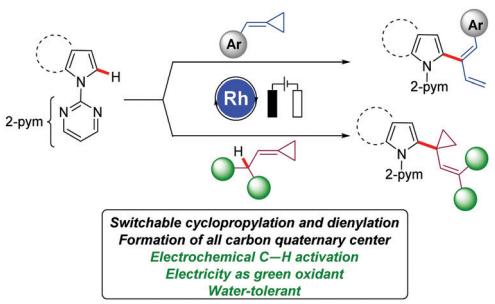
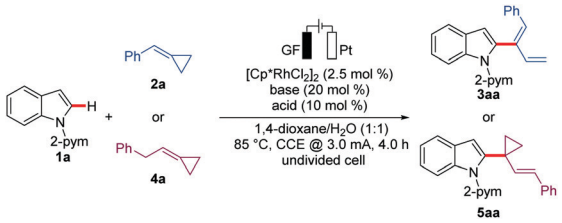


Fig. 1 Cyclopropylation and dienylation enabled by rhodaelectro-catalysis.

Institut für Organsiche und Biomolekulare Chemie and Wöhler Research Institute for Sustainable Chemistry, Georg-August-Universität Göttingen, Tammannstrasse 2, Göttingen 37077, Germany. E-mail: Lutz.Ackermann@chemie.uni-goettingen.de; Web: http://www.ackermann.chemie.uni-goettingen.de/, http://wisch.chemie.uni-goettingen.de/

† Electronic supplementary information (ESI) available. CCDC 2025011 (**3ap**) and 2025012 (**5pa**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc08123j

Table 1 Electrochemical C–H dienylation of indole[a]



Entry	Base	Acid	Yield (%)	*Z*/*E*
1	NaOAc	$CypCO_2H$	72	3.9/1
2	NaOPiv	$CypCO_2H$	78	3.5/1
3	NaO_2CMes	$CypCO_2H$	60	4.0/1
4	NaO_2CPh	$CypCO_2H$	82	3.6/1
5	NaO_2CAd	$CypCO_2H$	85	4.5/1
6[b]	NaO_2CAd	$CypCO_2H$	24	2.4/1
7[c]	NaO_2CAd	$CypCO_2H$	—	—
8[d]	NaO_2CAd	$CypCO_2H$	87	3.8/1
9[e]	NaO_2CAd	$CypCO_2H$	72	3.2/1
10	NaO_2CAd	$MesCO_2H$	78	3.8/1
11	NaO_2CAd	PivOH	82	3.3/1
12[f]	NaO_2CAd	$CypCO_2H$	82	6.0/1
13[fg]	NaO_2CAd	$CypCO_2H$	87	6.5/1
14[fgh]	**NaO_2CAd**	**$CypCO_2H$**	**89**	**7.0/1**
15[i]	**NaO_2CAd**	**$CypCO_2H$**	**95 (5aa)**	**<1/20**

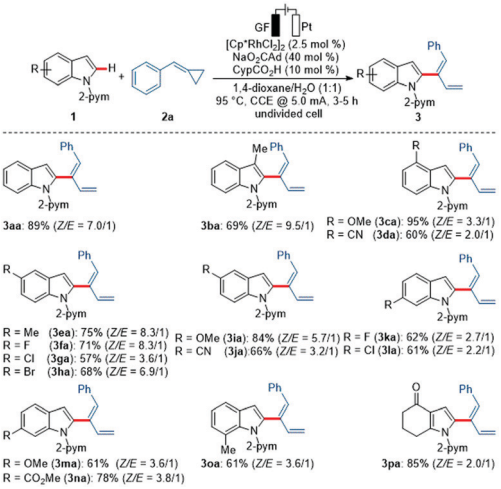
[a] Undivided cell, graphite felt anode (GF), platinum plate cathode (Pt), **1a** (0.1 mmol) **2a** (0.16 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), base (20 mol%), acid (10 mol%), 1,4-dioxane/H_2O (1 : 1, 4.0 mL), 85 °C, CCE @ 3.0 mA, under air, 4.0 h, yield of isolated product, *Z*/*E* ratio determined by ^1H NMR spectroscopy, $CypCO_2H$ = cyclopentanecarboxylic acid. [b] Without electricity, 12 h. [c] Without $[Cp^*RhCl_2]_2$. [d] CCE @ 2.0 mA, 6.0 h. [e] CCE @ 4.0 mA, 3.0 h. [f] NaO_2CAd (40 mol%). [g] 0.2 mmol scale, 1,4-dioxane/H_2O (1 : 1, 8.0 mL), CCE @ 5.0 mA, 3.0 h. [h] 95 °C. [i] **4a** instead of **2a** under the conditions of entry 14.

A higher reaction temperature improved the efficacy. Importantly, the novel cyclopropylated product **5aa** was obtained in high yield when using benzyl ACP **4a**.[14]

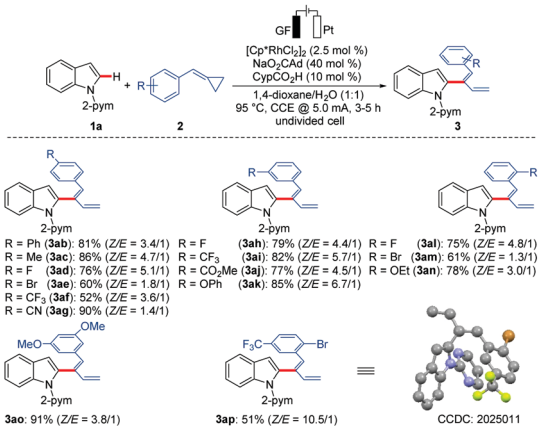
With the optimized reaction conditions for the electrochemical C–H dienylation in hand, its versatility was explored with substituted indoles **1** (Scheme 1). 3-, 5- or 7-Methyl indoles **1** delivered the desired products **3ba**, **3ea** and **3oa**, while the 3-methyl indole **1b** gave an improved selectivity. Fluorine- and methoxy-substituted indoles **1** were efficiently transformed, but 6-substituted indoles **1k** and **1m** displayed a slightly lower efficiency. Various functional groups were tolerated by the rhodium electrocatalyst, such as chloro, bromo and cyano substituents. Interestingly, indole **1n** with an ester functionality at the 6-position delivered diene **3na** in high yield. The dienylation protocol was also amenable to pyrrole **3pa**.[15]

Next, the robustness of the rhodaelectro-catalyzed C–H dienylation was evaluated with a variety of functionalized cyclopropanes (Scheme 2). Substrates containing bromide groups delivered chemo-selectively the products **3ae** and **3am**. In contrast to previous studies, electron-deficient heteroarenes showed an inherent high reactivity.[13] However, electron-rich substrates also performed well in the electrocatalysis. The connectivity of diene **3ap** was unambiguously confirmed by single-crystal X-ray analysis.‡

Thereafter, we turned our attention to the versatility of the unprecedented electrochemical C–H cyclopropylation of indoles **1**



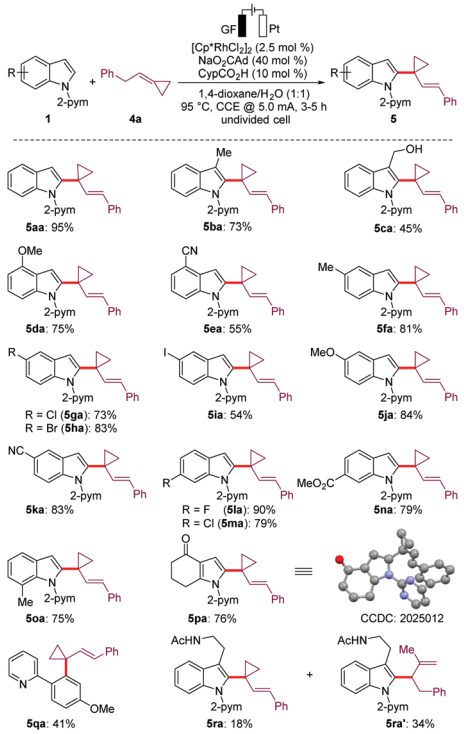
Scheme 1 Electrocatalytic C–H dienylation of indoles **1**.



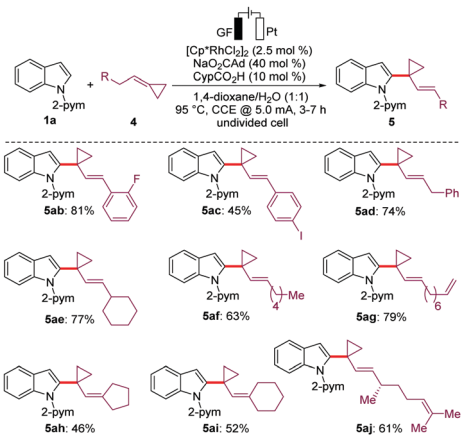
Scheme 2 Electrochemical C–H dienylation with ACPs **2**.

(Scheme 3). We found that an otherwise reactive hydroxyl was fully tolerated, despite being in close proximity (**5ca**). Halogen-containing indoles, even the reactive iodo-substituent, were likewise viable substrates. Indoles containing electron-withdrawing or electron-donating groups selectively underwent this transformation. For 7-methyl indole, the cyclopropylation showed a higher efficiency as compared to the dienylation (**5oa** *versus* **3oa**). The rhodaelectrocatalysis proved also applicable to pyrroles, while the structure of the cyclopropylated product **5pa** was confirmed by single-crystal X-ray analysis.‡ It is noteworthy that, 2-phenyl pyridine could also be employed for the electrocatalysis to deliver arene **5qa**. The tryptamine-derived substrate **1r** delivered the challenging ring-opening product **5ra′**.

Next, we explored the C–H cyclopropylation with differently substituted ACPs **4** (Scheme 4). Substrate **4c** bearing an iodo-substituent gave the desired product **5ac** with a small amount of the deiodinated product (**5aa:5ac** 1/3). The aqueous conditions were compatible with linear or branched alkyl-derived cyclopropanes (**5ad–5af**). The challenging cyclopropane **4g** bearing a terminal alkene was also found to be a viable



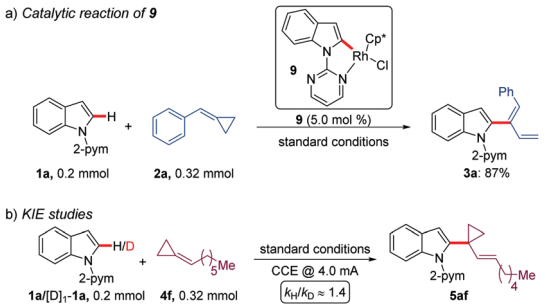
Scheme 3 Electrocatalyzed C–H cyclopropylation of indoles **1**, arenes and pyrroles.



Scheme 4 Rhodaelectro-catalyzed C–H cyclopropylation with ACPs **4**.

substrate, affording product **5ag** in 79% yield. The transformation was also tolerant to changes in the backbone of the cyclic alkanes and generated the desired products **5ah** and **5ai**. Indeed, the structurally more complex, natural product citronellol-derived starting material **4j** was chemo-selectively converted to the desired product **5aj**.

To gain insights into the reaction mechanism, control experiments were performed. The independently prepared cyclometalated complex **9**[16] was found to serve as a catalytically competent species (Scheme 5a). Under the standard conditions but without electricity, H/D exchange of indole **1a** with D_2O was



Scheme 5 Summary of key mechanistic findings.

observed with significant deuterium incorporation at the position C2 (Scheme S2 in the ESI†). However, a significant deuterium-incorporation into product **3aa** was not observed, when **1a** was reacted with **2a** under the electrochemical conditions using D_2O as the cosolvent (Scheme S3 in the ESI†). A kinetic isotope effect (KIE) study was next conducted. Parallel independent reactions resulted in a value of $k_H/k_D \approx 1.4$ (Scheme 5b), indicating that the C–H cleavage step is likely not involved in the rate-determining step.[14]

In order to further understand the catalyst's mode of action, we became interested in studying the rhodaelectro-catalyzed C–H cyclopropylation of indole **1a** with ACP **4a** by density functional theory (DFT). Geometry optimizations and frequency calculations were performed at the TPSS-D3(BJ)/def2-SVP level of theory, while single point energies were calculated at the PW6B95-D3(BJ)/def2-TZVP+SMD(1,4-dioxane) and PBE0-D3(BJ)/def2-TZVP+SMD(1,4-dioxane) level of theory.[14] All energies reported here were calculated at the PW6B95-D3(BJ)/def2-TZVP+SMD(1,4-dioxane)//TPSS-D3(BJ)/def2-SVP level of theory.[14] Our calculations indicated that after the migratory insertion of ACP **4a**, β-H elimination occurs from the intermediate **D** *via* **TS(D-E)** (Fig. S1, ESI†) with a barrier of 1.1 kcal mol^{-1}. Moreover, β–H elimination from the intermediate **D** results in the regioselective formation of the *E*-isomer as the major product, while the generation of *Z*-isomer is energetically not favourable.[14]

Based on our studies, we propose a plausible catalytic cycle for the unprecedented rhodaelectro-C–H-cyclopropylation, which is initiated by the formation of a catalytically competent mononuclear cationic Cp*Rh(III) species. As shown in Fig. 2, coordination of indole **1a** to Cp*Rh(III) and facile subsequent cyclorhodation at the 2-position affords rhodacycle **A**. Then, the insertion of alkene **4a** occurs to furnish intermediate **D**, which undergoes β-H elimination to generate the cyclopropylated product **5aa** along with a rhodium(I) intermediate. Finally, the Cp*Rh(III) species is regenerated by rate-limiting reoxidation of rhodium(I) at the anode, while generating molecular hydrogen as the byproduct at the cathode and completing the catalytic cycle. In terms of the dienylation, intermediate **D** undergoes β-C elimination to form intermediate **G** (Fig. S10 in the ESI†). Final β-H elimination then delivers the dienylated indole **3aa**.

In conclusion, we have reported on a versatile rhodaelectro-catalyzed C–H activation with alkylidenecyclopropanes under

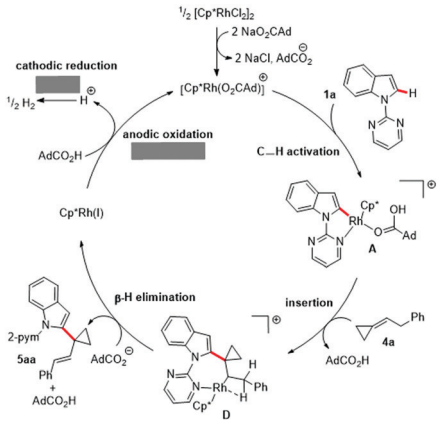


Fig. 2 Proposed mechanism for electro-C–H cyclopropylation with ACPs **4**.

aqueous conditions, devoid of stoichiometric amounts of chemical oxidants. Our unique strategy allowed for the control of selectivity within a bifurcated mechanistic pathway by the judicious choice of β-H over β-C elimination. Detailed studies by experiment and calculation provided key insights into the catalyst's mode of action, revealing β-H elimination as the key selectivity-determining process for an unprecedented C–H cyclopropylation. The reactive catalyst can be regenerated in a sustainable manner by anodic oxidation, yielding hydrogen as the sole stoichiometric byproduct. Thereby, a wealth of heteroarenes was functionalized with excellent chemo-, position- and diastereoselectivity.

Generous support by the DFG (Gottfried-Wilhelm-Leibniz award to L. A.) and the CSC (fellowship to Z. S.) is gratefully acknowledged. We thank Dr Christopher Golz (Göttingen University) for assistance with the X-ray diffraction analysis.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Deposition numbers 2025011 (**3ap**) and 2025012 (**5pa**) contain the supplementary crystallographic data for this paper.

1 For selected recent reviews, see: (*a*) S. Rej, Y. Ano and N. Chatani, *Chem. Rev.*, 2020, **120**, 1788–1887; (*b*) L. Ackermann, *Acc. Chem. Res.*, 2020, **53**, 84–104; (*c*) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, **119**, 2192–2452; (*d*) C. S. Wang, P. H. Dixneuf and J. F. Soule, *Chem. Rev.*, 2018, **118**, 7532–7585; (*e*) J. C. K. Chu and T. Rovis, *Angew. Chem., Int. Ed.*, 2018, **57**, 62–101.

2 For selected reviews, see: (*a*) Y. Cohen, A. Cohen and I. Marek, *Chem. Rev.*, 2021, **121**, 140–161; (*b*) P.-h. Chen, B. A. Billett, T. Tsukamoto and G. Dong, *ACS Catal.*, 2017, **7**, 1340–1360; (*c*) M. Murakami and N. Ishida, *J. Am. Chem. Soc.*, 2016, **138**, 13759–13769; (*d*) L. Souillart and N. Cramer, *Chem. Rev.*, 2015, **115**, 9410–9464.

3 (*a*) Y. Xia, G. Lu, P. Liu and G. Dong, *Nature*, 2016, **539**, 546–550; (*b*) T. Xu and G. Dong, *Angew. Chem., Int. Ed.*, 2012, **51**, 7567–7571.

4 (*a*) G.-W. Wang, N. G. McCreanor, M. H. Shaw, W. G. Whittingham and J. F. Bower, *J. Am. Chem. Soc.*, 2016, **138**, 13501–13504; (*b*) M. H. Shaw, E. Y. Melikhova, D. P. Kloer, W. G. Whittingham and J. F. Bower, *J. Am. Chem. Soc.*, 2013, **135**, 4992–4995.

5 (*a*) A. Vasseur and I. Marek, *Nat. Protoc.*, 2017, **12**, 74–87; (*b*) S. R. Roy, D. Didier, A. Kleiner and I. Marek, *Chem. Sci.*, 2016, **7**, 5989–5994; (*c*) A. Masarwa, D. Didier, T. Zabrodski, M. Schinkel, L. Ackermann and I. Marek, *Nature*, 2014, **505**, 199–203.

6 A review: (*a*) J. Wang, S. A. Blaszczyk, X. Li and W. Tang, *Chem. Rev.*, 2021, **121**, 110–139 for selected examples, see: (*b*) H. Wang, I. Choi, T. Rogge, N. Kaplaneris and L. Ackermann, *Nat. Catal.*, 2018, **1**, 993–1001; (*c*) S. Okumura, F. Sun, N. Ishida and M. Murakami, *J. Am. Chem. Soc.*, 2017, **139**, 12414–12417; (*d*) E. Ozkal, B. Cacherat and B. Morandi, *ACS Catal.*, 2015, **5**, 6458–6462; (*e*) H. Li, Y. Li, X.-S. Zhang, K. Chen, X. Wang and Z.-J. Shi, *J. Am. Chem. Soc.*, 2011, **133**, 15244–15247; (*f*) L. J. Gooßen, G. Deng and L. M. Levy, *Science*, 2006, **313**, 662–664.

7 For selected reviews, see: (*a*) L. Yu, M. Liu, F. Chen and Q. Xu, *Org. Biomol. Chem.*, 2015, **13**, 8379–8392; (*b*) D.-H. Zhang, X.-Y. Tang and M. Shi, *Acc. Chem. Res.*, 2014, **47**, 913–924; (*c*) A. de Meijere, S. I. Kozhushkov and H. Schill, *Chem. Rev.*, 2006, **106**, 4926–4996.

8 (*a*) L. A. Maslovskaya, A. I. Savchenko, C. J. Pierce, G. M. Boyle, V. A. Gordon, P. W. Reddell, P. G. Parsons and C. M. Williams, *Chem. – Eur. J.*, 2019, **25**, 1525–1534; (*b*) D. Y. K. Chen, R. H. Pouwer and J.-A. Richard, *Chem. Soc. Rev.*, 2012, **41**, 4631–4642.

9 (*a*) Y.-Q. Zhu, Y.-X. Niu, L.-W. Hui, J.-L. He and K. Zhu, *Adv. Synth. Catal.*, 2019, **361**, 2897–2903; (*b*) R. Feng, J. A. Smith and K. D. Moeller, *Acc. Chem. Res.*, 2017, **50**, 2346–2352; (*c*) A. Misale, S. Niyomchon and N. Maulide, *Acc. Chem. Res.*, 2016, **49**, 2444–2458; (*d*) S. Carosso and M. J. Miller, *Org. Biomol. Chem.*, 2014, **12**, 7445–7468; (*e*) W. Erb and J. Zhu, *Nat. Prod. Rep.*, 2013, **30**, 161–174.

10 R. Liu, Y. Wei and M. Shi, *Chem. Commun.*, 2019, **55**, 7558–7561.

11 (*a*) T. H. Meyer, I. Choi, C. Tian and L. Ackermann, *Chemistry*, 2020, **6**, 2484–2496; (*b*) D. Pollok and S. R. Waldvogel, *Chem. Sci.*, 2020, **11**, 12386–12400; (*c*) M. C. Leech, A. D. Garcia, A. Petti, A. P. Dobbs and K. Lam, *React. Chem. Eng.*, 2020, **5**, 977–990; (*d*) J. C. Siu, N. Fu and S. Lin, *Acc. Chem. Res.*, 2020, **53**, 547–560; (*e*) P. Xiong and H.-C. Xu, *Acc. Chem. Res.*, 2019, **52**, 3339–3350; (*f*) T. H. Meyer, L. H. Finger, P. Gandeepan and L. Ackermann, *Trends Chem.*, 2019, **1**, 63–76; (*g*) R. D. Little and K. D. Moeller, *Chem. Rev.*, 2018, **118**, 4483–4484; (*h*) K. D. Moeller, *Chem. Rev.*, 2018, **118**, 4817–4833; (*i*) D. Wang, A. B. Weinstein, P. B. White and S. S. Stahl, *Chem. Rev.*, 2018, **118**, 2636–2679; (*j*) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230–13319; (*k*) R. Francke and R. D. Little, *Chem. Soc. Rev.*, 2014, **43**, 2492–2521.

12 (*a*) K.-J. Jiao, Y.-K. Xing, Q.-L. Yang, H. Qiu and T.-S. Mei, *Acc. Chem. Res.*, 2020, **53**, 300–310; (*b*) P. Gandeepan, L. H. Finger, T. H. Meyer and L. Ackermann, *Chem. Soc. Rev.*, 2020, **49**, 4254–4272.

13 (*a*) Y. Zhang, J. Struwe and L. Ackermann, *Angew. Chem., Int. Ed.*, 2020, **59**, 15076–15080; (*b*) W.-J. Kong, Z. Shen, L. H. Finger and L. Ackermann, *Angew. Chem., Int. Ed.*, 2020, **59**, 5551–5556; (*c*) Z.-J. Wu, F. Su, W. Lin, J. Song, T.-B. Wen, H.-J. Zhang and H.-C. Xu, *Angew. Chem., Int. Ed.*, 2019, **58**, 16770–16774; (*d*) W.-J. Kong, L. H. Finger, A. M. Messinis, R. Kuniyil, J. C. A. Oliveira and L. Ackermann, *J. Am. Chem. Soc.*, 2019, **141**, 17198–17206.

14 Detailed information is given in the ESI†.

15 Under otherwise identical reaction conditions, alternative heterocycles thus far led to unsatisfactory results.

16 X. Zhou, Y. Pan and X. Li, *Angew. Chem., Int. Ed.*, 2017, **56**, 8163–8167.