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Carboxylate-assisted ruthenium(II)-catalyzed C–H activations of monodentate amides with conjugated alkenes†

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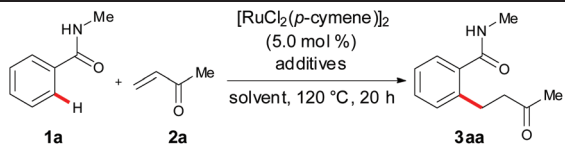
Carboxylate assistance enabled efficient and chemoselective ruthenium(II)-catalyzed hydroarylations of α,β -unsaturated ketones *via* C–H activation on monodentate benzamides. Furthermore, the versatile ruthenium(II) catalyst set the stage for oxidative C–H functionalization on acetanilides, furnishing diversely decorated quinolines in a step-economical fashion.

Transition metal-catalyzed C–H functionalizations have been recognized as increasingly viable tools for the step-economical formation of C–C bonds.¹ Particularly, metal-catalyzed hydroarylation reactions² *via* C–H activation are attractive because of their excellent atom-economy.³ Early findings by Lewis and Smith⁴ as well as Murai and co-workers^{5,6} indicated the considerable power of ruthenium(0) complexes as effective catalysts for hydroarylations through chelation-assisted C–H activation, which were proposed to proceed by oxidative addition of the C–H bond. Practical advances were achieved by Darses and Genet and co-workers through the *in situ* formation of $[\text{RuH}_2(\text{PPh}_3)_4]$ from $[\text{RuCl}_2(p\text{-cymene})]_2$, NaO_2CH and PPh_3 ,⁷ thus avoiding sensitive and expensive ruthenium(0) complexes, such as $[\text{Ru}_3(\text{CO})_{12}]$, $[\text{RuH}_2(\text{PPh}_3)_4]$, $[\text{Ru}(\text{CO})_2(\text{PPh}_3)_3]$, or $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$. As a part of our ongoing program on transition-metal-catalyzed C–H functionalizations,⁸ we recently developed ruthenium(II)-catalyzed hydroarylations *via* carboxylate-assisted C–H cleavages.⁹ Despite of these remarkable advances, the synthetically useful family of electron-deficient olefins,¹⁰ such as α,β -unsaturated ketones were thus far not viable substrates. While such transformations were accomplished with among others relatively expensive rhodium¹¹ or rhenium¹² catalysts, notable progress with ruthenium(II) complexes was very recently made by Chatani and co-workers highlighting that hydroarylations of α,β -unsaturated ketones could be realized, given that substrates displaying bidentate directing groups were employed.^{13,14} Herein, we report on an expedient access to β -aryl ketones and quinolines through ruthenium(II)-catalyzed hydroarylations and oxidative cascade annulations

with α,β -unsaturated ketones, respectively. It is noteworthy that the ruthenium(II)-catalyzed C–H activation strategy was realized with synthetically useful amides as atom-economical mono-dentate directing groups.

We initiated our studies by testing the feasibility of the envisioned ruthenium(II)-catalyzed C–H alkylation of benzamide **1a** with methyl vinyl ketone (**2a**) (Table 1). Interestingly, $\text{RuCl}_2(\text{PPh}_3)_3$, which was previously used for hydroarylations with bidentate directing groups,¹³ unfortunately, failed to deliver the desired product **3aa** with the assistance of the simple amide **1a** (entries 1 and 2). Similar trends were

Table 1 Optimization of ruthenium(II)-catalyzed C–H alkylation with benzamide **1a**^a



Entry	Additive A [mol%]	Additive B [equiv.]	Solvent	Yield ^b [%]
1	NaOAc (30)	—	PhMe	— ^c
2	NaOAc (30)	—	H ₂ O	— ^c
3	KPF ₆ (20)	—	H ₂ O	—
4	KPF ₆ (20)	NaOAc (2.00)	H ₂ O	—
5	PPh ₃ (15)	NaO ₂ CH (0.30)	PhMe	—
6	KOAc (30)	HOAc (1.00)	H ₂ O	64
7	KO ₂ CMes (30)	MesCO ₂ H (0.30)	H ₂ O	69
8	KO₂CMes (30)	MesCO₂H (1.00)	H₂O	80
9	KO ₂ CMes (30)	—	H ₂ O	51
10	KO ₂ CMes (30)	MesCO ₂ H (1.00)	H ₂ O	— ^d
11	—	MesCO ₂ H (1.00)	H ₂ O	29

^a General reaction conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (5.0 mol%), KO_2CMes (30 mol%), MesCO_2H (1.00 equiv.), solvent (2.0 mL), under N₂, 120 °C, 20 h. ^b Isolated yield. ^c $\text{RuCl}_2(\text{PPh}_3)_3$ (10 mol%). ^d Without [Ru].

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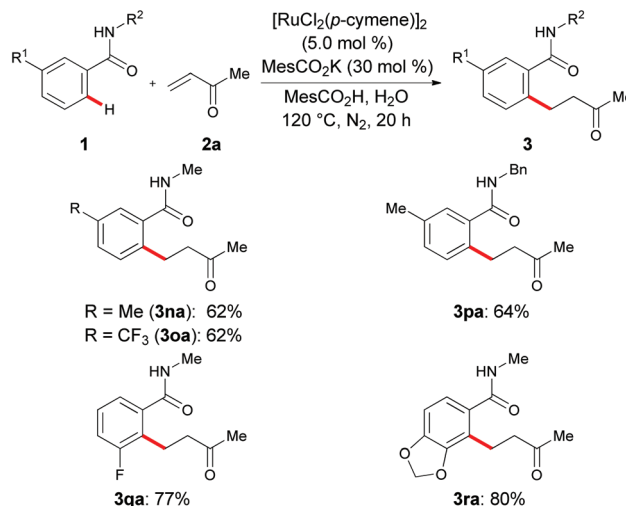
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5qo00167f



observed when employing $[\text{RuCl}_2(p\text{-cymene})]_2$ in combination with various additives (entries 3–5).

A significant improvement was realized using cocatalytic amounts of KOAc and stoichiometric amounts of HOAc as the additives with H_2O as inexpensive and nontoxic reaction medium^{15,16} (entry 6). Improved yields of the target compound **3aa** were obtained when employing the bulky MesCO_2K and MesCO_2H as the cocatalysts (entry 7). Here, the use of stoichiometric MesCO_2H provided the optimal results (entry 8). Furthermore, it is worth noting that the omission of either of the two additives resulted in significantly reduced yields of the alkylated benzamide **3aa** (entries 9–11).

With the optimized reaction conditions in hand, we tested its versatility in the C–H alkylation with weakly coordinating^{17,18} amides **1** (Scheme 1). Notably, in these chelation-assisted direct C–H alkylations, both electron-rich as well as electron-poor *para*-substituted benzamides **1a–1f** were identified as viable substrates. Moreover, a variation of the substitution pattern on the amide nitrogen with benzyl (**1g–i**), cyclohexyl (**1j**) or methoxyethyl (**1k**) groups, did not significantly alter the catalytic efficacy, while primary amides proved to be unsuitable substrates. More sterically hindered *ortho*-substituted benzamide **1l** was successfully alkylated as well, albeit the desired product **3la** was obtained in a slightly reduced yield. The widely applicable ruthenium(II) catalyst was not limited to aromatic benzamides **1**, but the reaction of hetero-



Scheme 2 Site-selective hydroarylations with *meta*-substituted arenes **1a**.

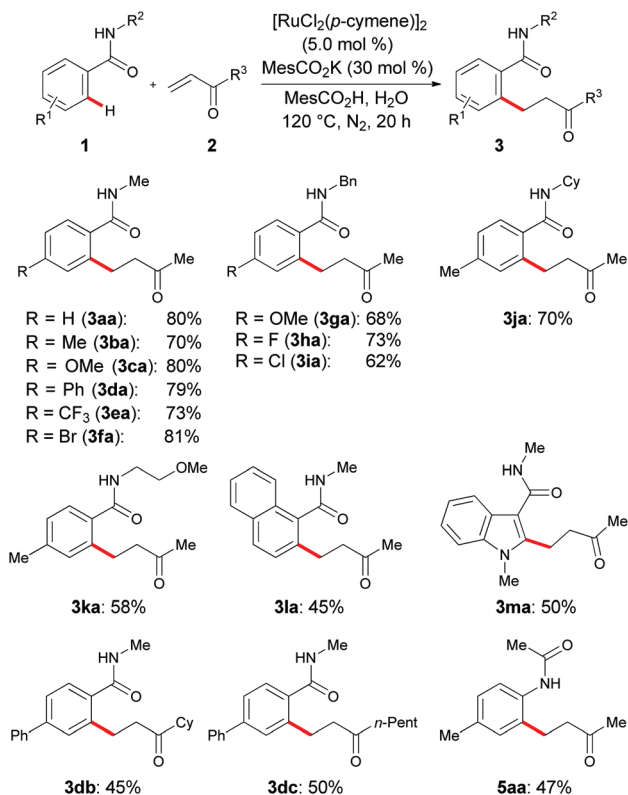
aromatic indole derivative **1m** also led to the site-selective C–H alkylation. In addition, among a representative set of α,β -unsaturated ketones, vinyl alkyl ketones **2b** and **2c** gave the alkylated products **3db** and **3dc**, respectively, in high yields. Interestingly, acetanilide **4a** was identified as a suitable substrate for hydroarylations likewise.

Intramolecular competition experiments with *meta*-methyl- or *meta*-trifluoromethyl-substituted arenes **1n–1p** were largely governed by steric interactions to site-selectively deliver the alkylated products **3na–3pa** at the sterically less hindered position (Scheme 2). In contrast, hydroarylations of the *meta*-substituted benzamides **1q** and **1r** featured a considerable *ortho*-orienting effect¹⁹ of the heteroatom substituent, thus leading to the site-selective formation of the sterically more hindered compounds **3qa** and **3ra**, respectively, as the sole products.

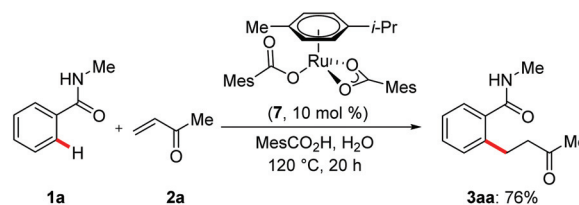
Remarkably, the well-defined, single-component $[\text{Ru}(\text{MesCO}_2)_2(p\text{-cymene})]^{20}$ catalyst **7** furnished the desired product, which illustrated the importance of carboxylate assistance (Scheme 3).²¹

An intermolecular competition experiment between arenes with different directing groups clearly highlighted that amides **1** are more powerful than ketone **8** in the chelation-assisted C–H alkylation (Scheme 4).

Given the unique reactivity of our carboxylate-assisted ruthenium(II) catalysis, we performed mechanistic studies to

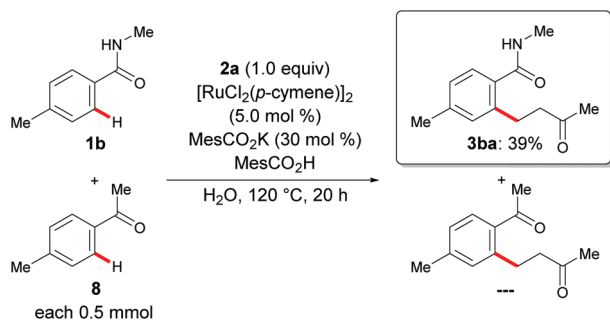


Scheme 1 Scope of the ruthenium(II)-catalyzed hydroarylation via C–H activation.



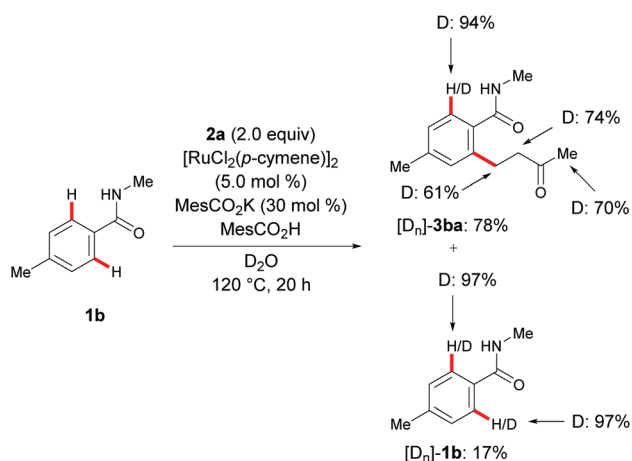
Scheme 3 C–H alkylation with single-component ruthenium(II) biscalboxylate catalyst **7**.



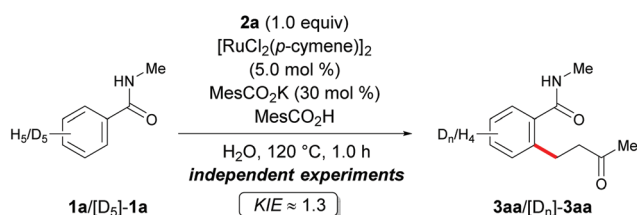
Scheme 4 Competition experiment between amide **1** and ketone **8**.

unravel its mode of action. To this end, strong evidence for a H/D exchange was gathered from C–H functionalization with starting material **1b** in the presence of the deuterated solvent D_2O (Scheme 5).^{9c} This observation can be rationalized in terms of a reversible C–H metalation step in the ruthenium(II)-catalyzed direct hydroarylation.

Moreover, the ruthenium-catalyzed C–H alkylation with isotopically labeled substrate $[D_5]$ -**1a** showed a negligible kinetic isotope effect (KIE) of $k_H/k_D \approx 1.3$ for the intermolecular KIE experiment (Scheme 6). This data again suggests the C–H bond metalation not to be the rate-determining step.



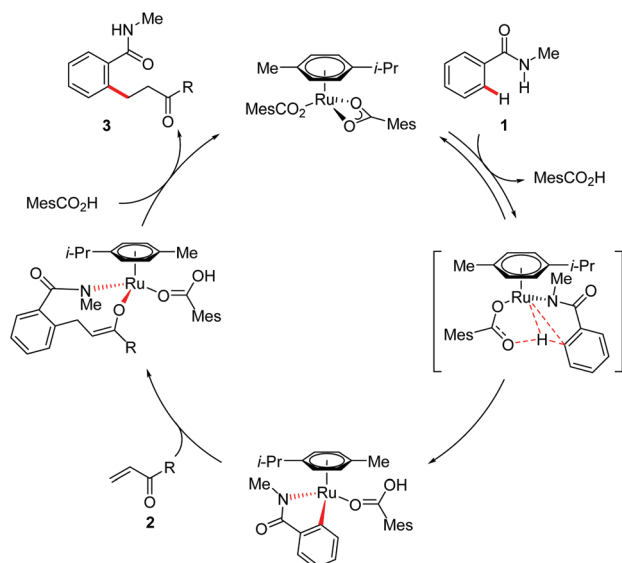
Scheme 5 H/D exchange experiment.



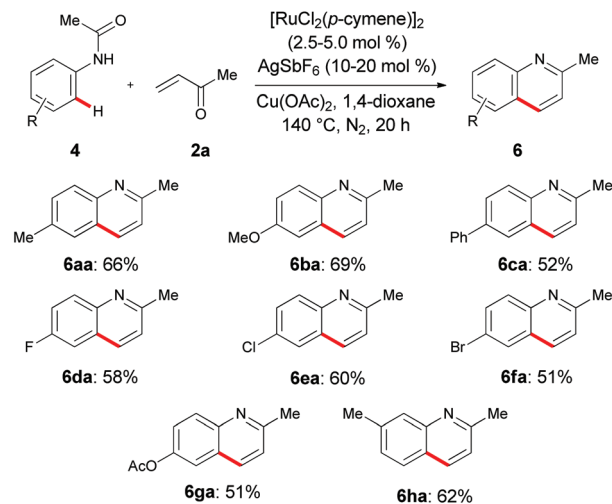
Scheme 6 Kinetic isotope effect (KIE) studies.

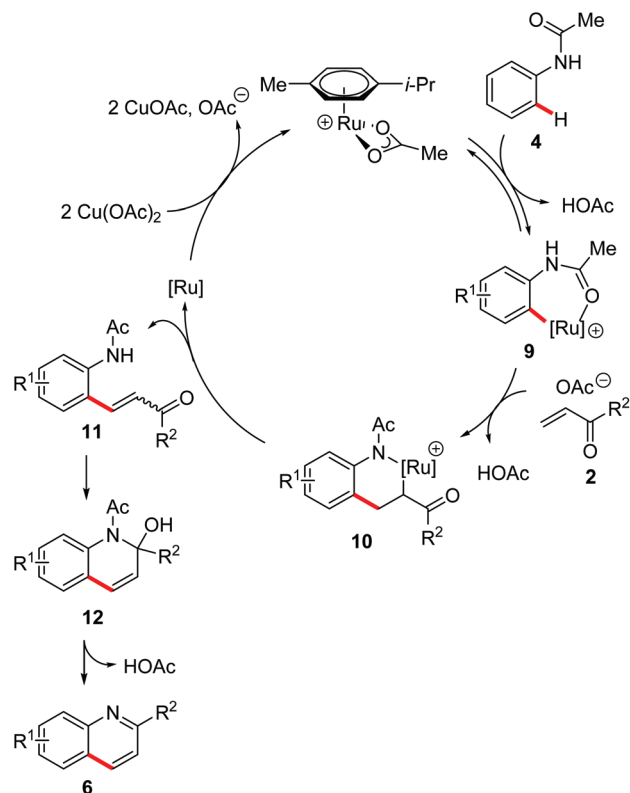
Based on these experimental findings and previous mechanistic insight, we propose a plausible catalytic cycle to involve an initial reversible C–H bond activation by carboxylate assistance, subsequent migratory insertion, and rate-determining reductive elimination (Scheme 7).

Inspired by our previous work on oxidative alkenylations,²² we subsequently probed the oxidative annulation of differently decorated acetanilides **4** with α,β -unsaturated ketone **2a** (Scheme 8). Importantly, the catalytic system was not limited to the use of electron-rich *N*-phenylacetamides **4a–4c**, but also allowed for the transformation of electron-poor substrates **4**. Valuable electrophilic functional groups, such as fluoro,



Scheme 7 Proposed catalytic cycle for carboxylate-assisted hydroarylation.

Scheme 8 Scope of the oxidative alkene annulations with substituted acetanilides **4**.



Scheme 9 Plausible catalytic cycle.

chloro, bromo and ester substituents, were well tolerated by the versatile ruthenium(II) catalyst. An intramolecular competition experiment with substrate **4h** bearing a *meta*-methyl substituent showed that the cyclization was governed by steric interactions to deliver the product **6ha** in high yield.

Based on our previous studies,²² we propose an initial C–H ruthenation to yield cycloruthenated complex **9** (Scheme 9). Thereafter, a migratory insertion of alkene **2** occurs to generate the intermediate **10**. Then, β -hydride-elimination furnishes the product of oxidative alkenylation **11**, while the catalytically active ruthenium(II) complex is regenerated by a sequence of reductive elimination and reoxidation. The desired quinoline **6** is obtained through an intramolecular nucleophilic attack of the anilide in intermediate **11**, followed by β -elimination of acetic acid to deliver the desired product **6**.

Conclusions

In summary, we have developed unprecedented ruthenium(II)-catalyzed hydroarylations and oxidative annulations on benzamides **1** and acetanilides **4** with α,β -unsaturated ketones **2** through C–H activation. The use of benzamides with monodentate directing groups renders our approach highly atom-economical, and the aqueous reaction conditions makes the process environmentally-benign. Detailed experimental mechanistic studies indicated a facile H/D-exchange. In

addition, a cascade oxidative annulation of α,β -unsaturated ketones **2a** with acetanilides **4** was developed to deliver decorated quinolines **6** in a highly step-economic fashion.

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Notes and references

- (a) X. Cui, J. Mo, L. Wang and Y. Liu, *Synthesis*, 2015, 439–459; (b) L. Ackermann, *Org. Process Res. Dev.*, 2015, **19**, 260–269; (c) A. F. Noisier and M. A. Brimble, *Chem. Rev.*, 2014, **114**, 8775–8806; (d) X.-S. Zhang, K. Chen and Z.-J. Shi, *Chem. Sci.*, 2014, **5**, 2146–2159; (e) V. S. Thirunavukkarasu, S. I. Kozhushkov and L. Ackermann, *Chem. Commun.*, 2014, **50**, 29–39; (f) N. Kuhl, N. Schröder and F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443–1460; (g) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879–5918; (h) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1292; (i) L. Ackermann, R. Vicente and A. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (j) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; and references cited therein.
- (a) K. Gao and N. Yoshikai, *Acc. Chem. Res.*, 2014, **47**, 1208–1219; (b) N. A. Foley, J. P. Lee, Z. Ke, T. B. Gunnoe and T. R. Cundari, *Acc. Chem. Res.*, 2009, **42**, 585–597; (c) A. M. Echavarren and C. Nevado, *Synthesis*, 2005, 167–182; F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077–1101.
- B. M. Trost, *Science*, 1991, **254**, 1471–1477.
- L. N. Lewis and J. F. Smith, *J. Am. Chem. Soc.*, 1986, **108**, 2728–2735.
- S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda and N. Chatani, *Nature*, 1993, **366**, 529–531.
- N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi and S. Murai, *J. Am. Chem. Soc.*, 2001, **123**, 10935–10941.
- (a) M.-O. Simon, R. Martinez, J.-P. Genet and S. Darses, *J. Org. Chem.*, 2010, **75**, 208–210; (b) R. Martinez, M. O. Simon, R. Chevalier, C. Pautigny, J. P. Genet and S. Darses, *J. Am. Chem. Soc.*, 2009, **131**, 7887–7895; (c) R. Martinez, J. P. Genet and S. Darses, *Chem. Commun.*, 2008, 3855–3857; (d) R. Martinez, R. Chevalier, S. Darses and J. P. Genet, *Angew. Chem., Int. Ed.*, 2006, **45**, 8232–8235.
- (a) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281–295; (b) L. Ackermann, *Isr. J. Chem.*, 2010, **50**, 652–663; (c) L. Ackermann, *Synlett*, 2007, 507–526.
- (a) M. Schinkel, L. Wang, K. Bielefeld and L. Ackermann, *Org. Lett.*, 2014, **16**, 1876–1879; (b) M. Schinkel, J. Wallbaum, S. I. Kozhushkov, I. Marek and L. Ackermann,



- Org. Lett.*, 2013, **15**, 4482–4484; (c) M. Schinkel, I. Marek and L. Ackermann, *Angew. Chem., Int. Ed.*, 2013, **52**, 3977–3980.
- 10 F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani and S. Murai, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 62–83.
- 11 (a) C. M. Filloux and T. Rovis, *J. Am. Chem. Soc.*, 2015, **137**, 508–517; (b) L. Yang, B. Qian and H. Huang, *Chem. – Eur. J.*, 2012, **18**, 9511–9515; (c) J. Ryu, S. Hwan Cho and S. Chang, *Angew. Chem., Int. Ed.*, 2012, **51**, 3677–3681; (d) F. W. Patureau, T. Besset and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 1064–1067; (e) L. Yang, C. A. Correia and C. J. Li, *Org. Biomol. Chem.*, 2011, **9**, 7176–7179; (f) F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9982–9983; (g) D. A. Colby, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2006, **128**, 5604–5605; (h) S.-G. Lim, J.-A. Ahn and C.-H. Jun, *Org. Lett.*, 2004, **6**, 4687–4690. For further transition metal catalysts, see also: (i) T. Shibata and H. Takano, *Org. Chem. Front.*, 2015, **2**, 383–387; (j) S. Pan, N. Ryu and T. Shibata, *Adv. Synth. Catal.*, 2014, **356**, 929–933; (k) Y. Kommagalla, K. Srinivas and C. V. Ramana, *Chem. – Eur. J.*, 2014, **20**, 7884–7889; (l) B. Zhou, P. Ma, H. Chen and C. Wang, *Chem. Commun.*, 2014, **50**, 14558–14561; (m) T. Shibata and T. Shizuno, *Angew. Chem., Int. Ed.*, 2014, **53**, 5410–5413; and references cited therein.
- 12 (a) H. Jin, Z. Zhu, N. Jin, J. Xie, Y. Chenga and C. Zhu, *Org. Chem. Front.*, 2015, **2**, 378–382; (b) Y. Kuninobu, K. Kikuchi, Y. Tokunaga, Y. Nishina and K. Takai, *Tetrahedron*, 2008, **64**, 5974–5981; (c) Y. Kuninobu, Y. Nishina, K. Okaguchi, M. Shouho and K. Takai, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 1393–1401.
- 13 G. Rouquet and N. Chatani, *Chem. Sci.*, 2013, **4**, 2201–2208.
- 14 For selected examples of using bidentate directing groups, see: (a) Q. Gu, H. H. Al Mamari, K. Graczyk, E. Diers and L. Ackermann, *Angew. Chem., Int. Ed.*, 2014, **53**, 3868–3871; (b) W. Song, S. Lackner and L. Ackermann, *Angew. Chem., Int. Ed.*, 2014, **53**, 2477–2480; (c) Y. Aihara and N. Chatani, *Chem. Sci.*, 2013, **4**, 664–670; (d) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154–13155.
- 15 B. Li and P. H. Dixneuf, *Chem. Soc. Rev.*, 2013, **42**, 5744–5767.
- 16 R. N. Butler and A. G. Coyne, *Chem. Rev.*, 2010, **110**, 6302–6337.
- 17 S. De Sarkar, W. Liu, S. I. Kozhushkov and L. Ackermann, *Adv. Synth. Catal.*, 2014, **356**, 1461–1479.
- 18 K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802.
- 19 E. Clot, O. Eisenstein, N. Jasim, S. A. Macgregor, J. E. McGrady and R. N. Perutz, *Acc. Chem. Res.*, 2011, **44**, 333–348.
- 20 (a) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (b) L. Ackermann, J. Pospesch and H. K. Potukuchi, *Org. Lett.*, 2012, **14**, 2146–2149; (c) S. Warratz, C. Kornhaas, A. Cajaraville, B. Niepötter, D. Stalke and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 5513–5517.
- 21 L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345.
- 22 Selected examples: (a) J. Li, M. John and L. Ackermann, *Chem. – Eur. J.*, 2014, **20**, 5403–5408; (b) L. Ackermann, L. Wang, R. Wolfram and A. V. Lygin, *Org. Lett.*, 2012, **14**, 728–731; a review: (c) S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, **4**, 886–896.

