ChemPubSoc Europe

DOI: 10.1002/chem.201503624

CHEMISTRY
A European Journal
Communication

C–H Activation

Cobalt(III)-Catalyzed C–H/N–O Functionalizations: Isohypsic Access to Isoquinolines

Hui Wang, Julian Koeller, Weiping Liu, and Lutz Ackermann*[a]

Abstract: C–H/N–O functionalizations by cobalt(III) catalysis allowed the expedient synthesis of a broad range of isoquinolines. Thus, internal and challenging terminal alkynes proved to be viable substrates for an isohypsic annulation, which was shown to proceed by a facile C–H cobaltation.

Transition-metal-catalyzed C–H functionalizations have emerged as increasingly powerful tools for sustainable organic syntheses.[1] Alkyne annulations by C–H/N–O functionalizations have proven to be particularly instrumental for the step-economical assembly of various heterocycles with activities of relevance to medicinal chemistry and biology.[2] Despite these undisputed advances, isohypsic alkyne annulations were thus far only realized with costly 4d or 5d transition-metal catalysts.[2,3] In light of the beneficial features of naturally abundant 3d transition metals, focus has shifted in recent years to the use of environmentally benign and less expensive base metal catalysts for C–H activation processes.[4] Versatile cobalt catalysts have been applied for chemoselective C–H transformations,[5] with notable progress being accomplished with cobalt(III) complexes as reported by Matsunaga/Kanai,[6] our group,[7] Glorius,[8] Ellman,[9] and Chang[10] among others.[11] Within our research program on cobalt-catalyzed C–H functionalizations,[12] we now report on cobalt-catalyzed C–H/N–O functionalizations for the redox-neutral preparation of isoquinolines (Figure 1). Notable features of our cobalt catalysis strategy include i) short reaction times of 15 min, ii) aromatic and aliphatic C–H activation, and iii) isohypsic C–H functionalizations that allowed cobalt-catalyzed alkyne annulations in the absence of external oxidants.

At the outset of our studies, we explored various reaction conditions for the envisioned isohypsic cobalt-catalyzed annulation of alkyne **2a** (Table 1, and Table S-1 in the Supporting Information).

Preliminary experiments indicated 1,2-dicholoroethane (DCE) to be the reaction medium of choice among a set of representative solvents (toluene, 1,4-dioxane, MeOH, H_2O), while $[Cp^*CoI_2(CO)]$[13] was the most powerful catalyst.

The C–H/N–O functionalization proceeded most efficiently with $AgSbF_6$ and NaOAc as the additives (Table 1, entries 1–10). This finding can be rationalized in terms of a carboxylate-as-

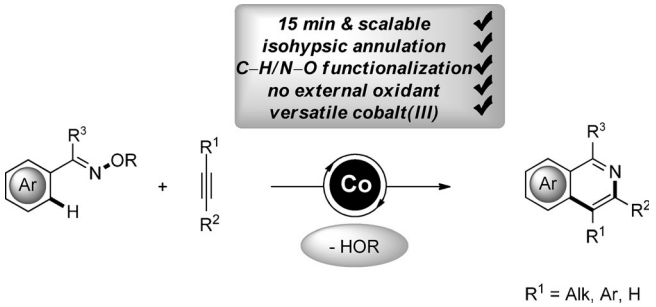
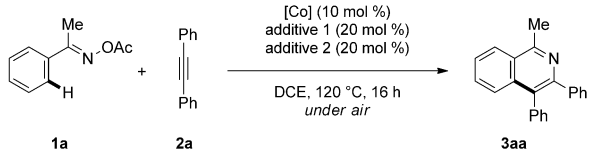


Figure 1. Expedient cobalt-catalyzed C–H aminocarbonylation.

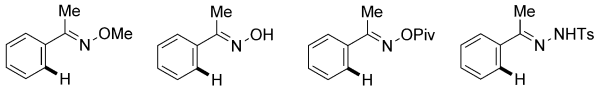
Table 1. Optimization of cobalt-catalyzed C–H/N–O functionalization.[a]



1a 2a 3aa

Entry	[Co]	Additive 1	Additive 2	Yield [%][b]
1	$[Cp^*CoI_2(CO)]$	–	NaOAc	12
2	$[Cp^*CoI_2(CO)]$	$AgPF_6$	NaOAc	29
3	$[Cp^*CoI_2(CO)]$	$AgBF_4$	NaOAc	55
4	$[Cp^*CoI_2(CO)]$	AgOTf	NaOAc	54
5	$[Cp^*CoI_2(CO)]$	$AgSbF_6$	HOPiv	48
6	$[Cp^*CoI_2(CO)]$	$AgSbF_6$	CsOAc	46
7	$[Cp^*CoI_2(CO)]$	$AgSbF_6$	KOAc	62
8	$[Cp^*CoI_2(CO)]$	$AgSbF_6$	NaOPiv	74
9	–	$AgSbF_6$	NaOAc	–
10	**$[Cp^*CoI_2(CO)]$**	**$AgSbF_6$**	**NaOAc**	**87**
11	$[Cp^*CoI_2(CO)]$	$AgSbF_6$	NaOAc	86[c]
12	$[Cp^*CoI_2(CO)]$	$AgSbF_6$	NaOAc	60[d]
13	$[Cp^*CoI_2(CO)]$	$AgSbF_6$	NaOAc	63[e]

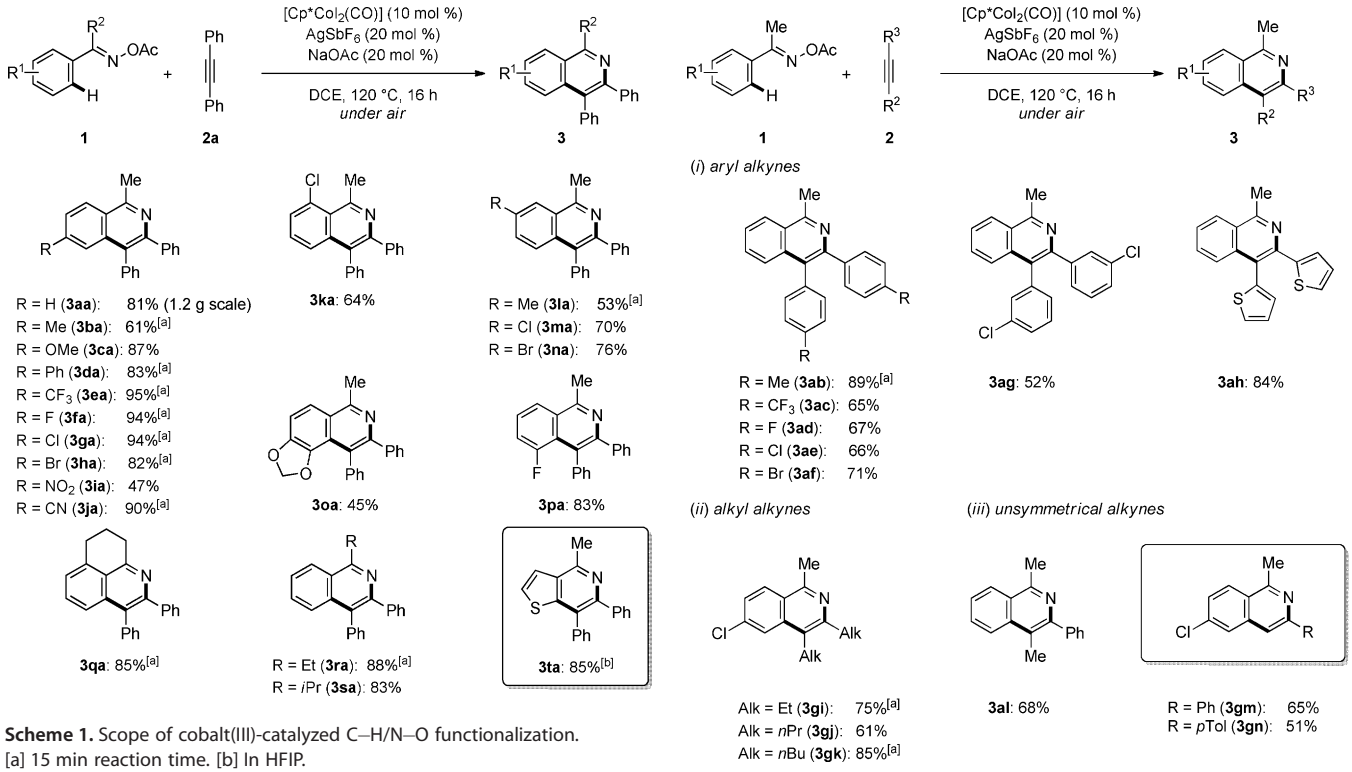
[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), [Co] (10 mol%), additive 1 (20 mol%), additive 2 (20 mol%), DCE (2.0 mL), under air, 120 °C, 16 h. [b] Yields of isolated product. [c] Under N_2. [d] 100 °C. [e] $[Cp^*CoI_2(CO)]$ (5 mol%). DCE = 1,2-dichloroethane.



4a: 20% **5a**: 53% **6a**: 76% **7a**: trace

[a] H. Wang, J. Koeller, W. Liu, Prof. Dr. L. Ackermann
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstraße 2, 37077 Göttingen (Germany)
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de
Homepage: http://www.ackermann.chemie.uni-goettingen.de/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201503624.

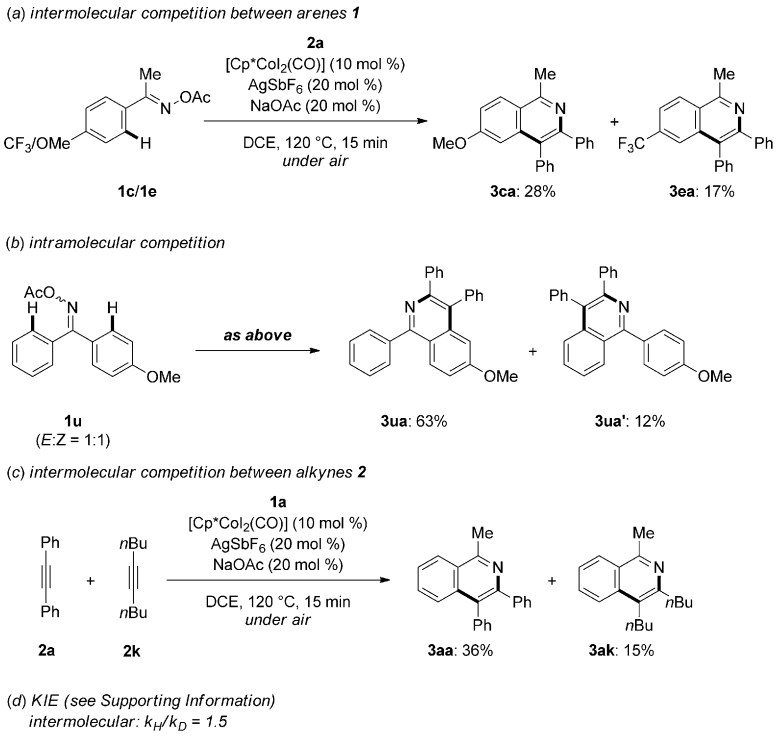


Scheme 1. Scope of cobalt(III)-catalyzed C–H/N–O functionalization. [a] 15 min reaction time. [b] In HFIP.

Scheme 2. Isohypsic annulation of alkynes **2**. [a] 15 min reaction time.

sisted[14] C–H activation by a cationic cobalt(III) catalyst. The robust nature of the cobalt(III)-catalyzed alkyne annulation was reflected by successfully performing the C–H activation under a most user-friendly atmosphere of ambient air, but the reaction also proved viable under a nitrogen atmosphere (entry 11). Notably, the reaction temperature and the catalyst loading could be reduced as well (entries 12 and 13). The cationic cobalt(III) catalyst was not limited to *O*-acetyl oxime **1a**. Indeed, oxime derivatives **4a–6a** were found to be amenable substrates as well, while the *N*-tosyl hydrazone **7a** only furnished traces of the desired product **3aa**.

With the optimized cobalt catalyst in hand, we evaluated its generality with a representative set of decorated arenes **1** (Scheme 1). Thus, a variety of *para*-substituted substrates **1a–1j** was converted in a chemoselective fashion, thereby tolerating valuable electrophilic functional groups, such as chloro, bromo, nitro, or cyano substituents. Likewise, more sterically hindered *ortho*-substituted *O*-acetyl oxime **1k** delivered the desired product **3ka** with a comparable catalytic efficacy. Intramolecular competition experiments with *meta*-substituted substrates were largely governed by steric interactions through



Scheme 3. Summary of key mechanistic studies.

the C–H functionalization at the less hindered site, unless secondary interactions dominated as in oxime derivatives **1o** and **1p**. The alkyne annulation with substituted arene **1q** set the stage for the assembly of the tricyclic product **3qa**. It is noteworthy that also heterocyclic substrate **1t** proved to be suitable for the isohypsic alkyne annulation, when employing hexafluoroisopropanol (HFIP) as the solvent. The unusually high catalytic activity of the cationic cobalt(III) catalyst was reflected by high-yielding C–H/N–O functionalizations within—in many cases—only 15 min.

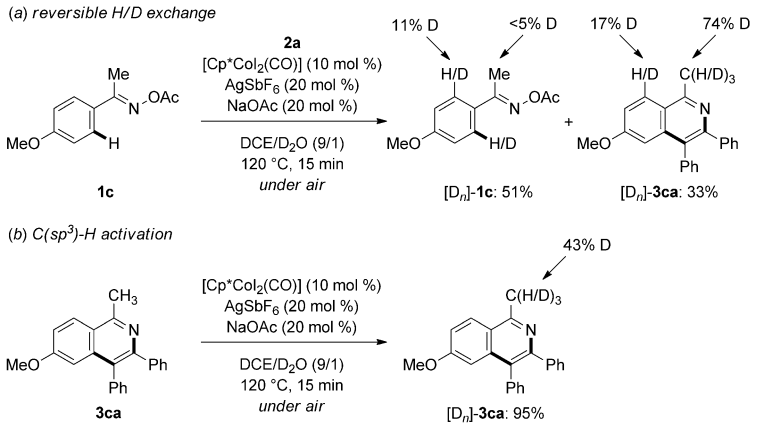
As to the alkyne scope, both aryl as well as alkyl-substituted substrates **2** were found to be viable (Scheme 2). In contrast to previously reported ruthenium(II)-catalyzed C–H/N–O transformations,[15] the broadly applicable cobalt(III)-catalyzed procedure enabled the challenging use of simple[16] terminal alkynes **2m** and **2n** as well.

Intrigued by the versatility and efficacy of the cobalt(III)-catalyzed C–H/N–O functionalizations, we conducted mechanistic studies to delineate its mode of action. To this end, inter- (Scheme 3a) and intramolecular (Scheme 3b) competition experiments revealed electron-rich arenes **1** to be inherently more reactive. This observation is in good agreement with a base-assisted intramolecular electrophilic-type substitution (BIES)[17] mechanism by a cationic cobalt catalyst. Moreover, the high overall yield of the C–H/N–O functionalization with the diastereomeric mixture of substrate **1u** revealed that a *Z*-configuration of the *O*-acetyl oximes **1** is not a prerequisite for the alkyne annulation. As to the relative reactivity of alkynes **2**, aromatic substituents increased the inherent reaction rate (Scheme 3c). In accordance with this hypothesis we found a minor kinetic isotope effect (KIE) of $k_H/k_D \approx 1.5$ (Scheme 3d),[18] being suggestive of the C–H metalation not being the rate-determining step.[19]

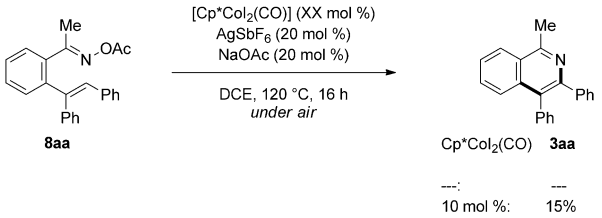
Studies with isotopically labeled compounds highlighted a considerable H/D exchange in the *ortho*-position of the re-isolated substrate [D$_n$]-**1c** and the product [D$_n$]-**3ca** (Scheme 4a). It is noteworthy that we also observed a significant H/D exchange at the C(sp^3)–H bonds, which was shown to proceed by chelation assistance (Scheme 4b), thereby showcasing the potential of cobalt(III) catalysis beyond aromatic C–H functionalization.

To probe the viability of a potential reaction sequence comprising of intermolecular hydroarylation[20] and electrocyclic reaction, we subjected the independently prepared *ortho*-alkenylated substrate **8aa** to the optimized reaction conditions (Scheme 5). Thus, a thermal pericyclic reaction did not occur, even after prolonged heating. Likewise, the attempted transformation of substrate **8aa** in the presence of the cobalt(III) catalyst provided results being considerably inferior to the ones observed for the isohypsic alkyne annulation, thus rendering a hydroarylation/electrocyclization sequence unlikely to be operative here.

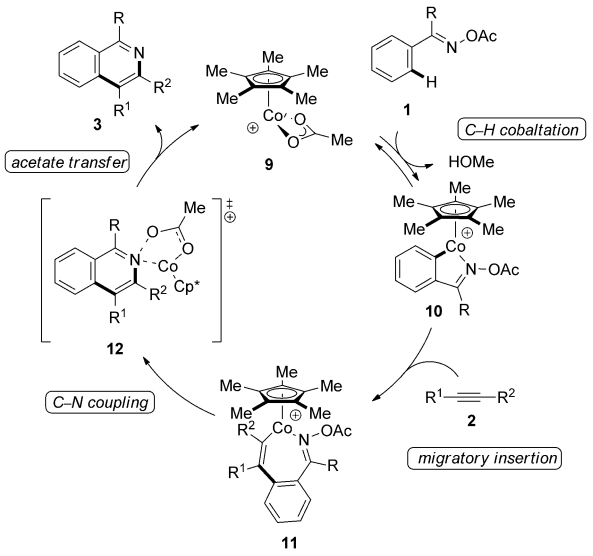
Based on our mechanistic studies we propose the cobalt(III)-catalyzed C–H/N–O functionalization to commence by a reversible C–H activation, along with a proposed migratory alkyne insertion, providing key intermediate **11** (Scheme 6). Next, the C–N formation is proposed to proceed, followed by a subsequent concerted acetate transfer to deliver the desired product **3**, and regenerate the catalytically competent cobalt(III) complex **9**.



Scheme 4. H/D exchange studies.



Scheme 5. Attempted cyclization of *ortho*-alkenylated arene **8aa**.



Scheme 6. Proposed catalytic cycle.

In summary, we have reported on a cobalt-catalyzed C–H/N–O functionalization. Thus, the isohypsic alkyne annulation has set the stage for an effective isoquinoline synthesis with ample substrate scope. The step-economical direct functionalization occurred by facile C–H activation, and circumvented the use of an external oxidant[21] for the regioselective alkyne functionalization process.[22]

Acknowledgements

Generous support by the European Research Council under the European Community's Seventh Framework Program (FP7 2007-2013)/ERC Grant agreement no. 307535, and the China Scholarship Program (fellowship to H. W. and W. L.) is gratefully acknowledged.

Keywords: alkyne · C–H activation · cobalt · isoquinoline · N-O cleavage

[1] Representative recent reviews on C–H activation: a) B. Ye, N. Cramer, *Acc. Chem. Res.* **2015**, *48*, 1308 – 1318; b) J. Li, S. De Sarkar, L. Ackermann, *Top. Organomet. Chem.* **2015**, DOI:10.1007/3418 2015 130; c) K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.* **2015**, *48*, 1040 – 1052; d) O. Daugulis, J. Roane, *Acc. Chem. Res.* **2015**, *48*, 1053 – 1064; e) Y. Segawa, T. Maekawa, K. Itami, *Angew. Chem. Int. Ed.* **2015**, *54*, 66 – 81; *Angew. Chem.* **2015**, *127*, 68 – 83; f) N. Kuhl, N. Schroeder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443 – 1460; g) T. Mesganaw, J. A. Ellman, *Org. Process Res. Dev.* **2014**, *18*, 1097 – 1104; h) S. Tani, T. N. Uehara, J. Yamaguchi, K. Itami, *Chem. Sci.* **2014**, *5*, 123 – 135; i) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74 – 100; *Angew. Chem.* **2014**, *126*, 76 – 103; j) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726 – 11743; *Angew. Chem.* **2013**, *125*, 11942 – 11959; k) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369 – 375; l) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242 – 3272; m) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792 – 9826; *Angew. Chem.* **2009**, *121*, 9976 – 10011; n) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094 – 5115; *Angew. Chem.* **2009**, *121*, 5196 – 5217; o) R. G. Bergman, *Nature* **2007**, *446*, 391 – 393, and references therein.

[2] a) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281 – 295; b) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212 – 11222.

[3] Recent reviews: a) H. Huang, X. Ji, W. Wu, H. Jiang, *Chem. Soc. Rev.* **2015**, *44*, 1155 – 1171; b) J. Mo, L. Wang, Y. Liu, X. Cui, *Synthesis* **2015**, 439 – 459.

[4] Recent authorative reviews on the use of inexpensive first-row transition-metal catalysts for C–H bond functionalization: a) K. Hirano, M. Miura, *Chem. Lett.* **2015**, *44*, 868 – 873; b) E. Nakamura, T. Hatakeyama, S. Ito, K. Ishizuka, L. Ilies, M. Nakamura, *Org. React.* **2014**, *83*, 1 – 209; c) J. Yamaguchi, K. Muto, K. Itami, *Eur. J. Org. Chem.* **2013**, 19 – 30; d) N. Yoshikai, *Synlett* **2011**, 1047 – 1051; e) Y. Nakao, *Chem. Rec.* **2011**, *11*, 242 – 251; f) E. Nakamura, N. Yoshikai, *J. Org. Chem.* **2010**, *75*, 6061 – 6067; g) A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087 – 4109, and references therein.

[5] Recent reviews: a) L. Ackermann, *J. Org. Chem.* **2014**, *79*, 8948 – 8954; b) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208 – 1219.

[6] a) Y. Suzuki, B. Sun, K. Sakata, T. Yoshino, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2015**, *54*, 9944 – 9947; *Angew. Chem.* **2015**, *127*, 10082 – 10085; b) Y. Suzuki, B. Sun, T. Yoshino, M. Kanai, S. Matsunaga, *Tetrahedron* **2015**, *71*, 4552 – 4556; c) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2014**, *136*, 5424 – 5431; d) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 1491 – 1495; e) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 2207 – 2211; *Angew. Chem.* **2013**, *125*, 2263 – 2267.

[7] a) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 8551 – 8554; *Angew. Chem.* **2015**, *127*, 8671 – 8674; b) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 3635 – 3638; *Angew. Chem.* **2015**, *127*, 3706 – 3709; c) M. Moselage, N. Sauermann, J. Koeller, W. Liu, D. Gelman, L. Ackermann, *Synlett* **2015**, 1596 – 1600.

[8] a) T. Gensch, S. Vasquez-Cespedes, D.-G. Yu, F. Glorius, *Org. Lett.* **2015**, *17*, 3714 – 3717; b) D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *54*, 4508 – 4511; *Angew. Chem.* **2015**, *127*, 4591 – 4594; c) D. G. Yu, T. Gensch, F. d. Azambuja, S. V. Céspedes, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17722 – 17725.

[9] a) J. R. Hummel, J. A. Ellman, *J. Am. Chem. Soc.* **2015**, *137*, 490 – 498; b) J. R. Hummel, J. A. Ellman, *Org. Lett.* **2015**, *17*, 2400 – 2403.

[10] a) P. Patel, S. Chang, *ACS Catal.* **2015**, *5*, 853 – 858; b) A. B. Pawar, S. Chang, *Org. Lett.* **2015**, *17*, 660 – 663.

[11] See also: a) L. Grigorjeva, O. Daugulis, *Org. Lett.* **2015**, *17*, 1204 – 1207; b) W. Ma, L. Ackermann, *ACS Catal.* **2015**, *5*, 2822 – 2825; c) L.-B. Zhang, X.-Q. Hao, Z.-J. Liu, X.-X. Zheng, S.-K. Zhang, J.-L. Niu, M.-P. Song, *Angew. Chem. Int. Ed.* **2015**, *54*, 623 – 626; *Angew. Chem.* **2015**, *127*, 633 – 636; d) L.-B. Zhang, X.-Q. Hao, S.-K. Zhang, Z.-J. Liu, X.-X. Zheng, J.-F. Gong, J.-L. Niu, M.-P. Song, *Angew. Chem. Int. Ed.* **2015**, *54*, 272 – 275; *Angew. Chem.* **2015**, *127*, 274 – 277; e) L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.* **2014**, *53*, 10209 – 10212; *Angew. Chem.* **2014**, *126*, 10373 – 10376, and references therein.

[12] a) M. Moselage, N. Sauermann, S. C. Richter, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 6352 – 6355; *Angew. Chem.* **2015**, *127*, 6450 – 6453; b) B. Punji, W. Song, G. A. Shevchenko, L. Ackermann, *Chem. Eur. J.* **2013**, *19*, 10605 – 10610; c) W. Song, L. Ackermann, *Angew. Chem. Int. Ed.* **2012**, *51*, 8251 – 8254; *Angew. Chem.* **2012**, *124*, 8376 – 8379.

[13] W. Li, L. Weng, G. Jin, *Inorg. Chem. Commun.* **2004**, *7*, 1174 – 1177.

[14] a) K. Fagnou, *Top. Curr. Chem.* **2009**, *292*, 35 – 56; b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 – 1345.

[15] a) F. Yang, L. Ackermann, *J. Org. Chem.* **2014**, *79*, 12070 – 12082; b) C. Kornhaaß, C. Kuper, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1619 – 1624; c) R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 3032 – 3035; d) R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Chem. Commun.* **2013**, *49*, 3703 – 3705; e) C. Kornhaass, J. Li, L. Ackermann, *J. Org. Chem.* **2012**, *77*, 9190 – 9198; f) B. Li, H. Feng, S. Xu, B. Wang, *Chem. Eur. J.* **2011**, *17*, 12573 – 12577; g) L. Ackermann, S. Fenner, *Org. Lett.* **2011**, *13*, 6548 – 6551. For related rhodium-catalyzed transformations, see: h) K. Parthasarathy, C.-H. Cheng, *J. Org. Chem.* **2009**, *74*, 9359 – 9364; i) P. C. Too, Y.-F. Wang, S. Chiba, *Org. Lett.* **2010**, *12*, 5688 – 5691; j) P. C. Too, Y.-F. Wang, S. Chiba, *J. Org. Chem.* **2010**, *12*, 5688 – 5691; k) X. Zhang, D. Chen, M. Zhao, J. Zhao, A. Jia, X. Li, *Adv. Synth. Catal.* **2011**, *353*, 719 – 723; l) T. K. Hyster, T. Rovis, *Chem. Commun.* **2011**, *47*, 11846 – 11848; m) Y. Yoshida, T. Kurahashi, S. Matsubara, *Chem. Lett.* **2011**, *40*, 1140 – 1142.

[16] For the use of boronates, see: H. Wang, C. Grohmann, C. Nimphius, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 19592 – 19595.

[17] a) K. Raghuvanshi, K. Rauch, L. Ackermann, *Chem. Eur. J.* **2015**, *21*, 1790 – 1794; b) C. Tirler, L. Ackermann, *Tetrahedron* **2015**, *71*, 4543 – 4551; c) W. Ma, R. Mei, G. Tenti, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 15248 – 15251.

[18] For detailed information, see the Supporting Information.

[19] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066 – 3072; *Angew. Chem.* **2012**, *124*, 3120 – 3126.

[20] Representative reviews on hydroarylations: a) See ref. [4e]; b) N. A. Foley, J. P. Lee, Z. Ke, T. B. Gunnoe, T. R. Cundari, *Acc. Chem. Res.* **2009**, *42*, 585 – 597; c) C. Nevado, A. M. Echavarren, *Synthesis* **2005**, 167 – 182; d) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731 – 1769; e) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633 – 639.

[21] F. W. Patureau, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 1977 – 1979; *Angew. Chem.* **2011**, *123*, 2021 – 2023.

[22] **Editorial Note (15.9.2015):** Two very closely related papers were submitted almost simultaneously to this one, see: B. Sun, T. Yoshino, M. Kanai, S. Matsunaga, *Angew. Chem. Int. Ed.* **2015**, *54*, DOI: 10.1002/anie.201507744; *Angew. Chem.* **2015**, *127*, DOI: 10.1002/ange.201507744 and M. Sen, D. Kalsi, B. Sundararaju, *Chem. Eur. J.* **2015**, *21*, DOI: 10.1002/chem.201503643.

Received: August 19, 2015
Revised: September 10, 2015
Published online on September 30, 2015