C–H Activation

International Edition: DOI: 10.1002/anie.201600490
German Edition: DOI: 10.1002/ange.201600490

Ruthenium(II)-Catalyzed Decarboxylative C–H Activation: Versatile Routes to *meta*-Alkenylated Arenes

*N. Y. Phani Kumar[+], Alexander Bechtoldt[+], Keshav Raghuvanshi, and Lutz Ackermann**

Abstract: *Ruthenium(II) bis(carboxylate)s proved highly effective for two decarboxylative C–H alkenylation strategies. The decarboxylation proceeded efficiently at rather low temperatures. The unique versatility of the decarboxylative ruthenium(II) catalysis is reflected in the oxidative olefinations with alkenes as well as the redox-neutral hydroarylations of alkynes.*

The alkenylation of otherwise inert C–H bonds[1] has emerged as an increasingly powerful platform for the late-stage manipulation of arenes.[2] In the recent years, particular advances were achieved with versatile ruthenium(II) complexes.[3] In this context, we have identified ruthenium(II) bis(carboxylate)s as catalysts for cross-dehydrogenative C–H functionalizations of benzoic acids with alkenes and alkynes, thereby providing step-economical access to phthalides and isocoumarins through C–H/C–H and C–H/O–H cleavage, respectively.[4] The oxidative C–H functionalization processes could be rendered aerobic by performing these transformations under an ambient atmosphere of air (Figure 1 a).[5] While performing further detailed investigations on these oxidative couplings between benzoic acids and alkenes, we probed representative oxidants under inert atmospheres. As a result of these studies, we identified reaction conditions for unprecedented decarboxylative C–H olefination by ruthenium(II) catalysis, on which we report herein. It is noteworthy that elegant decarboxylative[6] C–H couplings have previously been accomplished with palladium or rhodium catalysts and stoichiometric amounts of either silver(I) or copper(II) salts,[7] with key contributions towards useful *meta*-substituted arenes by the groups of Gooßen,[8] Miura,[9] Larossa,[10] and Su.[11] In contrast, our catalytic system features largely underappreciated[12] ruthenium[13] complexes. Notably, the optimized ruthenium(II) bis(carboxylate) catalysts[14] proved operative at rather low reaction temperatures and did not require any copper(II) or silver(I) salts,[15] thereby giving efficient access to *meta*-substituted[16] arenes (Figure 1 b). Moreover, the key insights into the oxidative decarboxylative alkenylation by ruthenium(II) catalysis also set the stage for novel redox-neutral hydroarylations[17] of alkynes, using the exact same ruthenium(II) bis(carboxylate) catalyst [Ru(O_2CMes)$_2$(*p*-cymene)].

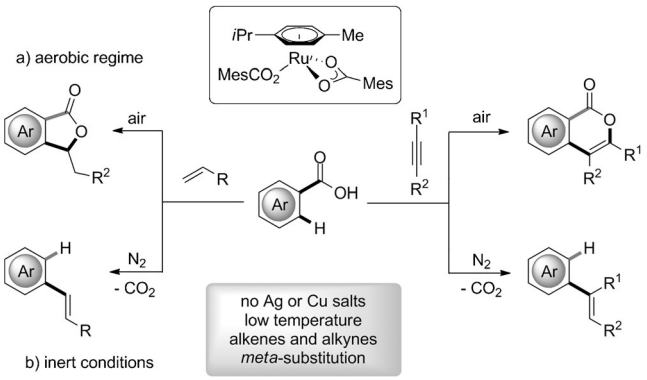
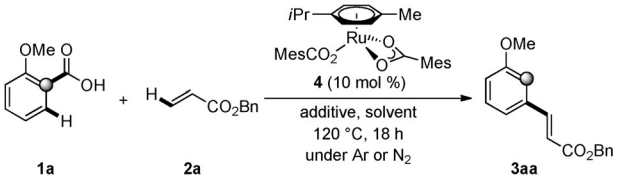


Figure 1. Ruthenium(II)-catalyzed decarboxylative C–H olefination.

We initiated our studies by probing reaction conditions for the ruthenium(II)-catalyzed C–H functionalization of the benzoic acid **1a** with the alkene **2a** (Table 1, and see Table S1 in the Supporting Information).[18] The decarboxylative C–H alkenylation occurred under an inert atmosphere of either

Table 1: Ruthenium(II)-catalyzed decarboxylative C–H alkenylation.[a]



1a 2a 3aa

Entry	Additive	Solvent	Yield [%][a]
1	–	PhMe	28
2	$Na_2S_2O_7$	PhMe	32
3	norbornadiene	PhMe	30
4	*t*BuC(O)Me	PhMe	31
5	MnO_2	PhMe	39
6	V_2O_5	H_2O	15
7	V_2O_5	DCE	22
8	V_2O_5	*n*-hexane	27
9	V_2O_5	MeCN	55
10	V_2O_5	DMF	48[b]
11	V_2O_5	DMSO	–[b]
12	V_2O_5	*m*-xylene	60[b]
13	V_2O_5	PhMe	–[c]
14	V_2O_5	PhMe	60

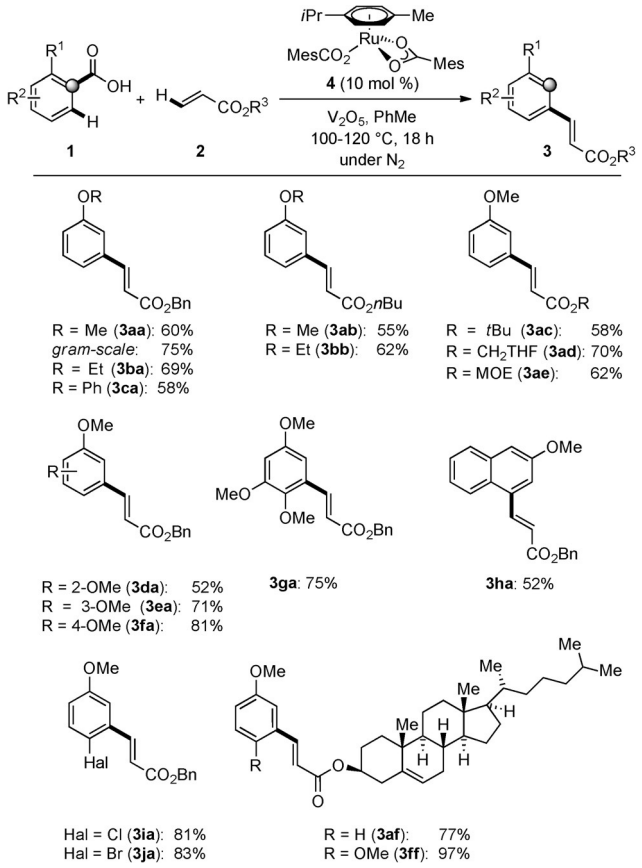
[a] Reaction conditions: **1a** (3.0 mmol), **2a** (1.0 mmol), **4** (10.0 mol%), additive (1.0 equiv), PhMe (3.0 mL), 18 h, under either Ar or N_2. Yield of isolated product. [b] 150 °C. [c] Without [Ru]. DCE = 1,2-dichloroethane. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide.

[*] N. Y. P. Kumar,[+] A. Bechtoldt,[+] K. Raghuvanshi, 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.org.chemie.uni-goettingen.de/ackermann/
[+] These authors contributed equally to this work.

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201600490.

ambient argon or nitrogen, and notably, even in the absence of an additional oxidant (entry 1). Yet, the decarboxylative oxidative C–H functionalization proved to be more effective when using additives. While sodium persulfate, norbornadiene, pinacolone, or MnO_2 failed to show any beneficial effect (entries 2–5), optimal results were obtained using V_2O_5, with the best solvent being toluene (entry 6–14). Moreover, the crucial importance of the ruthenium(II) catalyst was unambiguously verified (entries 13 and 14).

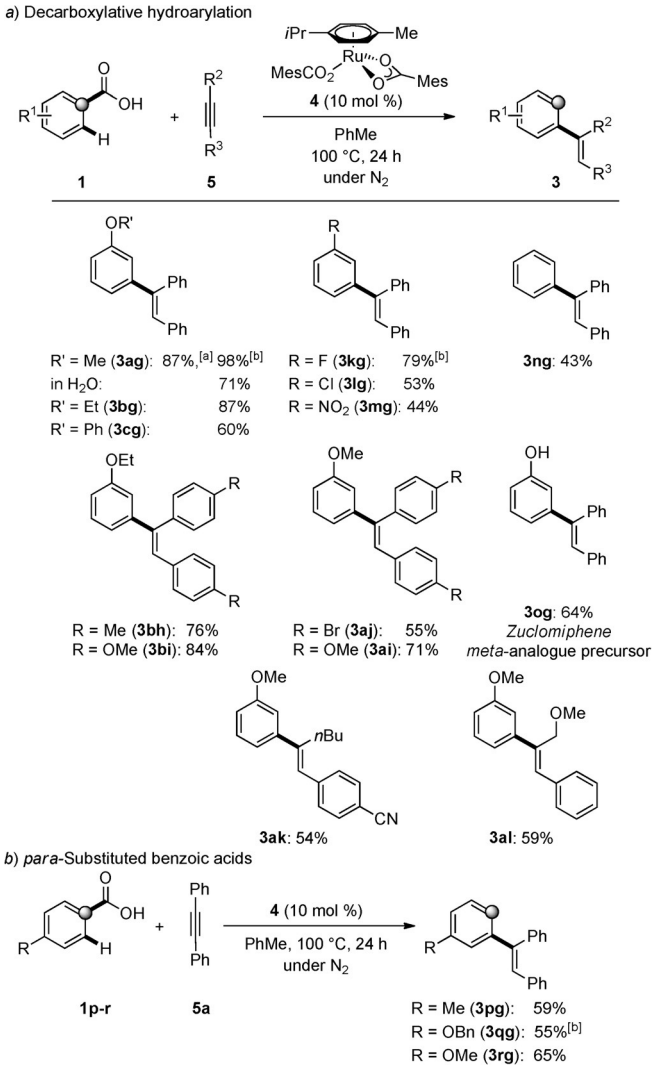
With the optimized reaction conditions in hand, we probed the versatility of the ruthenium(II)-catalyzed decarboxylative C–H alkenylation of benzoic acids (**1**) with alkenes **2** (Scheme 1). The ruthenium(II) bis(carboxylate) complex **4**



Scheme 1. Scope of the decarboxylative domino C–H alkenylation with benzoic acids (**1**) and alkenes (**2**). THF = tetrahydrofuran-2-yl, MOE = 2-methoxyethyl.

enabled the decarboxylative C–H alkenylation of various acids (**1**) with ample substrate scope. The robustness of the catalyst **4** was reflected by full toleration of a variety of valuable electrophilic functional groups, including ester, chloro, and bromo substituents, as well as the sensitive cholesteryl moiety in alkene **2f**.

In consideration of our previous successful use of alkynes **5** in ruthenium(II)-catalyzed oxidative annulations by benzoic acids,[4b,5b] we further explored the acetylene derivatives **5** under an inert atmosphere (Scheme 2, and see Table S2).[18] Interestingly, here we observed a novel isohypsic, that is, redox-neutral, decarboxylative hydroarylation, thus chemo-



Scheme 2. Decarboxylative hydroarylation.[a] **4** (5.0 mol%). [b] In DCE.

selectively furnishing the *meta*-alkenylated arenes **3**. Again, the versatile complex **4** proved chemoselective, as was illustrated by the synthesis of the products **3** featuring fluoro, chloro, bromo, and nitro groups among others. It is noteworthy that the simple benzoic acid **1n**, being devoid of a stabilizing *ortho*-substituent, could be employed as well, albeit with somewhat diminished efficacy. Furthermore, the unsymmetrical alkynes **5k**,**l** were successfully employed to furnish the corresponding *meta*-substituted products **3ak**,**al** with excellent regioselectivity, generally placing the aryl group distal to the benzoic acid's aromatic moiety. Importantly, the domino hydroarylation/decarboxylation protocol was not limited to substrates bearing stabilizing *ortho* groups. Indeed, the *para*-substituted benzoic acids **1p–r** proved amenable to the C–H olefination process as well, hence, allowing the synthesis of the *meta*-substituted products **3pg–rg** (Scheme 2b). In more general terms, the two decarboxylative C–H alkenylation approaches are complementary not only in terms of the reaction conditions, but also the viable substitution patterns.

To probe the decarboxylative nature of the ruthenium(II)-catalyzed oxidative C–H alkenylation regime we studied the CO_2 evolution during the course of the domino olefination (Figure 2, and see Table S3).[18] Our studies clearly illustrate

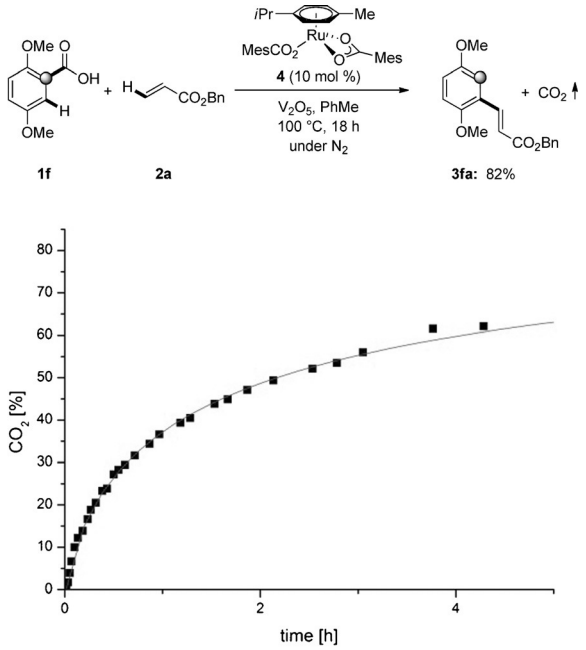


Figure 2. CO_2 evolution during ruthenium(II)-catalyzed C–H alkenylation.

that CO_2 is formed during the course of the C–H functionalization process. These observations further highlighted the considerable efficacy of the ruthenium(II) catalysis, with more than 60% conversion in 4 hours at a comparably low reaction temperature of only 100 °C. In addition, mechanistic studies provided strong support for a kinetically relevant C–H ruthenation event with a kinetic isotope effect (KIE) of $k_H/k_D \approx 2.6$.[18]

In summary, we have reported on unprecedented ruthenium-catalyzed decarboxylative oxidative C–H functionalizations which furnish *meta*-substituted arenes. Key to the success was carboxylate assistance which allowed domino[19] decarboxylation/alkenylations in the absence of either copper(II) or silver(I) salts at rather low[20] reaction temperatures. The ruthenium(II) bis(carboxylate) catalysis is highly chemo-, positional-, and regio-selective, and proceeds with ample substrate scope, including substrates without an activating *ortho* substituent. The unique versatility of the ruthenium(II) bis(carboxylate) complex [$Ru(O_2CMes)_2$(*p*-cymene)] is reflected in the two complementary protocols for decarboxylative C–H olefination which proved viable with both alkenes and alkynes.

Acknowledgments

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 DAAD (fellowships to N.Y.P.K. and K.R.) is gratefully acknowledged.

Keywords: alkenes · arenes · C–H activation · reaction mechanisms · ruthenium

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 6929–6932
Angew. Chem. **2016**, *128*, 7043–7046

[1] Representative reviews on C–H activation: a) J. G. Kim, K. Shin, S. Chang, *Top. Organomet. Chem.* **2016**, *55*, 29–51; b) B. Ye, N. Cramer, *Acc. Chem. Res.* **2015**, *48*, 1308–1318; c) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053–1064; d) Y. Segawa, T. Maekawa, K. Itami, *Angew. Chem. Int. Ed.* **2015**, *54*, 66–81; *Angew. Chem.* **2015**, *127*, 68–83; e) N. Kuhl, N. Schroeder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443–1460; f) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100; *Angew. Chem.* **2014**, *126*, 76–103; g) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375; h) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936–946; i) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212–11222; j) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; *Angew. Chem.* **2009**, *121*, 9976–10011; k) R. G. Bergman, *Nature* **2007**, *446*, 391–393, and references therein.

[2] For recent reviews that feature C–H olefinations, see: a) L. Zhou, W. Lu, *Chem. Eur. J.* **2014**, *20*, 634–642; b) S. I. Kozhushkov, L. Ackermann, *Chem. Sci.* **2013**, *4*, 886–896; c) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918; d) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170–1214; e) T. Satoh, M. Miura, *Synthesis* **2010**, 3395–3409.

[3] For recent reviews on ruthenium(II)-catalyzed C–H bond functionalizations, see: a) C. Bruneau, *Top. Organomet. Chem.* **2015**, *48*, 195–236; b) L. Ackermann, *Org. Process Res. Dev.* **2015**, *19*, 260–269; c) B. Li, P. H. Dixneuf, *Chem. Soc. Rev.* **2013**, *42*, 5744–5767; d) L. Ackermann, R. Vicente, *Top. Curr. Chem.* **2009**, *292*, 211–229, and references therein.

[4] a) L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153–4155; b) L. Ackermann, J. Pospech, K. Graczyk, K. Rauch, *Org. Lett.* **2012**, *14*, 930–933; c) M. Deponti, S. I. Kozhushkov, D. S. Yufit, L. Ackermann, *Org. Biomol. Chem.* **2013**, *11*, 142–148; see also: d) R. K. Chinnagollaa, M. Jeganmohan, *Chem. Commun.* **2012**, *48*, 2030–2032; e) H. Zhao, T. Zhang, T. Yan, M. Cai, *J. Org. Chem.* **2015**, *80*, 8849–8855.

[5] a) A. Bechtoldt, C. Tirler, K. Raghuvanshi, S. Warratz, C. Kornhaaß, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 264–267; *Angew. Chem.* **2016**, *128*, 272–267; b) S. Warratz, C. Kornhaaß, A. Cajaraville, B. Niepötter, D. Stalke, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 5513–5517; *Angew. Chem.* **2015**, *127*, 5604–5608.

[6] For reviews, see: a) J. Xuan, Z.-G. Zhang, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 15632–15641; *Angew. Chem.* **2015**, *127*, 15854–15864; b) W. I. Dzik, P. P. Lange, L. J. Gooßen, *Chem. Sci.* **2012**, *3*, 2671–2678; c) J. Cornella, I. Larrosa, *Synthesis* **2012**, 653–676; d) N. Rodríguez, L. J. Gooßen, *Chem. Soc. Rev.* **2011**, *40*, 5030–5048; e) J. D. Weaver, A. Recio, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846–1913; f) L. J. Gooßen, N. Rodriguez, K. Gooßen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120; *Angew. Chem.* **2008**, *120*, 3144–3164; g) L. J. Gooßen, K. Gooßen, N. Rodriguez, M. Blanchot, C. Linder, B. Zimmermann, *Pure Appl. Chem.* **2008**, *80*, 1725–1733.

[7] For representative examples, see: a) D. Lee, S. Chang, *Chem. Eur. J.* **2015**, *21*, 5364–5368; b) X. Qin, D. Sun, Q. You, Y. Cheng, J. Lan, J. You, *Org. Lett.* **2015**, *17*, 1762–1765; c) K. Yang, X. Chen, Y. Wang, W. Li, A. A. Kadi, H.-K. Fun, H. Sun,

Y. Zhang, G. Li, H. Lu, *J. Org. Chem.* **2015**, *80*, 11065 – 11072; d) L. Chen, L. Ju, K. A. Bustin, J. M. Hoover, *Chem. Commun.* **2015**, *51*, 15059 – 15062; e) L. Luo, D. Wu, W. Li, S. Zhang, Y. Ma, S. Yan, J. You, *Org. Lett.* **2014**, *16*, 6080 – 6083; f) K. Rousée, C. Schneider, S. Couve-Bonnaire, X. Pannecoucke, V. Levacher, C. Hoarau, *Chem. Eur. J.* **2014**, *20*, 15000 – 15004; g) K. Yang, C. Zhang, P. Wang, Y. Zhang, H. Ge, *Chem. Eur. J.* **2014**, *20*, 7241 – 7244; h) P. Hu, M. Zhang, X. Jie, W. Su, *Angew. Chem. Int. Ed.* **2012**, *51*, 227 – 231; *Angew. Chem.* **2012**, *124*, 231 – 235; i) C. Wang, S. Rakshit, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 14006 – 14008; j) J. Cornella, P. Lu, I. Larrosa, *Org. Lett.* **2009**, *11*, 5506 – 5509; k) C. Wang, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 4194 – 4195; decarboxylative Mizoroki-Heck-type reactions: l) D. Tanaka, S. P. Romeril, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 10323 – 10333, and references therein.

[8] a) S. Bhadra, W. I. Dzik, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 2959 – 2962; *Angew. Chem.* **2013**, *125*, 3031 – 3035; for pioneering work: b) L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662 – 664.

[9] a) S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2011**, *76*, 3024 – 3033; b) S. Mochida, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 5776 – 5779; c) M. Yamashita, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 2337 – 2340; d) A. Maehara, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1159 – 1162.

[10] a) J. Luo, S. Preciado, I. Larrosa, *J. Am. Chem. Soc.* **2014**, *136*, 4109 – 4112; b) R. Grainger, J. Cornella, D. C. Blakemore, I. Larrosa, J. M. Campanera, *Chem. Eur. J.* **2014**, *20*, 16680 – 16687; c) C. Arroniz, A. Ironmonger, G. Rassias, I. Larrosa, *Org. Lett.* **2013**, *15*, 910 – 913; d) J. Cornella, M. Righi, I. Larrosa, *Angew. Chem. Int. Ed.* **2011**, *50*, 9429 – 9432; *Angew. Chem.* **2011**, *123*, 9601 – 9604.

[11] Y. Zhang, H. Zhao, M. Zhang, W. Su, *Angew. Chem. Int. Ed.* **2015**, *54*, 3817 – 3821; *Angew. Chem.* **2015**, *127*, 3888 – 3892.

[12] a) H. Tan, H. Li, J. Wang, L. Wang, *Chem. Eur. J.* **2015**, *21*, 1904 – 1907; b) X.-Y. Shi, X.-F. Dong, J. Fan, K.-Y. Liu, J.-F. Wei, C.-J. Li, *Sci. China Chem.* **2015**, *58*, 1286 – 1291.

[13] For related transformations, see: a) L. Claes, J. Verduyckt, I. Stassen, B. Lagrain, D. E. D. Vos, *Chem. Commun.* **2015**, *51*, 6528 – 6531; b) J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan, A. Lei, *Angew. Chem. Int. Ed.* **2014**, *53*, 502 – 506; *Angew. Chem.* **2014**, *126*, 512 – 516; c) E. C. Burger, J. A. Tunge, *Org. Lett.* **2004**, *6*, 2603 – 2605, and references therein.

[14] a) M. Schinkel, I. Marek, L. Ackermann, *Angew. Chem. Int. Ed.* **2013**, *52*, 3977 – 3980; *Angew. Chem.* **2013**, *125*, 4069 – 4072; b) L. Ackermann, P. Novak, R. Vicente, N. Hofmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 6045 – 6048; *Angew. Chem.* **2009**, *121*, 6161 – 6164.

[15] For an elegant study, see: L. J. Gooßen, N. Rodriguez, C. Linder, P. P. Lange, A. Fromm, *ChemCatChem* **2010**, *2*, 430 – 442.

[16] J. Li, S. D. Sarkar, L. Ackermann, *Top. Organomet. Chem.* **2016**, *55*, 217 – 257.

[17] Recent reviews on catalytic hydroarylation reactions, see: a) K. Gao, N. Yoshikai, *Acc. Chem. Res. Acc. Chem. Soc.* **2014**, *47*, 1208 – 1219; b) Y. Nakao, *Chem. Rec.* **2011**, *11*, 242 – 251; c) A. Foley, J. P. Lee, Z. Ke, T. B. Gunnoe, T. R. Cundari, *Acc. Chem. Res.* **2009**, *42*, 585 – 597; d) M. Bandini, E. Emer, S. Tommasi, A. Umani-Ronchi, *Eur. J. Org. Chem.* **2006**, 3527 – 3544; e) C. Liu, C. F. Bender, X. Han, R. A. Widenhoefer, *Chem. Commun.* **2007**, 3607 – 3618; f) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077 – 1101, and references therein.

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

[19] L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[20] J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740 – 4761.

Received: January 16, 2016
Published online: March 21, 2016

