C–H Activation

International Edition: DOI: 10.1002/anie.201601560
German Edition: DOI: 10.1002/ange.201601560

Manganese(I)-Catalyzed Substitutive C–H Allylation

*Weiping Liu, Sven C. Richter, Yujiao Zhang, and Lutz Ackermann**

Abstract: *The first manganese(I)-catalyzed C–H allylations with ample scope were achieved by carboxylate assistance. The highly selective C–H/C–O functionalizations proved viable with densely substituted allyl carbonates, and the organometallic C–H allylation strategy set the stage for expedient late-stage diversification with excellent levels of positional selectivity.*

The functionalization of otherwise inert C–H bonds has been recognized as a transformative platform in molecular syntheses,[1] with enabling applications to inter alia material sciences,[2] drug development,[3] and natural product synthesis.[4] While the vast majority of C–H functionalizations was realized with precious 4d transition metals,[5] recent years have witnessed the emergence of increasingly powerful earth-abundant 3d transition-metal catalysts.[6] Particularly, organometallic[7] C–H functionalizations by manganese catalysis have gained significant momentum recently[8] with key contributions from the groups of Kuninobu and Takai,[9] Wang,[10] and Ackermann,[11] among others.[12] Despite these undisputable advances,[8–12] the manganese(I) catalysis regime has thus far largely been limited to hydroarylations by additions of C–H bonds onto C–C or C–Het multiple bonds. Within our program on sustainable C–H functionalizations with inexpensive 3d transition metals,[13] we have now devised reaction conditions for unprecedented manganese(I)-catalyzed intermolecular substitutive C–H allylations[14] (Figure 1),[15] which we report on herein.

Notable aspects of our approach include a) efficient manganese(I)-catalyzed C–H allylations with differently substituted electrophiles, b) excellent levels of positional and diastereocontrol, c) versatile late-stage diversification, and d) key mechanistic insights into the organometallic C–H manganesation manifold.

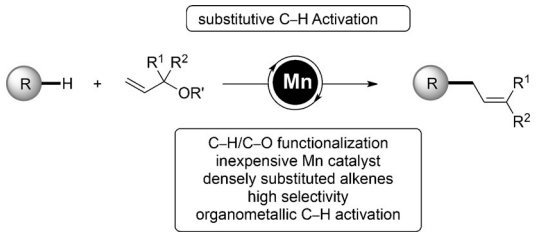


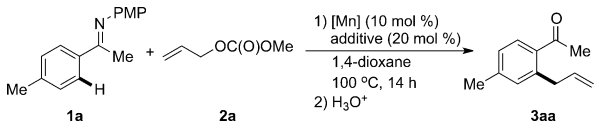
Figure 1. Substitutive C–H allylations by manganese(I) catalysis.

[*] W. Liu, S. C. Richter, Y. Zhang, 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/

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201601560.

We initiated our studies by exploring reaction conditions for the envisioned C–H allylation of the ketimine **1a** with the carbonate **2a** (Table 1). The desired C–H/C–O cleavage[16] failed to proceed in the absence of a manganese catalyst or when employing simple manganese(II) salts, such as $MnCl_2$ and $Mn(OAc)_2$ (entries 1–3). To our delight, $[MnBr(CO)_5]$, was identified as competent catalyst, thus delivering the C–H allylation product **3aa** in 76% yield upon hydrolytic work-up (entry 4). Among a set of co-catalytic additives, carboxylates[17] proved optimal (entries 4–10), with best results accomplished when using the sterically hindered KO_2CMes (entry 10). Likewise, the dimeric complex $[Mn_2(CO)_{10}]$ displayed a considerable catalytic efficacy, with NaOAc being the co-catalytic additive of choice here (entries 11–15). In addition to allyl carbonates, the manganese(I) catalysis proved amenable to allyl phosphates and carbamates.[18]

Table 1: Optimization of C–H allylation with the carbonate **2a**.[a]

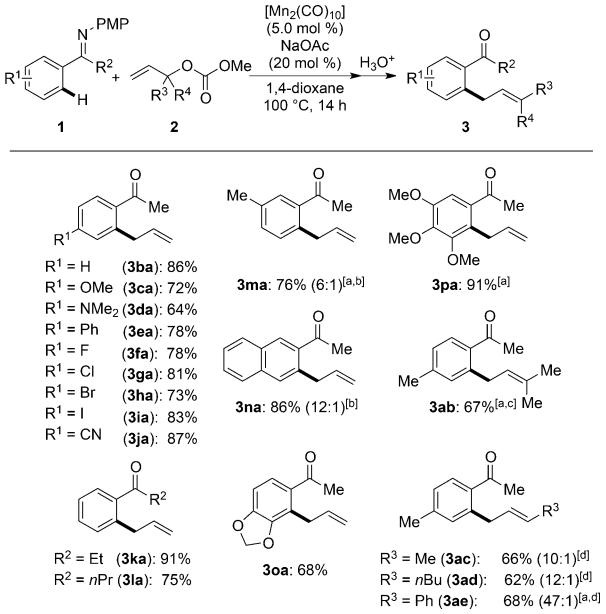


1a 2a 3aa

Entry	Catalyst	Additive	Yield [%][b]
1	–	NaOAc	–
2	$MnCl_2$	NaOAc	–
3	$Mn(OAc)_2$	NaOAc	–
4	$[MnBr(CO)_5]$	NaOAc	76
5	$[MnBr(CO)_5]$	–	11
6	$[MnBr(CO)_5]$	NaOMe	78
7	$[MnBr(CO)_5]$	KOAc	78
8	$[MnBr(CO)_5]$	LiOAc	34
9	$[MnBr(CO)_5]$	NaOPiv	83
10	$[MnBr(CO)_5]$	KO_2CMes	86
11	$[Mn_2(CO)_{10}]$	–	67
12	$[Mn_2(CO)_{10}]$	KO_2CMes	51
13	$[Mn_2(CO)_{10}]$	NaOPiv	75
14	$[Mn_2(CO)_{10}]$	KOAc	81
15	$[Mn_2(CO)_{10}]$	NaOAc	88

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), [Mn] (10 mol%), additive (20 mol%), 1,4-dioxane (1.0 mL), 14 h. [b] Yield of isolated product. Mes = mesityl, Piv = pivaloyl, PMP = 4-methoxyphenyl.

With the optimized catalytic system in hand, we explored its versatility in the carboxylate-assisted manganese(I)-catalyzed C–H allylation of imines **1** with differently substituted electrophiles **2** (Scheme 1). The chemoselectivity of the broadly applicable manganese(I) catalyst was reflected by fully tolerating valuable electrophilic functional groups, such as amino, fluoro, chloro, bromo, iodo, and cyano substituents. The positional selectivity of the C–H allylation process was largely governed by steric interactions (**3ma** and **3na**), with the exception of substrates featuring a *meta* substituent which

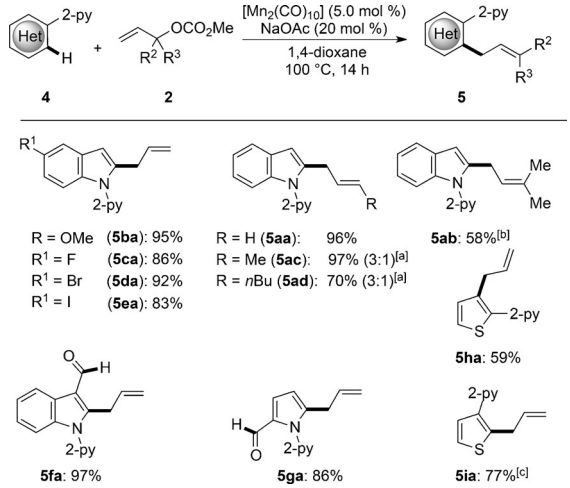


Scheme 1. Manganese(I)-catalyzed C–H allylation of imines **1**. [a] 120 °C. [b] Major regioisomer shown. Regioisomeric ratio given within parentheses. [c] $[Mn_2(CO)_{10}]$ (10 mol %), NaOAc (40 mol %). [d] *E*/*Z* ratio in parentheses.

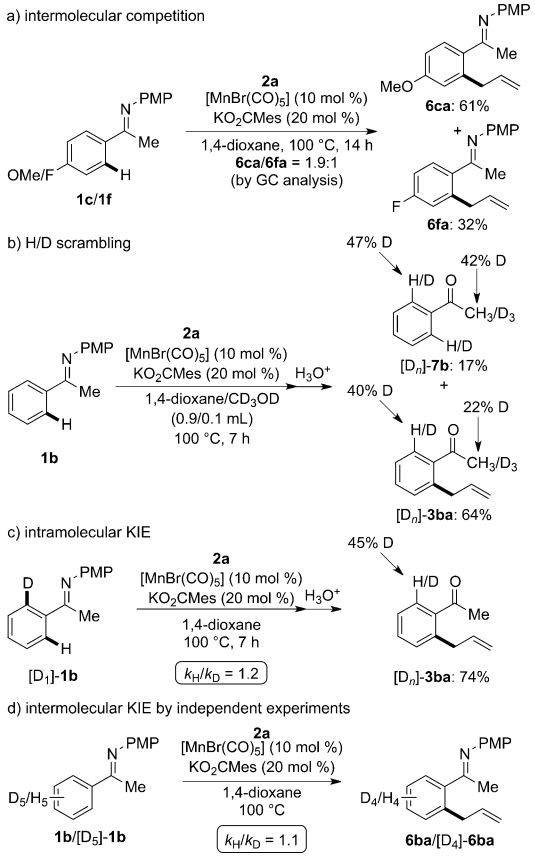
have a secondary directing-group capacity (**3oa**). The robust nature of the manganese(I) catalysis enabled the efficient C–H allylation of the ketimines **1k–l** as well as the challenging use of highly substituted allylic carbonates **2b–e** with excellent levels of diastereocontrol.[19] For all studied C–H allylations, potential double-bond isomerizations to the thermodynamically more stable styrene derivatives were not observed. These findings render the formation of manganese hydride intermediates less likely, thus providing support for an isohypsic, that is, redox-neutral, C–H manganesation mode of action.

The manganese(I)-catalyzed direct C–H allylation by C–H/C–O cleavage was not restricted to arenes **1**. Indeed, biologically relevant indole heterocycles **4**[20] also underwent the step-economical C–H allylation with high catalytic efficacy and ample substrate scope (Scheme 2). The chemoselectivity of the manganese(I)-catalyzed C–H activation set the stage for the high-yielding C–H allylation of the indole **4f** at the heteroaromatic moiety. Thus, the less stable formyl C–H bond remained untouched, again highlighting the organometallic nature of the C–H manganesation process. Notably, the optimized catalytic system was not limited to indole substrates, but also allowed the step-economical C–H allylation of the pyrrole **4g** and thiophenes **4h**,**i**.

In consideration of the unique features of the substitutive manganese(I)-catalyzed C–H allylation, we were interested in delineating the mode of action of the catalyst. To this end, we performed reactions with isotopically labeled substrates (Scheme 3). Hence, we conducted competition experiments and a manganese-catalyzed H–D exchange (Scheme 3a,b), and both observations were in good agreement with a base-assisted electrophilic substitution (BIES) type[21] of C–H activation.[18] In agreement with the latter finding, minor kinetic isotope effects (KIEs) were determined by intra- and



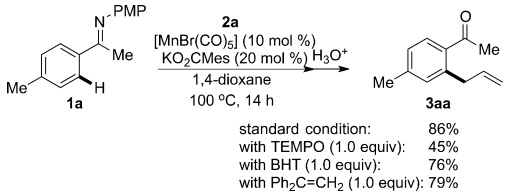
Scheme 2. Manganese(I)-catalyzed C–H allylation of heteroarenes **4**. [a] *E*/*Z* ratio given in parentheses. [b] $[Mn_2(CO)_{10}]$ (10 mol %), NaOAc (40 mol %), 120 °C. [c] The diallylated product **5ia′** (20 %) was also isolated.



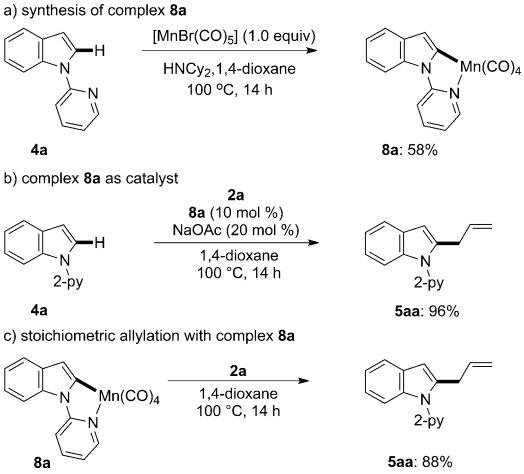
Scheme 3. Key mechanistic findings.

intermolecular (Scheme 3c,d) studies with the isotopically labeled substrates $[D_1]$-**1b** and $[D_5]$-**1b**, respectively. These observations are indicative of a fast C–H manganesation process.

Further evidence for the organometallic activation manifold was gathered by successful manganese(I)-catalyzed C–H functionalizations in the presence of stoichiometric amounts of typical radical scavengers (Scheme 4).



Scheme 4. Support for an organometallic C–H activation mode of action. BHT = 2,6-di-*tert*-butyl-4-methylphenol, and TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical.



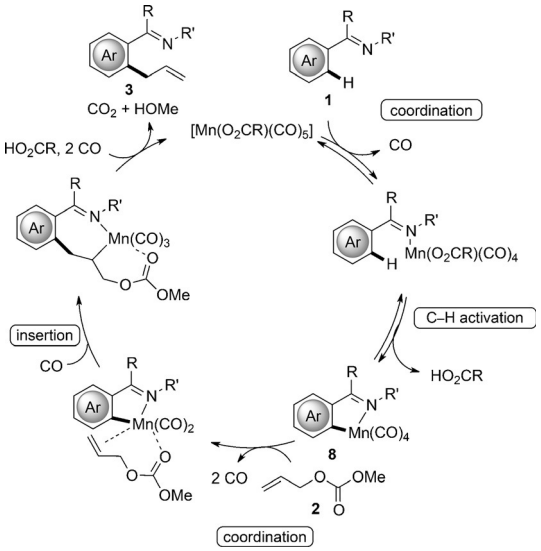
Scheme 5. C–H allylations with cyclometalated complex **8a**.

Subsequently, we independently prepared the cyclometalated complex **8a** by stoichiometric C–H manganesation (Scheme 5a). Notably, the manganese(I) complex **8a** proved to be highly competent in both the catalytic (Scheme 5b) as well as the stoichiometric (Scheme 5c) C–H allylation protocol.

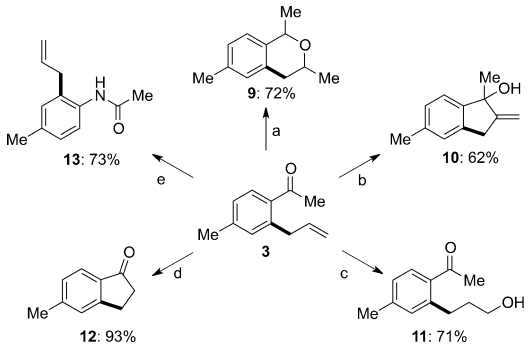
Our mechanistic studies are suggestive of a facile organometallic C–H manganesation by isohypsic carboxylate assistance, along with a subsequent migratory insertion of the electrophile **2** (Scheme 6). Alternatively, the activation of the allyl carbonate **2** could proceed by an oxidative addition. Finally, β-hydride elimination is proposed to liberate the desired product **3**, while decarboxylation and salt metathesis regenerate the catalytically active manganese(I) complex.

The unique transformative power of the manganese(I)-catalyzed C–H functionalization strategy was illustrated by the late-stage diversification[22] of the ketones **3**, thereby offering efficient access to a synthetically useful ether (**9**), indanol (**10**), alcohol (**11**), indanone (**12**), or anilide (**13**; Scheme 7).

In summary, we have reported on the first organometallic manganese(I)-catalyzed substitutive C–H activation for the step-economical allylation of arenes. The optimized manganese(I) catalyst is highly functional-group tolerant and allows C–H functionalizations on synthetically useful heteroarenes with ample scope. Detailed mechanistic studies provide strong support for an organometallic C–H manganesation regime by redox-neutral carboxylate assistance, which proved instrumental for applications to late-stage diversification in a step-economical fashion.



Scheme 6. Proposed catalytic cycle.



Scheme 7. Diversification of C–H activation products. Reagents and conditions: a) 1. $LiAlH_4$, Et_2O, 23 °C, 12 h. 2. KO*t*Bu, NMP, 100 °C, 1 h. b) $AlMe_3$, $[Ni(cod)_2]$ (20 mol%), PCy_3 (20 mol%), THF, 23 °C, 15 min. c) 1. 9-BBN, THF, 23 °C, 24 h. 2. aq. H_2O_2, NaOH, THF, 23 °C, 2 h. d) 1. LDA, TMSCl, THF, −78 °C, 2 h. 2. Grubbs-II (7.0 mol%), PhH, 65 °C, 1.5 h. e) 1. $HONH_2$·HCl, NaOAc, $MeOH/H_2O$, 100 °C, 1 h. 2. cyanuric chloride (5.0 mol%), $ZnCl_2$ (10 mol%), MeCN, 90 °C, 2 h. cod = 1,5-cyclooctadiene, LDA = lithiumdiisopropyl amide, NMP = *N*-methylpyrrolidone, THF = tetrahydrofuran.

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 Chinese Scholarship Program (fellowship to W.L.) is gratefully acknowledged.

Keywords: C–H activation · electrophiles · heteroarenes · manganese · reaction mechanisms

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 7747–7750
Angew. Chem. **2016**, *128*, 7878–7881

[1] Representative recent reviews on C–H activation: a) J. K. Kim, K. Shin, S. Chang, *Top. Organomet. Chem.* **2016**, *55*, 29–51; b) J. Li, L. Ackermann, *Nat. Chem.* **2015**, *7*, 686–687; 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) G. Song, X. Li, *Acc. Chem. Res.* **2015**, *48*, 1007 – 1020; f) N. Kuhl, N. Schroeder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443 – 1460; g) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74 – 100; *Angew. Chem.* **2014**, *126*, 76 – 103; h) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208 – 1219; i) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726 – 11743; *Angew. Chem.* **2013**, *125*, 11942 – 11959; j) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215 – 1292; k) Y. Kuninobu, K. Takai, *Chem. Rev.* **2011**, *111*, 1938 – 1953; l) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212 – 11222; m) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242 – 3272; n) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792 – 9826; *Angew. Chem.* **2009**, *121*, 9976 – 10011; o) R. G. Bergman, *Nature* **2007**, *446*, 391 – 393, and references therein.

[2] a) Y. Kuninobu, S. Suekia, *Synthesis* **2015**, 3823 – 3845; b) L. G. Mercier, M. Leclerc, *Acc. Chem. Res.* **2013**, *46*, 1597 – 1605; c) D. J. Schipper, K. Fagnou, *Chem. Mater.* **2011**, *23*, 1594 – 1600.

[3] L. Ackermann, *Org. Process Res. Dev.* **2015**, *18*, 260 – 269.

[4] J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960 – 9009; *Angew. Chem.* **2012**, *124*, 9092 – 9142.

[5] For selected examples of precious metal-catalyzed allylations by hydroarylations of allenes, see: a) S. Nakanowatari, L. Ackermann, *Chem. Eur. J.* **2015**, *21*, 16246 – 16251; b) B. Ye, N. Cramer, *J. Am. Chem. Soc.* **2013**, *135*, 636 – 639; c) H. Wang, B. Beiring, D. G. Yu, K. D. Collins, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 12430 – 12434; *Angew. Chem.* **2013**, *125*, 12657 – 12661; d) R. Zeng, C. Fu, S. Ma, *J. Am. Chem. Soc.* **2012**, *134*, 9597 – 9600; e) Y. J. Zhang, E. Skucas, M. J. Krische, *Org. Lett.* **2009**, *11*, 4248 – 4250.

[6] Reviews on the use of inexpensive first-row transition-metal catalysts for C–H functionalization: a) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498 – 525; 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. A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087 – 4109.

[7] Selected recent examples of outer-sphere activation: a) W. Liu, J. T. Groves, *Angew. Chem. Int. Ed.* **2013**, *52*, 6024 – 6027; *Angew. Chem.* **2013**, *125*, 6140 – 6143; b) J. J. Dong, D. Unjaroen, F. Mecozzi, E. C. Harvey, P. Saisaha, D. Pijper, J. W. de Boer, P. Alsters, B. L. Feringa, W. R. Browne, *ChemSusChem* **2013**, *6*, 1774 – 1778; c) W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard III, J. T. Groves, *Science* **2012**, *337*, 1322 – 1325; d) X. Wu, M. S. Seo, K. M. Davis, Y.-M. Lee, J. Chen, K.-B. Cho, Y. N. Pushkar, W. Nam, *J. Am. Chem. Soc.* **2011**, *133*, 20088 – 20091; e) W. Liu, J. T. Groves, *J. Am. Chem. Soc.* **2010**, *132*, 12847 – 12849; f) J. F. Hull, D. Balcells, E. L. O. Sauer, C. Raynaud, G. W. Brudvig, R. H. Crabtree, O. Eisenstein, *J. Am. Chem. Soc.* **2010**, *132*, 7605 – 7616; g) S. Das, C. D. Incarvito, R. H. Crabtree, G. W. Brudvig, *Science* **2006**, *312*, 1941 – 1943, and references therein.

[8] C. Wang, *Synlett* **2013**, 1606 – 1613.

[9] a) S. Sueki, Z. Wang, Y. Kuninobu, *Org. Lett.* **2016**, *18*, 304 – 307; b) Y. Kuninobu, Y. Nishina, T. Takeuchi, K. Takai, *Angew. Chem. Int. Ed.* **2007**, *46*, 6518 – 6520; *Angew. Chem.* **2007**, *119*, 6638 – 6640.

[10] a) B. Zhou, Y. Hu, C. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 13659 – 13663; *Angew. Chem.* **2015**, *127*, 13863 – 13867; b) B. Zhou, P. Ma, H. Chen, C. Wang, *Chem. Commun.* **2014**, *50*, 14558 – 14561; c) R. He, Z.-T. Huang, Q.-Y. Zheng, C. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4950 – 4953; *Angew. Chem.* **2014**, *126*, 5050 – 5053; d) B. Zhou, H. Chen, C. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 1264 – 1267.

[11] a) W. Liu, D. Zell, M. John, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 4092 – 4096; *Angew. Chem.* **2015**, *127*, 4165 – 4169; b) W. Liu, J. Bang, Y. Zhang, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 14137 – 14140; *Angew. Chem.* **2015**, *127*, 14343 – 14346.

[12] L. Shi, X. Zhong, H. She, Z. Lei, F. Li, *Chem. Commun.* **2015**, *51*, 7136 – 7139.

[13] L. Ackermann, *J. Org. Chem.* **2014**, *79*, 8948 – 8954.

[14] For C–H allylations with metals other than manganese, see: a) C. Feng, D. Feng, T. P. Loh, *Chem. Commun.* **2015**, *51*, 342 – 345; b) G. Cera, T. Haven, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 1484 – 1488; *Angew. Chem.* **2016**, *128*, 1506 – 1510; c) 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; d) N. Barsu, D. Kalsi, B. Sundararaju, *Chem. Eur. J.* **2015**, *21*, 9364 – 9368; e) L. Ackermann, M. Moselage, N. Sauermann, J. Koeller, W. Liu, D. Gelman, *Synlett* **2015**, 1596 – 1600; f) D. G. Yu, T. Gensch, F. de Azambuja, S. Vasquez-Cespedes, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17722 – 17725; g) S. Yu, X. Li, *Org. Lett.* **2014**, *16*, 1200 – 1203; h) M. Kim, S. Sharma, N. K. Mishra, S. Han, J. Park, M. Kim, Y. Shin, J. H. Kwak, S. H. Han, I. S. Kim, *Chem. Commun.* **2014**, *50*, 11303 – 11306; i) S. Asako, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2013**, *135*, 17755 – 17757; j) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2013**, *135*, 5308 – 5311; k) H. Wang, N. Schroder, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 5386 – 5389; *Angew. Chem.* **2013**, *125*, 5495 – 5499; l) Y. Makida, H. Ohmiya, M. Sawamura, *Angew. Chem. Int. Ed.* **2012**, *51*, 4122 – 4127; *Angew. Chem.* **2012**, *124*, 4198 – 4203; m) S. Fan, F. Chen, X. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 5918 – 5923; *Angew. Chem.* **2011**, *123*, 6040 – 6045; n) Y. Kuninobu, K. Ohta, K. Takai, *Chem. Commun.* **2011**, *47*, 10791 – 10793; o) T. Yao, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2011**, *50*, 2990 – 2299; *Angew. Chem.* **2011**, *123*, 3046 – 3050; p) S. Oi, Y. Tanaka, Y. Inoue, *Organometallics* **2006**, *25*, 4773 – 4778, and references therein.

[15] Review on C–H alkylations: L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866 – 4877.

[16] A review: S. I. Kozhushkov, H. K. Potukuchi, L. Ackermann, *Catal. Sci. Technol.* **2013**, *3*, 562 – 571.

[17] L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 – 1345.

[18] For detailed information see the Supporting Information.

[19] Under otherwise identical reaction conditions, the use of the allyl carbonates **2** bearing disubstituted alkenes gave unsatisfactory results.

[20] Selected reviews on the preparation and functionalization of indoles: a) B. Zhang, A. Studer, *Chem. Soc. Rev.* **2015**, *44*, 3505 – 3521; b) M. Bandini, *Org. Biomol. Chem.* **2013**, *11*, 5206 – 5212; c) M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29 – 41; d) K. Krüger née Alex, A. Tillack, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2153 – 2167; e) L. Ackermann, *Synlett* **2007**, 507 – 526; f) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875 – 2911, and references therein.

[21] a) R. Mei, J. Loup, L. Ackermann, *ACS Catal.* **2016**, *6*, 498 – 525; b) W. Ma, R. Mei, G. Tenti, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 15248 – 15251.

[22] J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369 – 375.

Received: February 13, 2016
Published online: April 20, 2016

