C–C Activation

International Edition: DOI: 10.1002/anie.201701231
German Edition: DOI: 10.1002/ange.201701231

Ruthenium(II)-Catalyzed C–C Arylations and Alkylations: Decarbamoylative C–C Functionalizations

*Marc Moselage[+], Jie Li[+], Frederik Kramm, and Lutz Ackermann**

Abstract: *Ruthenium(II)biscarboxylate catalysis enabled selective C–C functionalizations by means of decarbamoylative C–C arylations. The versatility of the ruthenium(II) catalysis was reflected by widely applicable C–C arylations and C–C alkylations of aryl amides, as well as acids with modifiable pyrazoles, through facile organometallic C–C activation.*

The recent progress in C–H activation chemistry has arguably revolutionized the way in which molecular synthesis is conducted.[1] In sharp contrast, selective functionalizations of otherwise inert C–C σ-bonds continue to be scarce,[2] with notable recent progress achieved by ruthenium(II) catalysis.[3] In spite of undisputable advances, ruthenium-catalyzed C–C activations are thus far largely restricted to decarboxylation[4] manifolds being devoid of *ipso*-C–C functionalization. Within our ongoing program on ruthenium(II)-catalyzed[5] step-economical diversifications,[6] we have identified reaction conditions for the first ruthenium-catalyzed[7] decarbamoylative C–C functionalization, on which we report herein. Notable features of our findings are not limited to 1) versatile ruthenium(II)-catalyzed decarbamoylative C–C arylations, 2) expedient C–C arylations and C–C alkylations on modifiable[8] pyrazoles, as well as 3) detailed mechanistic insights into organometallic C–C cleavage reactions (Figure 1).

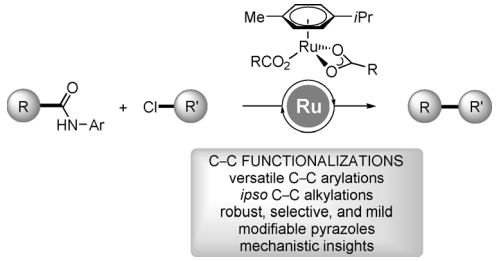
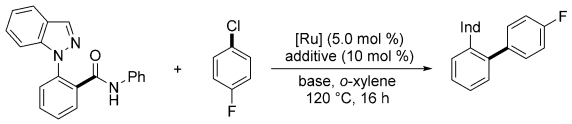


Figure 1. C–C functionalizations by ruthenium(II) catalysis.

Table 1: Ruthenium(II)-catalyzed decarbamoylative C–C arylation.[a]



1a 2a 3aa

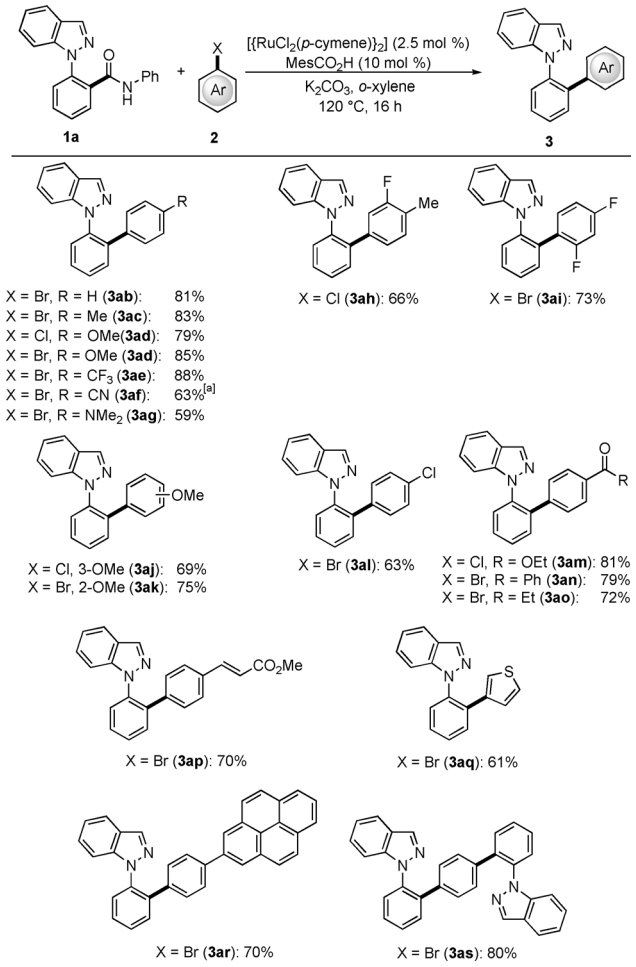
Entry	[Ru]	Additive	Base	Yield [%]
1	$[\{RuCl_2(p\text{-cymene})\}_2]$	$MesCO_2H$	KOAc	5
2	$[\{RuCl_2(p\text{-cymene})\}_2]$	PPh_3	K_2CO_3	–
3	$[\{RuCl_2(p\text{-cymene})\}_2]$	PCy_3	K_2CO_3	–
4	$[\{RuCl_2(p\text{-cymene})\}_2]$	AcOH	K_2CO_3	5
5	$[\{RuCl_2(p\text{-cymene})\}_2]$	$PhCO_2H$	K_2CO_3	51
6	$[\{RuCl_2(p\text{-cymene})\}_2]$	1-$AdCO_2H$	K_2CO_3	64
7	$[\{RuCl_2(p\text{-cymene})\}_2]$	$MesCO_2H$	Na_2CO_3	38
8	$[\{RuCl_2(p\text{-cymene})\}_2]$	$MesCO_2H$	Cs_2CO_3	66
9	**$[\{RuCl_2(p\text{-cymene})\}_2]$**	**$MesCO_2H$**	**K_2CO_3**	**78**
10	**$[Ru(O_2CMes)_2(p\text{-cymene})]$ (4)**	**–**	**K_2CO_3**	**71**
11	$[\{RuCl_2(p\text{-cymene})\}_2]$	$MesCO_2H$	K_2CO_3	75[b]
12	$[Ru_3(CO)_{12}]$	—	K_2CO_3	–
13	$RuCl_3\cdot(H_2O)_n$	$MesCO_2H$	K_2CO_3	–
14	$[\{RuCl_2(p\text{-cymene})\}_2]$	–	K_2CO_3	11
15	–	$MesCO_2H$	K_2CO_3	–
16	$[\{RuCl_2(p\text{-cymene})\}_2]$	$MesCO_2H$	–	–

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), [Ru] (5.0 mol%), additive (10 mol%), *o*-xylene (0.5 mL), 120 °C, 16 h. [b] Under microwave irradiation at 200 W for 30 min. Ad = adamantyl, Ind = *N*-indazolyl.

Our studies were initiated by probing various reaction conditions for the envisioned C–C functionalization of the indazolyl (Ind) amide **1a** with the aryl chloride **2a** (Table 1; see Table S1 in the Supporting Information). We were pleased to observe that $[\{RuCl_2(p\text{-cymene})\}_2]$ enabled the desired C–C arylation, however with low efficacy when using KOAc as the base (entry 1). A careful interrogation of additives and bases revealed $MesCO_2H$ and K_2CO_3 to be optimal (entries 2–9). Likewise, the well-defined complex $[Ru(O_2CMes)_2(p\text{-cymene})]$ (**4**)[9] proved to be active as a user-friendly single-component catalyst (entry 10). It is also noteworthy that the C–C arylation could be performed by means of microwave irradiation, thus furnishing the C–C arylation product within only 30 minutes (entry 11). Reactions conducted with other typical ruthenium sources, such as $[Ru_3(CO)_{12}]$[3f] or $RuCl_3\cdot(H_2O)_n$, failed to give any conversion of the substrate **1a** (entries 12 and 13). Further, control experiments verified the essential role of the base, the additive, and the ruthenium catalyst (entries 14–16).

With the optimized ruthenium(II) catalyst in hand, we tested its versatility in the C–C arylation of **1a** with a representative set of aryl halides (**2**; Scheme 1). Thus, we were delighted to observe that aryl bromides, as well as more challenging aryl chlorides, proved to be viable substrates in the C–C functionalization process. The remarkable chemo-

[*] M. Moselage,[+] Dr. J. Li,[+] F. Kramm, 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://ackermann.chemie.uni-goettingen.de
[+] These authors contributed equally to this work.
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201701231.

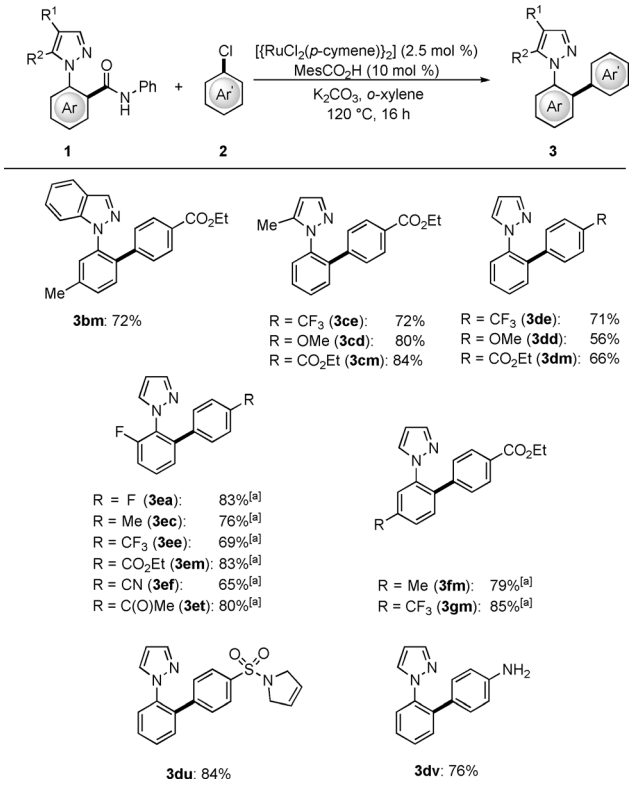


Scheme 1. Decarbamoylative C–C arylation with the aryl halides **2**. [a] [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %).

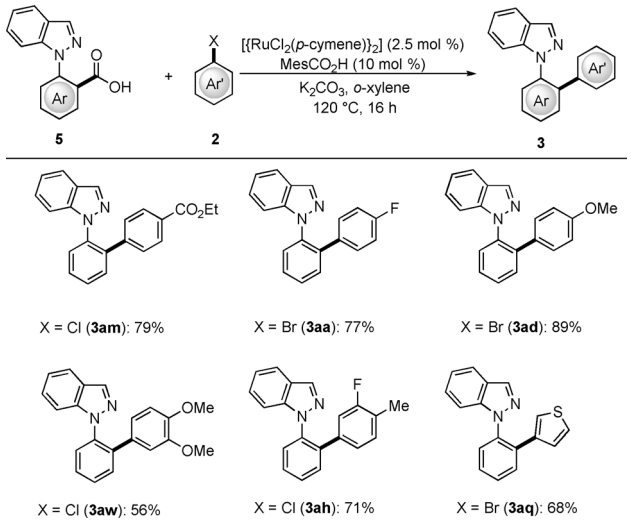
selectivity of the ruthenium(II) catalyst was reflected by fully tolerating valuable functional groups, including nitriles, amines, halides, activated alkenes, esters, and enolazible ketones, in either the *ortho*-, *meta*-, or *para*-position. The widely applicable ruthenium(II) biscarboxylate catalyst proved effective for the conversion of both electron-deficient as well as electron-rich, thus deactivated, aryl halides. Hence, the direct introduction of either heteroarenes (**3aq**) or the fluorescent pyrene motif (**3ar**) was enabled. The twofold C–C activation also proved viable to furnish the product **3as**.

Thereafter, we explored the scope of amenable pyrazoyl-substituted arenes **1** in the C–C arylation regime (Scheme 2). Here, the site selectivity of an intramolecular competition experiment with the *meta*-substituted arene **1b** was guided by repulsive steric interactions. In addition, various pyrazolyl-substituted arenes delivered the desired products **3** with excellent mono-selectivity. The outstanding robustness of the ruthenium C–C activation catalyst was reflected by fully tolerating, among others, cyano or free NH_2 amino functional groups.

The widely applicable ruthenium(II) catalysis regime was not restricted to C–C cleavages with amides **1**. Indeed, decarboxylative C–C arylations proved to be viable under otherwise identical reaction conditions (Scheme 3). In contrast to recently reported protocols,[3a–d] the arylation did not occur at the *ortho*-position, but instead with *ipso*-selectivity. It is noteworthy that the decarboxylative C–C functionalization was viable in the absence of either copper(II) or silver(I) salts, which are typically required for either palladium- or rhodium-catalyzed decarboxylative transformations.[10] Generally, the versatile ruthenium(II) biscarboxylate catalyst allowed C–C arylation with aryl bromides and demanding chlorides.

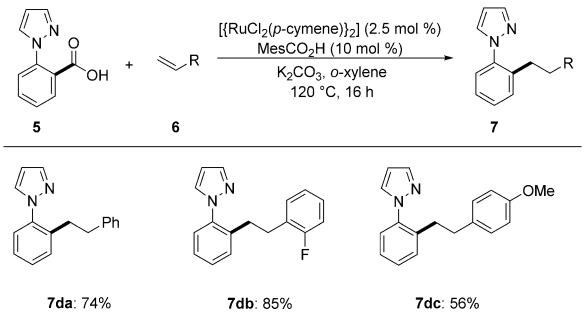


Scheme 2. Decarbamoylative C–C arylation of the arenes **1**. [a] **1** (0.20 mmol), **2a** (0.50 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol %), PhMe (1.0 mL), 120 °C, 18 h.



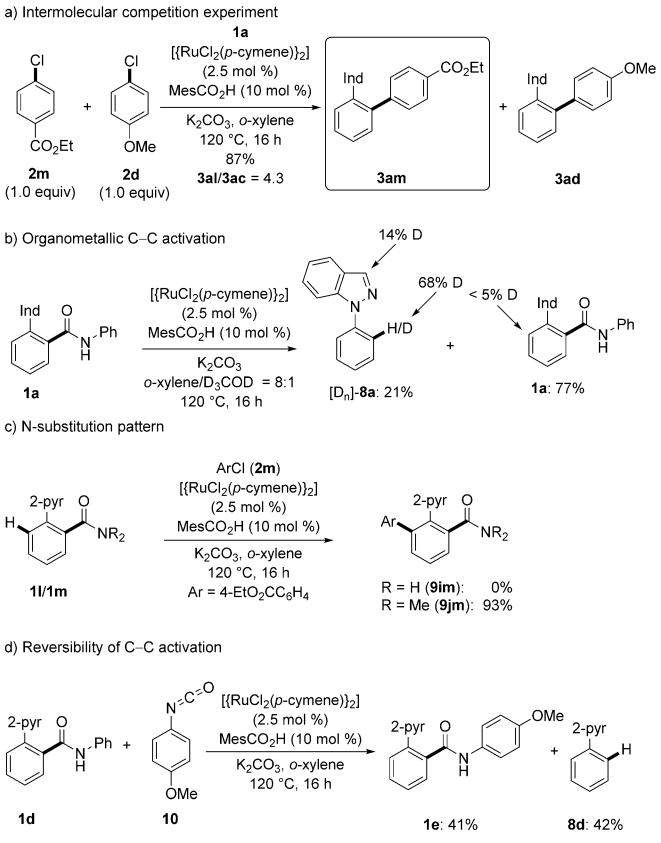
Scheme 3. Decarboxylative C–C arylation with the aromatic acids **5**.

The power of the ruthenium(II)-catalyzed C–C functionalization approach was further illustrated by enabling efficient C–C alkylations when using the alkenes **6**,[11] thereby selectively delivering the monoalkylated products **7** (Scheme 4).



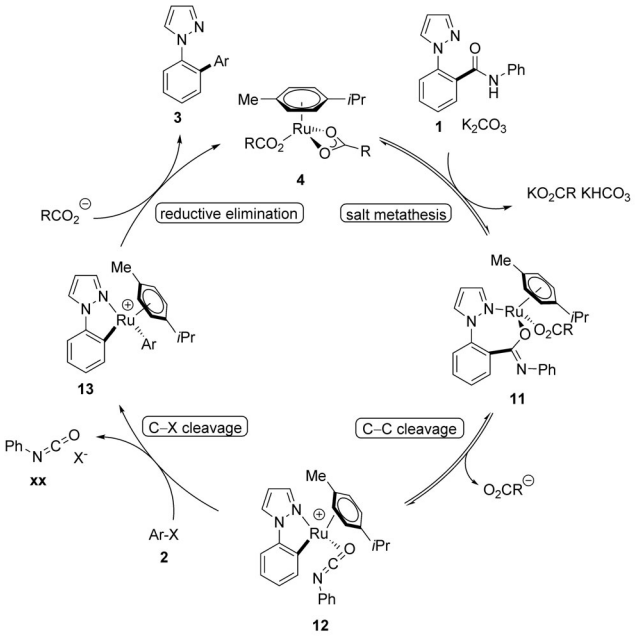
Scheme 4. Ruthenium-catalyzed C–C alkylation.

Given the unique features of the ruthenium(II)-catalyzed C–C functionalization, we became intrigued in unravelling its mode of action. To this end, we first performed competition experiments using an electron-deficient aryl halide **2**, which is inherently more reactive (Scheme 5a). Second, reactions performed in the presence of BHT and TEMPO led to partial and complete inhibition, respectively, of the catalytic activity.[12] Third, C–C arylations with the isotopically labelled cosolvent $[D_4]$MeOH delivered the partially deuterated arene $[D_n]$**8a**, thus providing strong support for the organometallic nature of the C–C cleavage step (Scheme 5b). Fourth, variation of the N-substitution pattern was probed. Thus, the NH_2 amide **1l** failed to give any arylation product, whereas an intramolecular competition with the tertiary amide **1m** solely led to C–H arylation (Scheme 5c). These observations highlight the importance of a deprotonatable N–H bond to initiate the decarbamoylative C–C cleavage. Fifth, the use of the isocyanate[13] **10** provided evidence for a facile reversible C–C metalation.



Scheme 5. Summary of key mechanistic findings.

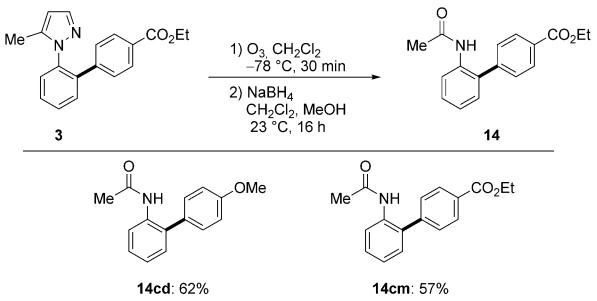
On the basis of our mechanistic findings we propose a plausible catalytic cycle to commence with a rapid organometallic C–C cleavage induced by the formation of the ruthenium(II) complex **11** (Scheme 6). Thereafter, the activation of the C–Hal bond occurs by the action of the intermediate **12**, arguably through an SET-type (SET = single-electron transfer) process. Finally, reductive elimination delivers the C–C arylation product **3**, while regenerating the catalytically active ruthenium(II) catalyst **4**.



Scheme 6. Proposed catalytic cycle for the ruthenium-catalyzed C–C arylation.

Finally, the synthetic utility of the ruthenium(II)-catalyzed C–C activation strategy was illustrated by the successful late-stage diversification by ozonolysis[14] to provide access to the arylated anilides **14** (Scheme 7).

In summary, we have reported on the unprecedented ruthenium-catalyzed decarbamoylative σ-C–C arylation. Hence, a versatile ruthenium(II) catalyst enabled efficient decarbamoylative C–C arylations with modifiable pyrazoles as well as *ipso*-C–C arylations and alkylations of benzoic acids. Mechanistic studies provided strong support for an organometallic mode of action through facile C–C cleavage.



Scheme 7. Facile access to the biarylanilides **14**.

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 Council (fellowship to J.L.) is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amides · arylation · C–C activation · reaction mechanisms · ruthenium

[1] a) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053 – 1064; b) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726 – 11743; *Angew. Chem.* **2013**, *125*, 11942 – 11959; c) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212 – 11222; d) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242 – 3272; e) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792 – 9826; *Angew. Chem.* **2009**, *121*, 9976 – 10011; f) R. G. Bergman, *Nature* **2007**, *446*, 391 – 393, and references therein.

[2] For reviews, see: a) G. Fumagalli, S. Stanton, J. F. Bower, *Chem. Rev.* **2017**, DOI: 10.1021/acs.chemrev.6b00599; b) M. Murakami, N. Ishida, *J. Am. Chem. Soc.* **2016**, *138*, 13759 – 13769; c) E. T. C. Vogt, B. M. Weckhuysen, *Chem. Soc. Rev.* **2015**, *44*, 7342 – 7370; d) L. Souillart, N. Cramer, *Chem. Rev.* **2015**, *115*, 9410 – 9464; e) T. Xu, A. Dermenci, G. Dong, *Top. Curr. Chem.* **2014**, *346*, 233 – 257; f) F. Chen, T. Wang, N. Jiao, *Chem. Rev.* **2014**, *114*, 8613 – 8661; g) M. Murakami, T. Matsuda, *Chem. Commun.* **2011**, *47*, 1100 – 1105; h) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem. Int. Ed.* **2011**, *50*, 7740 – 7752; *Angew. Chem.* **2011**, *123*, 7884 – 7896; i) C.-H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610 – 618; For a pioneering report, see: j) M. Murakami, H. Amii, Y. Ito, *Nature* **1994**, *370*, 540 – 541; for examples of C–C activation by means of rhodium catalysis, see: k) T. Matsuda, K. Kato, T. Goya, S. Shimada, M. Murakami, *Chem. Eur. J.* **2016**, *22*, 1941 – 1943; l) L. Deng, T. Xu, H. Li, G. Dong, *J. Am. Chem. Soc.* **2016**, *138*, 369 – 374; m) X. Zhou, G. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 13715 – 13721; n) R. Zeng, G. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 1408 – 1411; o) A. Yada, S. Fujita, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 7217 – 7220; p) H. M. Ko, G. Dong, *Nat. Chem.* **2014**, *6*, 739 – 744; q) N. Ishida, W. Ikemoto, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 5912 – 5915; r) L. Souillart, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 9640 – 9644; *Angew. Chem.* **2014**, *126*, 9794 – 9798; s) L. Souillart, E. Parker, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 3001 – 3005; *Angew. Chem.* **2014**, *126*, 3045 – 3049; t) L. Souillart, N. Cramer, *Chem. Sci.* **2014**, *5*, 837 – 840; u) N. Ishida, S. Sawano, Y. Masuda, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 17502 – 17504; v) T. Seiser, N. Cramer, *J. Am. Chem. Soc.* **2010**, *132*, 5340 – 5341; w) L. Liu, N. Ishida, M. Murakami, *Angew. Chem. Int. Ed.* **2012**, *51*, 2485 – 2488; *Angew. Chem.* **2012**, *124*, 2535 – 2538, and references therein.

[3] a) J. Zhang, R. Shrestha, J. F. Hartwig, P. Zhao, *Nat. Chem.* **2016**, *8*, 1144 – 1151; b) A. Biafora, T. Krause, D. Hackenberger, F. Belitz, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2016**, *55*, 14752 – 14755; *Angew. Chem.* **2016**, *128*, 14972 – 14975; c) L. Huang, A. Biafora, G. Zhang, V. Bragoni, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2016**, *55*, 6933 – 6937; *Angew. Chem.* **2016**, *128*, 7047 – 7051; d) N. Y. P. Kumar, A. Bechtoldt, K. Raghuvanshi, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 6929 – 6932; *Angew. Chem.* **2016**, *128*, 7043 – 7046; e) T. Ueyama, S. Mochida, T. Fukutani, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 706 – 708; f) N. Chatani, Y. Ie, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1999**, *121*, 8645 – 8646.

[4] a) J. Cornella, I. Larrosa, *Synthesis* **2012**, 653 – 676; b) N. Rodríguez, L. J. Goossen, *Chem. Soc. Rev.* **2011**, *40*, 5030 – 5048.

[5] For selected reviews on ruthenium(II)-catalyzed C–H functionalizations, see: a) V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun.* **2014**, *50*, 29 – 39; b) B. Li, P. H. Dixneuf, *Chem. Soc. Rev.* **2013**, *42*, 5744 – 5767; c) L. Ackermann, R. Vicente, *Top. Curr. Chem.* **2010**, *292*, 211 – 229, and references therein.

[6] L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281 – 295.

[7] For an elegant palladium-catalyzed process that yields multiple-arylated heteroarenes, see: a) T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286 – 5287; See also: b) C. Li, P. Li, J. Yang, L. Wang, *Chem. Commun.* **2012**, *48*, 4214 – 4216; c) S. Zhao, Y.-J. Liu, S.-Y. Yan, F.-J. Chen, Z.-Z. Zhang, B.-F. Shi, *Org. Lett.* **2015**, *17*, 3338 – 3341.

[8] a) F. Zhang, D. R. Spring, *Chem. Soc. Rev.* **2014**, *43*, 6906 – 6919; b) G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450 – 2494; *Angew. Chem.* **2011**, *123*, 2498 – 2543.

[9] a) L. Ackermann, R. Vicente, H. K. Potukuchi, V. Pirovano, *Org. Lett.* **2010**, *12*, 5032 – 5035; a review: b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 – 1345.

[10] M. Pichette Drapeau, L. J. Gooßen, *Chem. Eur. J.* **2016**, *22*, 18654 – 18677.

[11] Under otherwise identical reaction conditions, alkyl-substituted alkenes have, thus far, given less satisfactory results.

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

[13] a) K. Muralirajan, K. Parthasarathy, C.-H. Cheng, *Org. Lett.* **2012**, *14*, 4262 – 4265; b) S. De Sarkar, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 13932 – 13936.

[14] C. Kashima, S. Hibi, T. Maruyama, K. Harada, Y. Omote, *J. Heterocycl. Chem.* **1987**, *24*, 637 – 639.

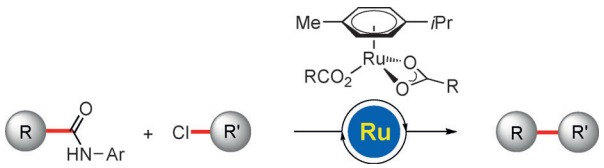
Manuscript received: February 3, 2017
Final Article published: ■■ ■■, ■■■■

Communications

C–C Activation

M. Moselage, J. Li, F. Kramm, L. Ackermann* ——— ■■■■–■■■■

Ruthenium(II)-Catalyzed C–C Arylations and Alkylations: Decarbamoylative C–C Functionalizations



Amid the methods: Amide σ-C–C arylations were accomplished by versatile ruthenium(II) carboxylate decarbamoylative catalysis, which enabled decarboxylative *ipso* C–C alkylations by facile organometallic C–C cleavage. The method is versatile, robust, and mild, and mechanistic insights are discussed.