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Distal Weak Coordination of Acetamides in Ruthenium(II)-Catalyzed C–H Activation Processes

Qingqing Bu,[+] Torben Rogge,[+] Vladislav Kotek, and Lutz Ackermann*

Abstract: C–H activations with challenging arylacetamides were accomplished by versatile ruthenium(II) biscarboxylate catalysis. The distal C–H functionalization was characterized by ample scope, including twofold oxidative C–H functionalizations and alkyne hydroarylations, through facile base-assisted internal electrophilic-type substitution (BIES) C–H ruthenation by weak *O*-coordination.

Substituted acetamides are key structural motifs in a plethora of bioactive compounds, drugs and crop protection agents (Figure 1). For instance, atenolol is a selective β_1-receptor antagonist primarily used for cardiovascular diseases,[1] while 1-naphthaleneacetamide serves as auxin for rooting hormone.[2] As a consequence, there is a continued strong demand for general strategies that provide access to substituted arylacetamides in a sustainable fashion.

In recent years, catalyzed C–H activation has emerged as a transformative tool for molecular syntheses.[3] While direct functionalizations of simple benzamides have thus been accomplished,[4] C–H activations of distal weakly-coordinating acetamides *via* unfavorable six-membered metalacycles continue to be scarce, with pioneering contributions by *inter alia* Yu, Maiti and Dong in palladium catalysis.[5,6] Despite of undisputable recent progress by versatile, less expensive[7a] ruthenium catalysis,[7] C–H functionalizations of challenging arylacetamides have thus far proven elusive, which is largely due to the tautomerizable nature of the distal *O*-coordinating acetamides.

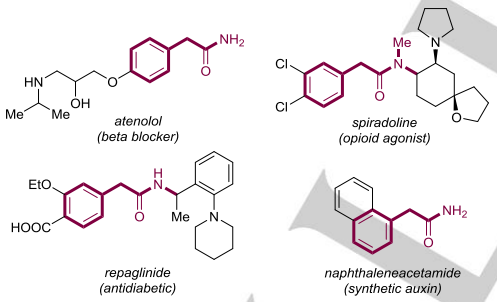
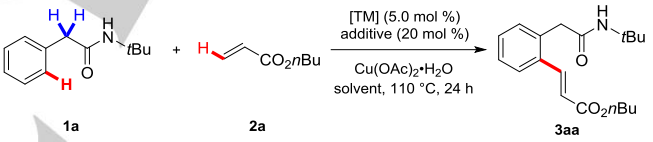


Figure 1. Selected bioactive compounds featuring arylacetamides.

Within our program on cost-effective C–H activation,[8] we have now developed uniquely effective oxidative C–H alkenylations[9] of weakly coordinating acetamides, on which we report herein. Notable features of our approach include (i) efficient C–H activation of challenging arylacetamides by ruthenium(II) catalysis, (ii) ample substrate scope with tertiary, secondary and primary amides, (iii) step- and atom-economical alkyne hydroarylations,[10] and (iv) key mechanistic insights by detailed experimental and computational studies.

We initiated our studies by probing various reaction parameters for the envisioned oxidative C–H olefination of challenging arylacetamide **1a** (Table 1). We were pleased to observe that cationic ruthenium(II) carboxylate[11a] complexes that were generated *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and $Cu(OAc)_2{\bullet}H_2O$ displayed outstanding performance. Biomass-derived γ-valerolactone (GVL)[11b] and THF emerged as the optimal solvents (entries 1-8). It is noteworthy that typical rhodium, iridium and cobalt catalysts delivered less satisfactory results (entries 9–11).

Table 1. Development of oxidative C–H alkenylation of acetamide **1a**.[a]



1a + **2a** → **3aa**

Entry	[TM]	Additive	Solvent	Yield [%]
1	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DCE	13
2	$[Ru_3(CO)_{12}]$	—	THF	—
3	$[RuCl_2(p\text{-cymene})]_2$	—	THF	—
4	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	DMA	—
5	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	MeCN	—
6	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	*t*AmOH	72
7	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	GVL	73
8	**$[RuCl_2(p\text{-cymene})]_2$**	**$AgSbF_6$**	**THF**	**84**
9	$[Cp^*RhCl_2]$	$AgSbF_6$	THF	74
10	$[Cp^*IrCl_2]$	$AgSbF_6$	THF	30
11	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	THF	—

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), [TM] (5.0 mol %), additive (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.0 mmol), solvent (2.0 mL), 110 °C, 24 h, yields of isolated products.

With the optimized ruthenium(II) catalyst in hand, we explored its scope in the C–H olefination by distal *O*-acetamide

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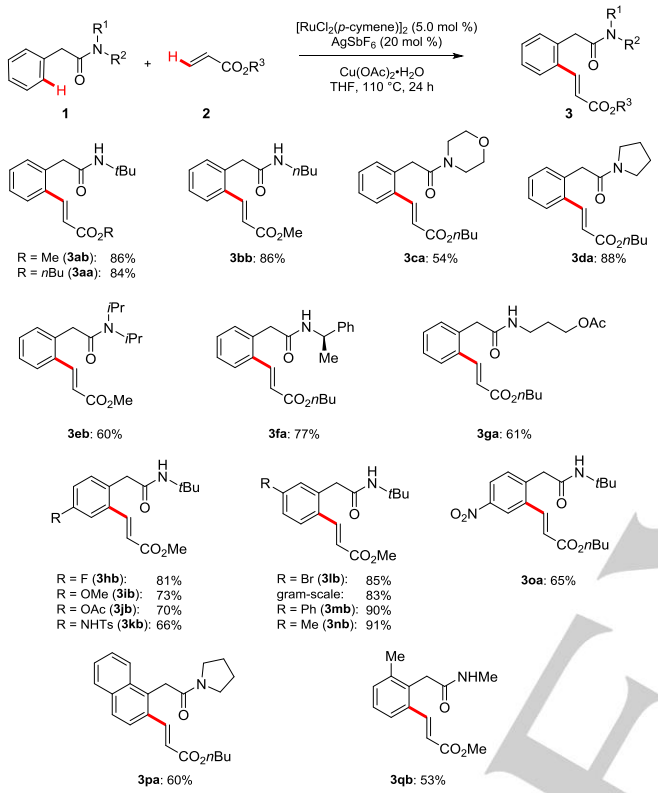
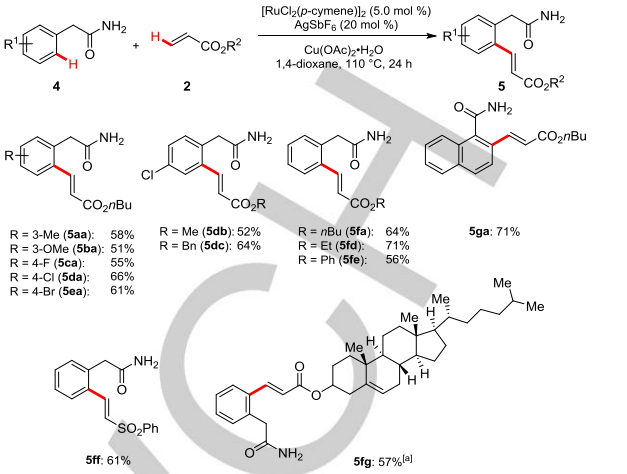
10.1002/anie.201711108

assistance, first exploring the influence of the arene substitution pattern (Scheme 1). Thus, both electron-donating and electron-withdrawing substituents were smoothly accommodated in the oxidative C–H alkenylation. The robustness of the ruthenium(II) catalysis was reflected by an excellent chemo-selectivity, tolerating valuable electrophilic groups, such as bromo or nitro substituents, racemization-free conditions, and the gram-scale synthesis of product **3lb**.



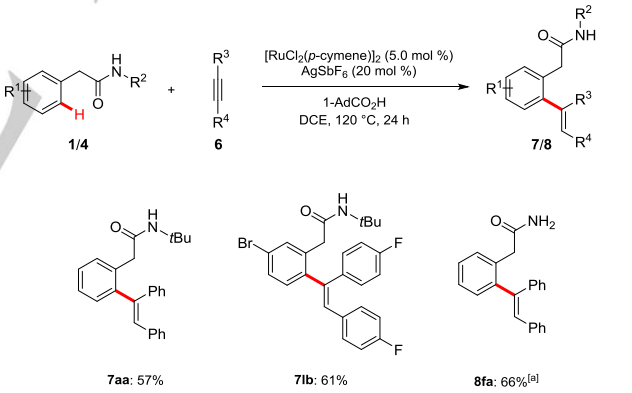
Scheme 1. C–H alkenylation of secondary and tertiary acetamides **1**.

The versatile ruthenium(II) catalyst was not limited to secondary and tertiary acetamides **1**. Indeed, we were pleased to identify more challenging primary amides **4** as viable substrates in the oxidative C–H alkenylation likewise (Scheme 2). Here, the ruthenium(II) catalyst was characterized by high chemo-selectivity, highlighting aryl chlorides and bromides as well as the sensitive cholesteryl moiety.



Scheme 2. Oxidative C–H alkenylation of primary amides **4**. [a] 120 °C, 1,4-dioxane/PhMe (9:1).

Intrigued by the versatility of the ruthenium(II) carboxylate catalysis, we became attracted by C–H alkenylations through redox-neutral alkyne hydroarylations. By simply switching the carboxylate source from $Cu(OAc)_2 \cdot H_2O$ to 1-$AdCO_2H$ the desired C–H addition onto alkynes **6** proved viable (Table S1 in the SI[12] and Scheme 3). Thereby, the ruthenium(II)-catalyzed C–H activation provided a complementary diastereo-selectivity in accessing tri-substituted alkenes **7** and **8**, again with both secondary and challenging primary amides **1** and **4**, respectively.

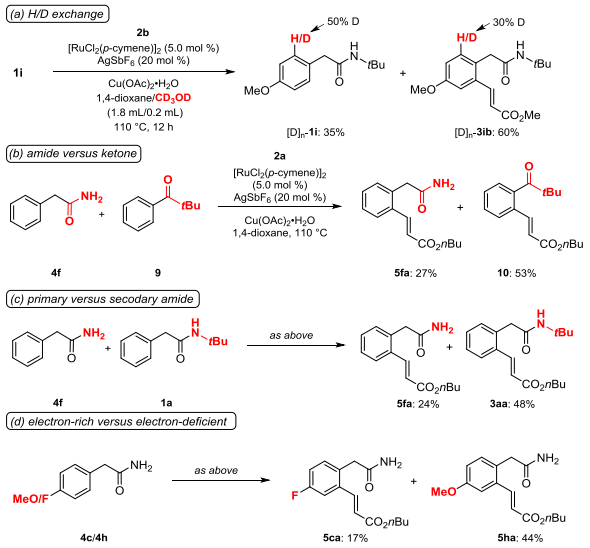


Scheme 3. Ruthenium(II)-catalyzed hydroarylation of alkynes. [a] $[RuCl_2(p\text{-cymene})]_2$ (10 mol %) in 1,4-dioxane as solvent.

Given the high catalytic efficacy of the ruthenium(II) biscarboxylates by distal weak coordination, we became intrigued by delineating its mode of action. To this end, C–H alkenylations with isotopically-labeled compounds provided evidence for a facile C–H activation (Scheme 4a), with no significant kinetic isotope effect as explored by *in-operando* IR spectroscopy (k_H/k_D = 1.02).[12] Further, competition experiments were performed, highlighting the challenging nature of distal acetamide C–H functionalizations, particularly, with primary amides being even more difficult than ketones. (Scheme 4b,c).

10.1002/anie.201711108

Electron-rich arenes reacted preferentially (Scheme 4d), which is not in agreement with a concerted metalation/deprotonation (CMD)[13] mechanism. Instead, the observations are better rationalized by an base-assisted internal electrophilic-type substitution (BIES) manifold,[14] which is supported by Mayer bond order analysis of the transition state structure (Table S2).[12]



Scheme 4. Key experimental mechanistic findings.

Based on our experimental studies, we became attracted to better understand the details of the catalyst's working mode through DFT studies. Geometry optimizations and frequency calculations were performed at the TPSS-D3(BJ)/def2-TZVP[15] level of theory, and single point energies at the COSMO-B3LYP-D3(BJ)/def2-TZVP[16] level of theory.[12] The key six-membered ruthenacycle **C** is formed within a carboxylate-assisted BIES[14] C–H activation of *O*-coordinated intermediate **B** (Figure 2). Here, the formation of an agostic complex[17] was not found. Compared to the corresponding five-membered analogue **C**[5] the six-membered ruthenacycle **C** is destabilized by 6.9 kcal mol^{-1}, whilst the deprotonative transition-state is 2.8 kcal mol^{-1} higher in energy (Figure S2 in the SI).[12] Overall, these findings mirror the challenging nature of arylacetamides in C–H activation. Thereafter, ligand exchange and rate-limiting migratory insertion delivers eight-membered ruthenacycle **E**, which finally undergoes *β*-hydride elimination to form alkene-coordinated complex **G**. A careful analysis of Grimme's D3 dispersion correction revealed a significant stabilization[18] of intermediates and transition states,[19] with energy differences of up to 10.6 kcal mol^{-1} for the key eight-membered intermediate **E** (Figure S3 in the SI).[12] Comparable results were obtained when using Truhlar's PW6B95 with D3 correction.[20]

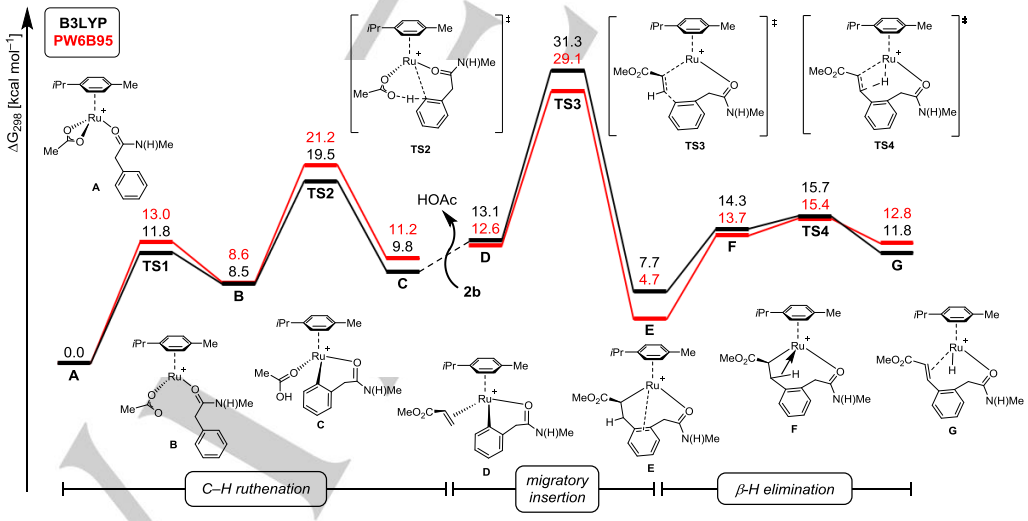


Figure 2. . Relative Gibbs free energy profile for the reaction of **1r** with **2b** at the B3LYP-D3(BJ) (black) or PW6B95-D3(BJ) (red) level of theory.

In summary, we have reported on the first ruthenium(II)-catalyzed C–H activations of weakly-*O*-coordinating arylacetamides through challenging six-membered ruthenacycles. Thus, oxidative C–H alkenylations and alkyne hydroarylations proved viable with ample scope on tertiary, secondary and even primary amides, providing step-economical access to substituted olefines with high levels of chemo-, positional- and stereo-selectivity control. Mechanistic studies unraveled a facile BIES C–H activation, and highlighted the challenging nature of C–H functionalizations with distal acetamides.

Acknowledgements

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Keywords: C–H activation • Density functional theory • homogeneous catalysis • mechanism • ruthenium

References:

[1] V. Martínez, M. I. Maguregui, R. M. Jiménez, R. M. Alonso, *J. Pharmaceut. Biomed.* **2000**, *23*, 459-468.

[2] A. Y. Kocaman, B. Guven, *Cytotechnology* **2016**, *68*, 947-956.

[3] For recent reviews see: a) J. A. Leitch, C. G. Frost, *Chem. Soc. Rev.* **2017**, DOI: 10.1039/C7CS00496F; b) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh, A. Lei, *Chem. Rev.* **2017**, *117*, 9016-9085; c) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754-8786; d) Q.-Z. Zheng, N. Jiao, *Chem. Soc. Rev.* **2016**, *45*, 4590-4627; e) R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2016**, *55*, 10578-10599; f) C. Borie, L. Ackermann, M. Nechab, *Chem. Soc. Rev.* **2016**, *45*, 1368-1386; g) B. Ye, N. Cramer, *Acc. Chem. Res.* **2015**, *48*, 1308-1318; h) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053-1064; i) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369-375; j) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743; k) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009; l) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215-1292; m) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115; n) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826, and cited references.

[4] Selected examples of C–H functionalizations of benzamides: a) H. W. Wang, Y. Lu, B. Zhang, J. He, H. J. Xu, Y. S. Kang, W. Y. Sun, J. Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 7449-7453; b) M. Shang, Q. Shao, S. Z. Sun, Y. Q. Chen, H. Xu, H. X. Dai, J. Q. Yu, *Chem. Sci.* **2017**, *8*, 1469-1473; c) W. Liu, L. Ackermann, *Chem. Commun.* **2014**, *50*, 1878-1881; d) Z. Shi, C. Grohmann, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 5393-5397; e) Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428-429; f) F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 1064-1067, and cited references.

[5] For pioneering contributions, see: a) G. Li, L. Wan, G. Zhang, D. Leow, J. Spangler, J. Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 4391-4397; b) P. X. Shen, X. C. Wang, P. Wang, R. Y. Zhu, J. Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 11574-11577; c) X.-C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 10326-10329; d) M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058-14059; e) A review: K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788-802, and cited references.

[6] Further examples by palladium catalysis: a) Y. Jaiswal, Y. Kumar, R. Thakur, J. Pal, R. Subramanian, A. Kumar, *J. Org. Chem.* **2016**, *81*, 12499-12505; b) A. Deb, S. Bag, R. Kancherla, D. Maiti, *J. Am. Chem. Soc.* **2014**, *136*, 13602-13605; c) J. Park, M. Kim, S. Sharma, E. Park, A. Kim, S. H. Lee, J. H. Kwak, Y. H. Jung, I. S. Kim, *Chem. Commun.* **2013**, *49*, 1654-1656; d) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci.* **2010**, *1*, 331-336.

[7] a) In November 2017, the prices of rhodium, iridium, palladium, and ruthenium were 1375, 970, 987, and 125 US $ per troy oz, respectively. See: http://www.infomine.com/investment/precious-metals/. For recent reviews, see: b) W. Ma, P. Gandeepan, J. Li, L. Ackermann, *Org. Chem. Front.* **2017**, *4*, 1435-1467; c) S. Ruiz, P. Villuendas, E. P. Urriolabeitia, *Tetrahedron Lett.* **2016**, *57*, 3413-3432; d) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461-1479; e) B. Li, P. H. Dixneuf, *Chem. Soc. Rev.* **2013**, *42*, 5744-5767; f) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879-5918; g) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077-1101.

[8] L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281-295.

[9] For selected examples of C–H alkenylations see: a) W. Ma, H. Dong, D. Wang, L. Ackermann, *Adv. Synth. Catal.* **2017**, *359*, 966-973; b) J. A. Leitch, P. B. Wilson, C. L. McMullin, M. F. Mahon, Y. Bhonoah, I. H. Williams, C. G. Frost, *ACS Catal.* **2016**, *6*, 5520-5529; c) K. J. Xiao, L. Chu, J. Q. Yu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2856-2860; d) A. Bechtoldt, C. Tirler, K. Raghuvanshi, S. Warratz, C. Kornhaaß, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 264-267; e) J. Kim, S. W. Park, M. H. Baik, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 13448-13451; f) K. S. Singh, P. H. Dixneuf, *Organometallics* **2012**, *31*, 7320-7323; g) L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153-4155; h) H. Weissman, X. Song, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 337-338; i) a review: S. I. Kozhushkov, L. Ackermann, *Chem. Sci.* **2013**, *4*, 886-896, and cited references.

[10] For recent reviews on hydroarylation see: a) Y. Yamamoto, *Chem. Soc. Rev.* **2014**, *43*, 1575-1600; b) Y. Nakao, *Chem. Rec.* **2011**, *11*, 242-251; c) N. A. Foley, J. P. Lee, Z. Ke, T. B. Gunnoe, T. R. Cundari, *Acc. Chem. Res.* **2009**, *42*, 585-597; d) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826-834.

[11] a) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315-1345; b) S. Santoro, F. Ferlin, L. Luciani, L. Ackermann, L. Vaccaro, *Green Chem.* **2017**, *19*, 1601-1612.

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

[13] a) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848-10849; b) a pertinent review: D. L. Davies, S. A. Macgregor, C. L. McMullin, *Chem. Rev.* **2017**, *117*, 8649-8709.

[14] a) D. Zell, M. Bursch, V. Müller, S. Grimme, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 10378-10382; b) W. Ma, R. Mei, G. Tenti, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 15248-15251.

[15] a) J. Tao, J. P. Perdew, V. N. Staroverov, G. E. Scuseria, *Phys. Rev. Lett.* **2003**, *91*, 146401; b) S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456-1465; c) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297-3305; d) A. Schäfer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, *97*, 2571-2577.

[16] a) A. Klamt, G. Schuurmann, *J. Chem. Soc., Perkin Trans. 2* **1993**, 799-805; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648-5652; c) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623-11627.

[17] J. A. Leitch, P. B. Wilson, C. L. McMullin, M. F. Mahon, Y. Bhonoah, I. H. Williams, C. G. Frost, *ACS Catal.* **2016**, *6*, 5520-5529.

[18] For reviews, see: a) S. Grimme, A. Hansen, J. G. Brandenburg, C. Bannwarth, *Chem. Rev.* **2016**, *116*, 5105-5154; b) J. P. Wagner, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2015**, *54*, 12274-12296.

[19] a) L. Goerigk, A. Hansen, C. Bauer, S. Ehrlich, A. Najibi, S. Grimme, *Phys. Chem. Chem. Phys.* **2017**, DOI: 10.1039/C7CP04913G; b) L. Goerigk, S. Grimme, *Phys. Chem. Chem. Phys.* **2011**, *13*, 6670-6688.

[20] Y. Zhao, D. G. Truhlar, *J. Phys. Chem. A*, **2005**, *109*, 5656-5667.

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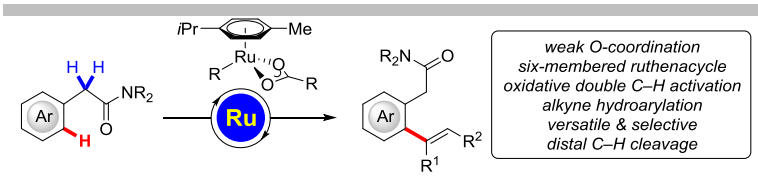

C–H Activation
*Q. Bu,[+] T. Rogge,[+] V. Kotek, L Ackermann**
Page No. – Page No.
Distal Weak Coordination of Acetamides in Ruthenium(II)-Catalyzed C–H Activation Processes

From a distance: Distal C–H activations were accomplished by versatile ruthenium(II) catalysis through facile C–H cleavage by weak coordination.