C–H Activation

International Edition: DOI: 10.1002/anie.201603260
German Edition: DOI: 10.1002/ange.201603260

Overcoming the Limitations of C–H Activation with Strongly Coordinating N-Heterocycles by Cobalt Catalysis

*Hui Wang[+], Mélanie M. Lorion[+], and Lutz Ackermann**

Abstract: *Strongly coordinating nitrogen heterocycles, including pyrimidines, oxazolines, pyrazoles, and pyridines, were fully tolerated in cobalt-catalyzed C–H amidations by imidate assistance. Structurally complex quinazolines are thus accessible in a step-economic manner. Our findings also establish the relative powers of directing groups in cobalt(III)-catalyzed C–H functionalization for the first time.*

Methods for C–H functionalization have emerged as an increasingly powerful platform in modern organic synthesis.[1] Despite tremendous advances during the past decade, strongly coordinating N-heterocycles continue to pose major challenges to transition-metal catalysts, often resulting in the inhibition of catalytic turnover. More importantly, biologically relevant N-heterocycles, such as pyrazoles, oxazolines, pyrimidines, or pyridines, strongly coordinate to the active transition-metal catalyst, resulting in proximity-induced C–H activation in the *ortho* position (Figure 1 a),[2] which severely limits the application of these methods in medicinal[1e] and pharmaceutical[3] chemistry or the materials sciences.[4] Position-selective C–H functionalizations of substrates with strongly coordinating N-heterocycles have only very recently been accomplished by means of palladium(II) catalysis with *N*-methoxy benzamides, as elegantly devised by Dai, Yu, and co-workers (Figure 1 b).[5]

In the past few years, the focus in C–H activation chemistry has shifted towards the use of naturally abundant first-row transition metals.[6] Considerable progress was accomplished by the development of high-valent cobalt(III) catalyzed C–H functionalizations,[7] with notable contributions by the groups of Matsunaga/Kanai,[8] Ellman,[9] Chang,[10] Glorius,[11] Shi,[12] Jiao,[13] and Ackermann,[14] among others.[15] Despite these major advances, cobalt C–H activation catalysts that fully tolerate strongly coordinating heterocycles have unfortunately proven elusive. Within our program on base-metal catalysis,[16] we have recently reported on cobalt(III)-catalyzed C–H amidations[17] with dioxazolones[18] by the assistance of cyclic imidates.[19] Consequently, we became intrigued by probing acyclic imidates as the site-selectivity-ensuring entities in cobalt(III)-catalyzed C–H amidations,[20] on which we report herein.[21] Notable features of our findings include 1) efficient imidate-assisted C–H nitrogenation by cost-effective base-metal catalysis, 2) expedient access to unique heterocycle-decorated quinazolines, and 3) first detailed insight into the potencies of various directing groups in cobalt-catalyzed[22] C–H activation, which 4) enabled the development of a C–H amidation method that fully tolerates strongly coordinating pyrazoles, oxazolines, pyrimidines, and pyridines (Figure 1 c).

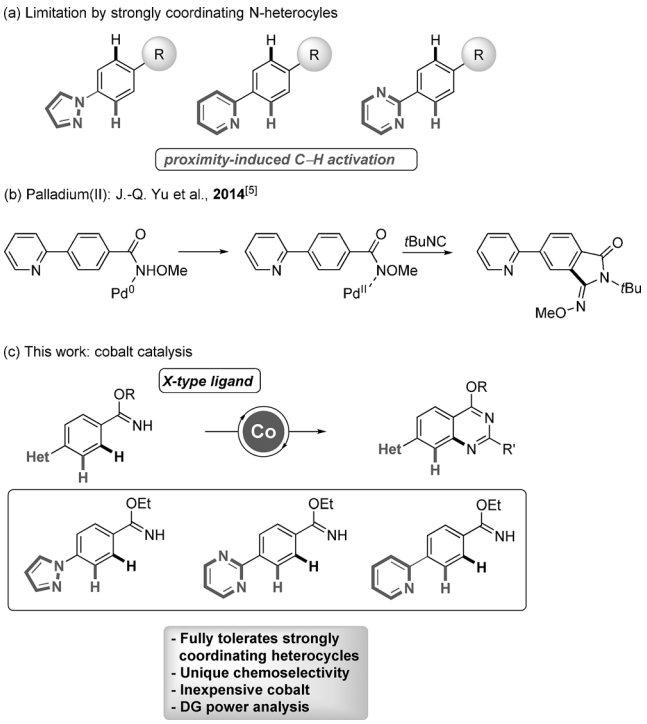
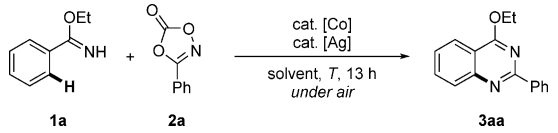


Figure 1. C–H activation in the presence of strongly coordinating heterocycles. a) Challenges. b) Palladium(II) catalysis.[5] c) Heterocycle-tolerating cobalt catalysis.

We initiated our studies by exploring reaction conditions for the envisioned C–H nitrogenation of benzimidate **1a** by cobalt catalysis (Table 1; see also the Supporting Information, Table S1).[23] Preliminary studies indicated the facile formation of quinazoline **3aa**, even in the absence of $Cu(OAc)_2$ or NaOAc additives (entries 1–4). The reaction temperature and catalyst loading could be significantly reduced, which also set the stage for the adjustment of the substrate ratio (entries 4–7). Among a variety of cocatalytic silver(I) additives, optimal results were obtained with $AgSbF_6$ (entries 7–12). The robustness of the cobalt(III) catalysis was reflected by the high

[*] H. Wang,[+] Dr. M. M. Lorion,[+] 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/
[+] These authors contributed equally to this work.
Supporting information and the ORCID identification numbers for the authors of this article can be found under http://dx.doi.org/10.1002/anie.201603260.

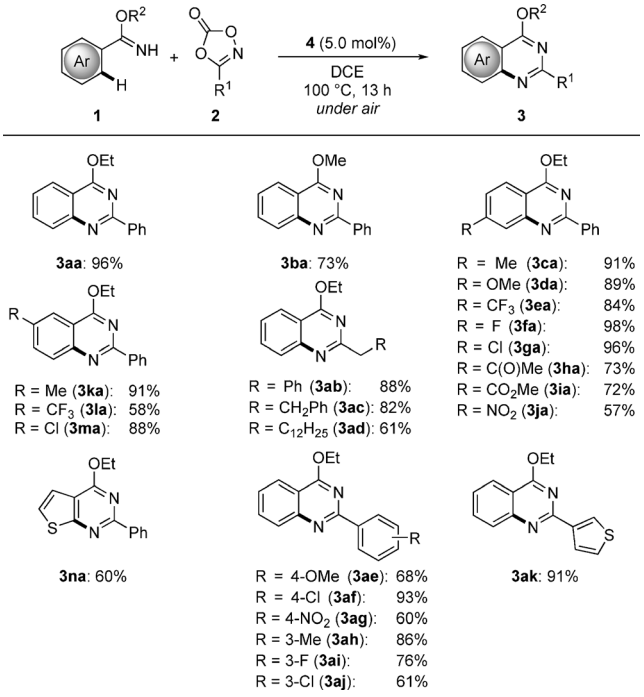
Table 1: Optimization of the cobalt-catalyzed C–H amidation of imidate **1a**.[a]



1a **2a** **3aa**

Entry	Catalyst (mol%)	Ag salt (mol%)	*T* [°C]	Yield [%]
1[b,c,d]	$Cp^*CoI_2(CO)$ (10)	$AgSbF_6$ (20)	120	81
2[c,d]	$Cp^*CoI_2(CO)$ (10)	$AgSbF_6$ (20)	120	85
3[d]	$Cp^*CoI_2(CO)$ (10)	$AgSbF_6$ (20)	120	99
4[d]	$Cp^*CoI_2(CO)$ (5)	$AgSbF_6$ (10)	120	99
5[d]	$Cp^*CoI_2(CO)$ (5)	$AgSbF_6$ (10)	100	99
6[d]	$Cp^*CoI_2(CO)$ (5)	$AgSbF_6$ (10)	80	83
7	**$Cp^*CoI_2(CO)$ (5)**	**$AgSbF_6$ (10)**	**100**	**99**
8	$Cp^*CoI_2(CO)$ (5)	$AgBF_4$ (10)	100	96
9	$Cp^*CoI_2(CO)$ (5)	$AgPF_6$ (10)	100	99
10	$Cp^*CoI_2(CO)$ (5)	AgOTf (10)	100	80
11	$Cp^*CoI_2(CO)$ (5)	$AgNTf_2$ (10)	100	88
12	$Cp^*CoI_2(CO)$ (5)	AgOTs (10)	100	19
13	$Cp^*CoI_2(CO)$ (5)	–	100	56
14	$Co(OAc)_2$ (5)	$AgSbF_6$ (10)	100	–
15	$Co(acac)_3$ (5)	$AgSbF_6$ (10)	100	–
16	–	$AgSbF_6$ (10)	120	–
17[e]	**4** (5)	–	100	94
18	**4 (5)**	**–**	**100**	**96**

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (1.2 equiv), DCE (1.0 mL), *T*, 13 h; yields of isolated products are given. [b] $Cu(OAc)_2$ (2.0 equiv). [c] NaOAc (20 mol%). [d] **2a** (2.0 equiv). [e] Under N_2.



Scheme 1. Cobalt-catalyzed C–H nitrogenation of imidates **1**.

catalytic efficiency under an atmosphere of ambient air. Interestingly, the C–H amidation even occurred with $Cp^*CoI_2(CO)$ as the sole catalyst component in the absence of silver(I) salts, albeit with reduced efficacy (entry 13). In contrast, other typically used cobalt(II) or cobalt(III) salts failed short in delivering the desired quinazoline **3aa** (entries 14–16). In consideration of the user-friendly nature of single-component catalysts in homogenous catalysis,[24] we were delighted that C–H nitrogenation was highly efficient with the well-defined complex $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ (**4**) as the catalyst in the absence of any additives (entries 17 and 18).

With the optimized single-component catalyst **4** in hand, we initially probed its versatility in the silver-free C–H nitrogenation of benzimidates **1** (Scheme 1). Diversely decorated arenes **1** underwent the desired reaction to yield quinazolines **3** with excellent chemoselectivity, which was highlighted by the reaction fully tolerating a broad range of electrophilic functional groups, such as fluoro, chloro, ester, ketone, and nitro substituents. The C–H nitrogenation reactions proceeded with excellent levels of positional selectivity at the less hindered C–H bond. Catalyst **4** enabled not only the transformation of carbocyclic aromatic benzimidates, but thiophene imidate **1n** proved viable as well. Likewise, various benzyl-, alkyl-, aryl-, and even heteroaryl-substituted dioxazolones **2** proved amenable to the cobalt-catalyzed syntheses of quinazolines **3aa**–**3ak**.

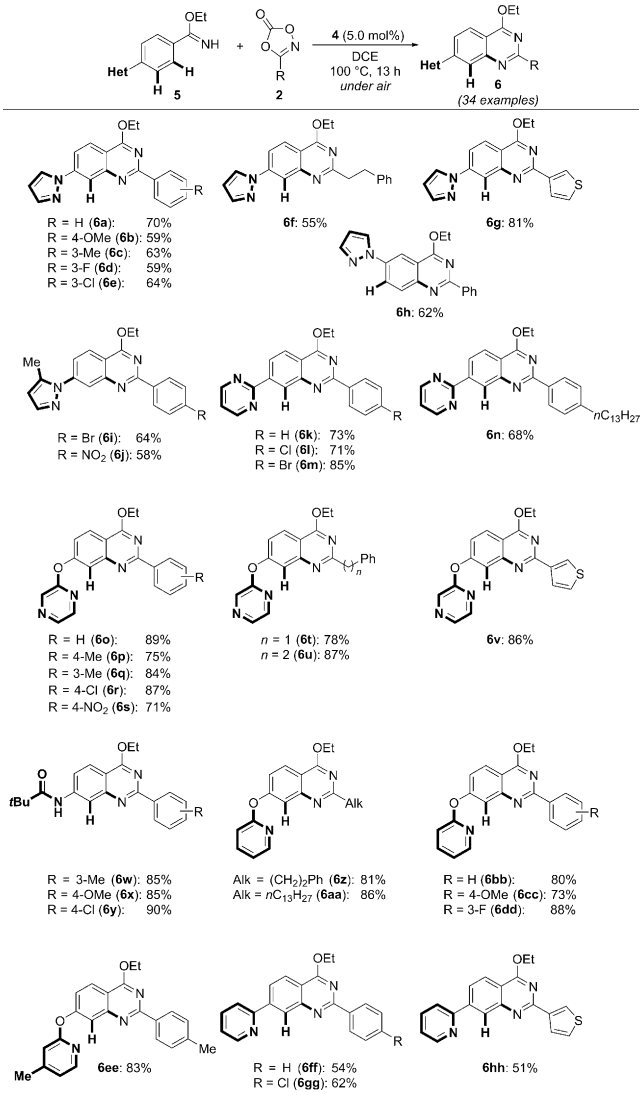
Intrigued by the excellent tolerance of functional groups, we focused on the originally envisioned amidation of imidates **5**, which also contain challenging, strongly coordinating N-heterocyclic directing groups (Scheme 2). Surprisingly, the cobalt(III) catalyst **4** set the stage for a chemoselective C–H nitrogenation by imidate assistance, delivering quinazolines **6** as the sole products. Thus strongly coordinating heterocycles that are themselves usually employed for directed C–H functionalization strategies, such as pyrazoles, pyrimidines, pyrazines, and even pyridines, were fully tolerated by the cobalt(III) catalyst. These observations should prove instrumental for further applications to drug design in medicinal chemistry.

The unique chemoselectivity with the difunctional substrates **5**, which bear strongly coordinating N-heteroarenes, was further reflected by intermolecular competition experiments with benzimidate **1a** and arenes **7a**–**17a** (Scheme 3). It is noteworthy that in all intermolecular settings, the X-type imidate outcompeted the strongly coordinating L-type carbamate, pyrazole, oxazoline, pyrimidine, and pyridine directing groups.

Based on these competition experiments, the potencies of various directing groups in cobalt(III)-catalyzed C–H functionalization were established for the first time, and decrease in the order:

$$\text{imidate} \geq \text{pyridine} \approx \text{pyrazole} > \text{oxazoline} > \text{pyrimidine}$$

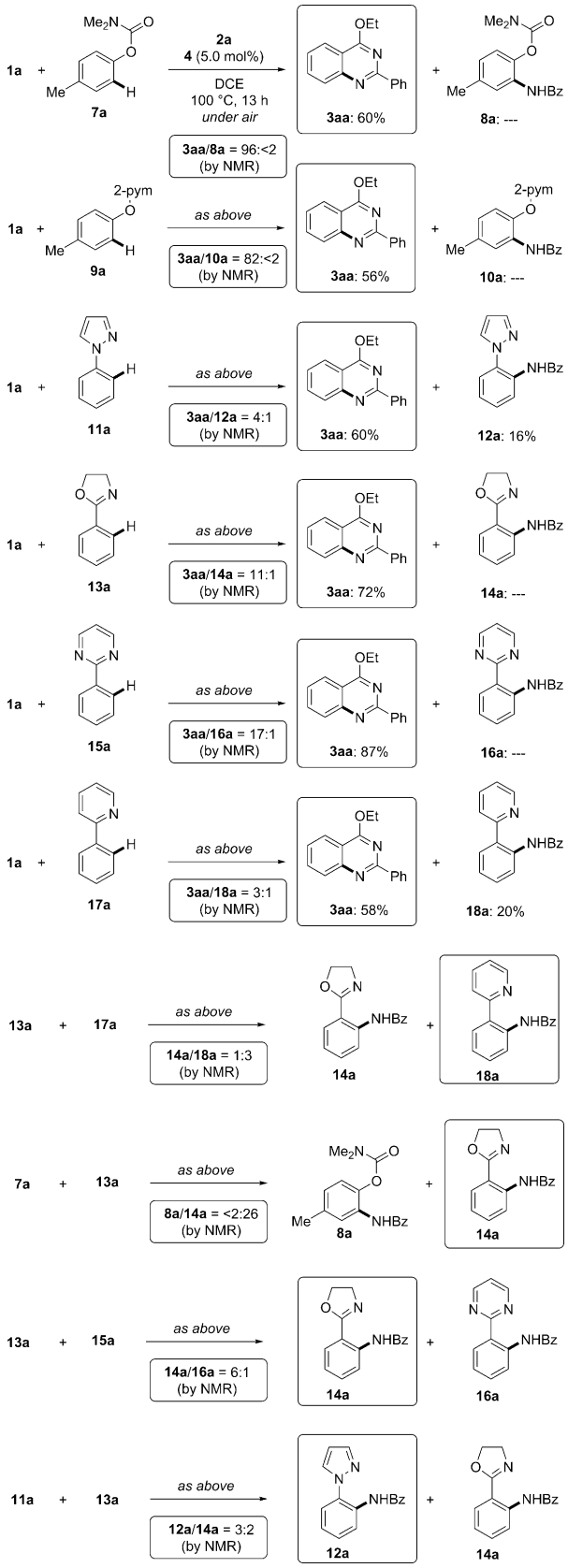
To estimate the positional selectivity of the key C–H activation step, we further performed stoichiometric reactions with complex **4**, and determined the extent of C–H metalation by subsequent treatment with CD_3CO_2D (Scheme 4). These findings indicate that the selectivity is determined in the C–N bond-forming step.



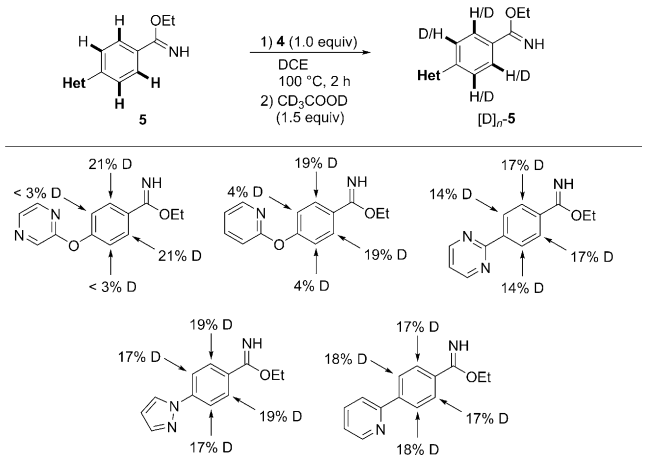
Scheme 2. Overriding the conventional selectivity dictated by strongly coordinating heterocycles.

As to the reaction mechanism, the cobalt-catalyzed C–H amidation displayed a notable kinetic isotope effect (KIE) of $k_H/k_D \approx 2.4$, did not show significant H/D scrambling, and typical radical scavengers did not inhibit the reaction.[23] Furthermore, intermolecular competition experiments between differently substituted benzimidates **1d** and **1e** revealed that electron-rich arenes react preferentially.[23] These observations can be rationalized in terms of a rate-determining C–H metalation with an electrophilic, cationic cobalt(III) catalyst. The elementary step of C–H activation is proposed to proceed by σ-bond metathesis[25] by means of ligand-to-ligand hydrogen transfer. Thereafter, selectivity-determining migratory insertion occurs by CO_2 extrusion (Scheme 5), along with the liberation of amide **23**, which was detected by GC/MS analysis of the crude reaction mixture.

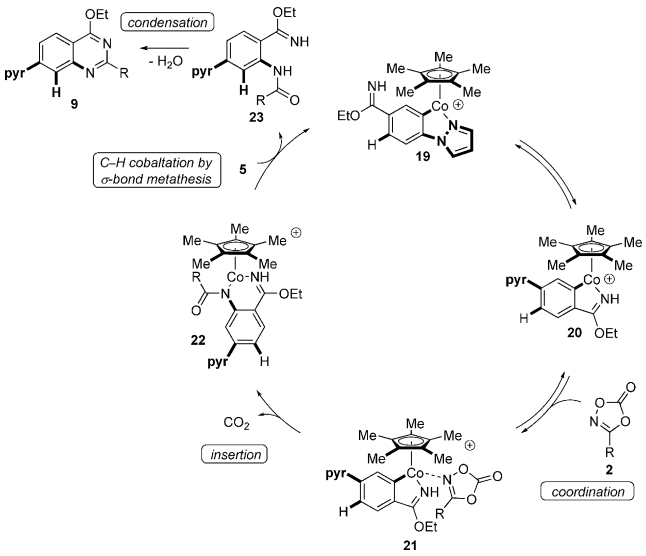
In summary, we have reported the first base-metal-catalyzed C–H functionalization that fully tolerates strongly coordinating heterocycles. Biologically important oxazolines, pyrazoles, pyrimidines, and pyridines were, among others,



Scheme 3. Directing group powers in cobalt-catalyzed C–H functionalization; yields of isolated products are given. Product ratios were determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard. Bz = benzoyl, 2-pym = 2-pyrimidyl.



Scheme 4. Positional selectivity in stoichiometric C–H cobaltation.



Scheme 5. Proposed catalytic cycle.

fully accepted in the developed cobalt(III)-catalyzed C–H amidation by imidate assistance. Structurally diverse quinazolines were accessed in a step-economic fashion with ample substrate scope. Our findings provide a first comparative study on the powers of various directing groups in cobalt(III)-catalyzed C–H functionalization chemistry, which should prove instrumental for the future design of novel processes involving cobalt-catalyzed C–H activation.

Acknowledgements

Generous support by the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013; ERC Grant agreement 307535), the DFG (SPP 1807), and the Chinese Scholarship Program (fellowships to H.W.) is gratefully acknowledged.

Keywords: C–H activation · cobalt · directing groups · heterocycles · imidates

[1] For representative recent reviews on C–H activation, see: 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) K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.* **2015**, *48*, 1040 – 1052; d) O. Daugulis, J. Roane, L. D. Tran, *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) G. Song, X. Li, *Acc. Chem. Res.* **2015**, *48*, 1007 – 1020; g) N. Kuhl, N. Schröder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443 – 1460; h) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74 – 100; *Angew. Chem.* **2014**, *126*, 76 – 103; i) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726 – 11743; *Angew. Chem.* **2013**, *125*, 11942 – 11959; j) D. J. Schipper, K. Fagnou, *Chem. Mater.* **2011**, *23*, 1594 – 1600; k) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215 – 1292; 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) 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; p) R. G. Bergman, *Nature* **2007**, *446*, 391 – 393, and references therein.

[2] For selected reviews, see: a) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624 – 655; b) T. Satoh, M. Miura, *Top. Organomet. Chem.* **2007**, *24*, 61 – 84; c) L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35 – 60; d) I. Omae, *Coord. Chem. Rev.* **2004**, *248*, 995 – 1023.

[3] L. Ackermann, *Org. Process Res. Dev.* **2015**, *19*, 260 – 269.

[4] L. G. Mercier, M. Leclerc, *Acc. Chem. Res.* **2013**, *46*, 1597 – 1605.

[5] Y. J. Liu, H. Xu, W. J. Kong, M. Shang, H. X. Dai, J. Q. Yu, *Nature* **2014**, *515*, 389 – 393.

[6] For recent authorative reviews on the use of inexpensive first-row transition-metal catalysts for C–H bond functionalization, see: a) W. Liu, L. Ackermann, *ACS Catal.* **2016**, *6*, 3743 – 3752; b) E. Nakamura, T. Hatakeyama, S. Ito, K. Ishizuka, L. Ilies, M. Nakamura, *Org. React.* **2014**, *83*, 1 – 209; c) L. Ackermann, *J. Org. Chem.* **2014**, *79*, 8948 – 8954; 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.

[7] For recent reviews, see: a) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498 – 525; b) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208 – 1219.

[8] a) B. Sun, T. Yoshino, M. Kanai, S. Matsunaga, *Angew. Chem. Int. Ed.* **2015**, *54*, 12968 – 12972; *Angew. Chem.* **2015**, *127*, 13160 – 13164; b) 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; c) Y. Suzuki, B. Sun, T. Yoshino, M. Kanai, S. Matsunaga, *Tetrahedron* **2015**, *71*, 4552 – 4556; d) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 1491 – 1495; e) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2014**, *136*, 5424 – 5431; f) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Chem. Eur. J.* **2013**, *19*, 9142 – 9146; g) T. Andou, Y. Saga, H. Komai, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 3213 – 3216; *Angew. Chem.* **2013**, *125*, 3295 – 3298; h) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 2207 – 2211; *Angew. Chem.* **2013**, *125*, 2263 – 2267.

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

[10] a) J. Park, S. Chang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14103 – 14107; *Angew. Chem.* **2015**, *127*, 14309 – 14313; b) P. Patel, S. Chang, *ACS Catal.* **2015**, *5*, 853 – 858; c) A. B. Pawar, S. Chang, *Org. Lett.* **2015**, *17*, 660 – 663.

[11] a) J. H. Kim, S. Greßies, F. Glorius, *Angew. Chem. Int. Ed.* **2016**, *55*, 5577 – 5581; *Angew. Chem.* **2016**, *128*, 5667 – 5671; b) A. Lerchen, S. Vásquez-Céspedes, F. Glorius, *Angew. Chem. Int. Ed.* **2016**, *55*, 3208 – 3211; *Angew. Chem.* **2016**, *128*, 3261 – 3265; c) Q. Lu, S. Vásquez-Céspedes, T. Gensch, F. Glorius, *ACS Catal.* **2016**, *6*, 2352 – 2356; d) 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; e) T. Gensch, S. Vásquez-Céspedes, D. G. Yu, F. Glorius, *Org. Lett.* **2015**, *17*, 3714 – 3717; f) D. G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17722 – 17725.

[12] a) Z.-Z. Zhang, B. Liu, J.-W. Xu, S.-Y. Yan, B.-F. Shi, *Org. Lett.* **2016**, *18*, 1776 – 1779; b) Z.-Z. Zhang, B. Liu, C.-Y. Wang, B.-F. Shi, *Org. Lett.* **2015**, *17*, 4094 – 4097.

[13] Y. Liang, Y.-F. Liang, C. Tang, Y. Yuan, N. Jiao, *Chem. Eur. J.* **2015**, *21*, 16395 – 16399.

[14] a) D. Zell, Q. Bu, M. Feldt, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 7408 – 7412; *Angew. Chem.* **2016**, *128*, 7534 – 7538; b) J. Li, M. Tang, L. Zang, X. Zhang, Z. Zhang, L. Ackermann, *Org. Lett.* **2016**, *18*, 2742 – 2745; c) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 8551 – 8554; *Angew. Chem.* **2015**, *127*, 8671 – 8674; d) M. Moselage, N. Sauermann, J. Koeller, W. Liu, D. Gelman, L. Ackermann, *Synlett* **2015**, 1596 – 1600; e) W. Ma, L. Ackermann, *ACS Catal.* **2015**, *5*, 2822 – 2825; f) N. Sauermann, M. J. González, L. Ackermann, *Org. Lett.* **2015**, *17*, 5316 – 5319; g) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 3635 – 3638; *Angew. Chem.* **2015**, *127*, 3706 – 3709.

[15] a) S. Prakash, K. Muralirajan, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2016**, *55*, 1844 – 1848; *Angew. Chem.* **2016**, *128*, 1876 – 1880; b) 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*, 10012 – 10015; *Angew. Chem.* **2015**, *127*, 10150 – 10153; c) 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; d) L. Grigorjeva, O. Daugulis, *Org. Lett.* **2015**, *17*, 1204 – 1207; e) L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.* **2014**, *53*, 10209 – 10212; *Angew. Chem.* **2014**, *126*, 10373 – 10376.

[16] For recent examples, see: a) Z. Ruan, S. Lackner, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 3153 – 3157; *Angew. Chem.* **2016**, *128*, 3205 – 3209; b) G. Cera, T. Haven, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 1484 – 1488; *Angew. Chem.* **2016**, *128*, 1506 – 1510; c) W. Liu, J. Bang, Y. Zhang, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 14137 – 14140; *Angew. Chem.* **2015**, *127*, 14343 – 14346.

[17] For reviews on C–H nitrogenation, see: a) H. Kim, S. Chang, *ACS Catal.* **2016**, *6*, 2341 – 2351; b) S. Dana, M. R. Yadav, A. K. Sahoo, *Top. Organomet. Chem.* **2016**, *55*, 189 – 215; c) Y. Park, S. Jee, J. G. Kim, S. Chang, *Org. Process Res. Dev.* **2015**, *19*, 1024 – 1029; d) Y. Liang, Y.-F. Liang, N. Jiao, *Org. Chem. Front.* **2015**, *2*, 403 – 415; e) T. Wang, N. Jiao, *Acc. Chem. Res.* **2014**, *47*, 1137 – 1145; f) M.-L. Louillat, F.-W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901 – 910; g) V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun.* **2014**, *50*, 29 – 39, and references therein.

[18] For representative recent references on dioxazolones, see: a) Y. Park, K. T. Park, J. G. Kim, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 4534 – 4542; b) V. Bizet, L. Buglioni, C. Bolm, *Angew. Chem. Int. Ed.* **2014**, *53*, 5639 – 5642; *Angew. Chem.* **2014**, *126*, 5745 – 5748, and references therein.

[19] R. Mei, J. Loup, L. Ackermann, *ACS Catal.* **2016**, *6*, 793 – 797.

[20] For recent examples of C–H amidations catalyzed by precious transition metals, see: a) G. N. Hermann, P. Becker, C. Bolm, *Angew. Chem. Int. Ed.* **2016**, *55*, 3781 – 3784; *Angew. Chem.* **2016**, *128*, 3845 – 3848; b) H. Hwang, J. Kim, J. Jeong, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 10770 – 10776; c) T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 4141 – 4144; d) D. G. Yu, M. Suri, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 8802 – 8805; e) K. Shin, Y. Baek, S. Chang, *Angew. Chem. Int. Ed.* **2013**, *52*, 8031 – 8036; *Angew. Chem.* **2013**, *125*, 8189 – 8194; f) V. S. Thirunavukkarasu, K. Raghuvanshi, L. Ackermann, *Org. Lett.* **2013**, *15*, 3286 – 3289; g) J. Kim, J. Kim, S. Chang, *Chem. Eur. J.* **2013**, *19*, 7328 – 7333; h) Q.-Z. Zheng, Y.-F. Liang, C. Qin, N. Jiao, *Chem. Commun.* **2013**, *49*, 5654 – 5656; i) M.-Z. Shang, S.-H. Sun, S. Zheng, H.-X. Dai, J.-Q. Yu, *Org. Lett.* **2013**, *15*, 5286 – 5289; j) J.-Y. Kim, S.-H. Park, J. Ryu, S.-H. Cho, S.-H. Kim, S. Chang, *J. Am. Chem. Soc.* **2012**, *134*, 9110 – 9113; k) E.-J. Yoo, S. Ma, T.-S. Mei, S.-L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7652 – 7656; l) K.-H. Ng, A. S.-C. Chan, Y.-W. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12862 – 12866; m) P. Gandeepan, K. Parthasarthy, C.-H. Cheng, *J. Am. Chem. Soc.* **2010**, *132*, 8569 – 8571, and references therein.

[21] During and after the submission of our manuscript, independent reports on C–H activation with benzimidates and *N*-sulfinyl imines and silver(I) salts were disclosed; see: a) F. Wang, H. Wang, Q. Wang, S. Yu, X. Li, *Org. Lett.* **2016**, *18*, 1306 – 1309; b) T. X. Wang, A. Lerchen, F. Glorius, *Org. Lett.* **2016**, *18*, 2090 – 2093.

[22] L. V. Desai, K. J. Stowers, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, *130*, 13285 – 13293.

[23] See the Supporting Information for details.

[24] For recent progress, see: a) D. Zell, S. Warratz, D. Gelman, S. J. Garden, L. Ackermann, *Chem. Eur. J.* **2016**, *22*, 1248 – 1252; b) S. Ge, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 12837 – 12841; *Angew. Chem.* **2012**, *124*, 13009 – 13013; c) L. Ackermann, P. Novák, R. Vicente, N. Hofmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 6045 – 6048; *Angew. Chem.* **2009**, *121*, 6161 – 6164, and references therein.

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

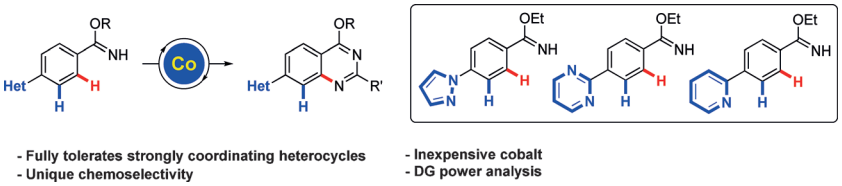
Received: April 3, 2016
Revised: June 13, 2016
Published online: ■■ ■■, ■■■■

Communications

C–H Activation

H. Wang, M. M. Lorion,
L. Ackermann* ———— ■■■■–■■■■

Overcoming the Limitations of C–H Activation with Strongly Coordinating N-Heterocycles by Cobalt Catalysis



Strongly coordinating nitrogen heterocycles are fully tolerated by a versatile cobalt-catalyzed C–H amidation method, which provides access to structurally complex quinazolines. The powers of various directing groups in cobalt-catalyzed C–H activation were thus delineated.

