Organic LETTERS
Letter
pubs.acs.org/OrgLett

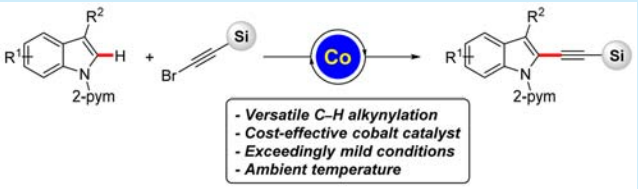
Cobalt(III)-Catalyzed C−H Alkynylation with Bromoalkynes under Mild Conditions

Nicolas Sauermann, María J. González, and Lutz Ackermann*

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstraße 2, 37077 Göttingen, Germany

Supporting Information

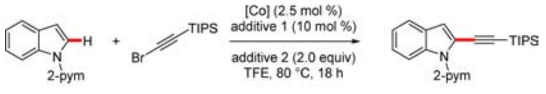
ABSTRACT: Expedient cobalt-catalyzed C−H alkynylation was achieved under exceedingly mild reaction conditions. Thus, chelation-assisted direct alkynylations of heteroarenes occurred with 1-bromoalkynes and ample substrate scope. The optimized catalytic system allowed for step-economical C−H functionalizations with a mild base K_2CO_3 at reaction temperatures as low as 25 °C.



Selectively substituted indoles and pyrroles represent key structural motifs in bioactive compounds of relevance to medicinal chemistry and drug development, among others.[1] Therefore, there is a continued strong demand for flexible syntheses and diversifications of these heteroaromatic scaffolds.[2] In recent years, metal-catalyzed C−H activations have emerged as particularly effective tools for the assembly and late-stage modification of heteroarenes.[3] While various protocols for direct arylations, alkenylations, and alkylations have been established, C−H alkynylations[4] of heteroarenes continue to be scarce. Thus far, methods for direct heteroarene alkynylations have mostly been achieved with rather costly 5d and 4d transition metal catalysts, largely exploiting chelation assistance.[5] The recent few years have witnessed the emergence of homogeneous catalysts based on naturally abundant, environmentally benign first row transition metals.[6] Hence, cobalt complexes have specifically been identified as increasingly viable catalysts for C−H activation reactions,[7] with considerable progress being accomplished with high-valent cobalt complexes, as reported by Kanai/Matsunaga,[8] Ackermann,[9] Daugulis,[10] Glorius,[11] Ellman,[12] and Chang,[13] among others.[14] Within our program on base metal-catalyzed C−H functionalizations,[15] we became interested in devising methods for cobalt-catalyzed direct alkynylations. A recent independent report from Shi[16] on cobalt-catalyzed reactions with hypervalent iodine(III) reagents and the strong base MgO*t*-Bu at 110 °C prompted us to report our results on an efficient protocol for cobalt(III)-catalyzed C−H alkynylations with easily accessible 1-bromoalkynes. Notable features of our strategy are not limited to (*i*) versatile cobalt(III) catalyzed C−H alkynylations, (*ii*) excellent functional group tolerance, and (*iii*) in contrast to a very recent report,[16] exceedingly mild reaction conditions:[17] room temperature (25 °C), using the mild base K_2CO_3.

We initiated our studies by probing reaction conditions for the envisioned C−H alkynylation of indole **1a**[18] with bromoalkyne **2a** (Table 1). Among a variety of different cobalt complexes, $[Cp^*CoI_2]_2$ proved to give optimal results (entries 1−5). Cocatalytic amounts of a silver(I) salt were essential for the C−H alkynylation to proceed, with $AgSbF_6$ being ideal (entries 5−9). These findings can be rationalized with the formation of a cationic cobalt(III) complex as the active catalyst. Replacing KOAc by PivOH led to catalyst inhibition (entry 10), highlighting carboxylate assistance.[19] Further, bases other than KOAc enabled efficient C−H activations by chelation assistance (entries 11−14), and the mild K_2CO_3 furnished the desired product **3aa** in virtually quantitative yield (entries 14 and 15), which allowed for the site-selective C−H functionalization at a room temperature of 25 °C (entry 15).

Table 1. Cobalt-Catalyzed C−H Alkynylation[a]



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

entry	[Co]	additive 1	additive 2	**3aa** (%)
1	–	$AgSbF_6$	KOAc	–
2	$Co(OAc)_2$	$AgSbF_6$	KOAc	–
3	$[Cp^*Co(C_6H_6)][PF_6]_2$	–	KOAc	–
4	$[Cp^*CoI_2(CO)]$	$AgSbF_6$	KOAc	68
5	$[Cp^*CoI_2]_2$	$AgSbF_6$	KOAc	75
6	$[Cp^*CoI_2]_2$	–	KOAc	–
7	$[Cp^*CoI_2]_2$	$AgBF_4$	KOAc	66
8	$[Cp^*CoI_2]_2$	$AgPF_6$	KOAc	72
9	$[Cp^*CoI_2]_2$	$Zn(OTf)_2$	KOAc	–
10	$[Cp^*CoI_2]_2$	$AgSbF_6$	PivOH	<5
11	$[Cp^*CoI_2]_2$	$AgSbF_6$	K_3PO_4	52
12	$[Cp^*CoI_2]_2$	$AgSbF_6$	KOTs	–
13	$[Cp^*CoI_2]_2$	$AgSbF_6$	–	–
14	$[Cp^*CoI_2]_2$	$AgSbF_6$	K_2CO_3	91
15	$[Cp^*CoI_2]_2$	$AgSbF_6$	K_2CO_3	**96**[b]

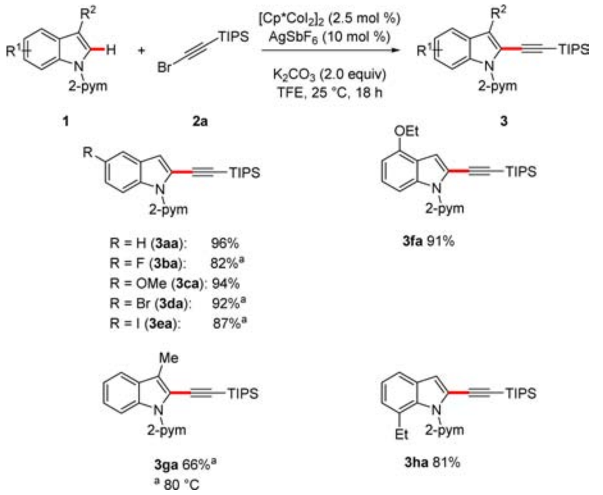
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (1.1 equiv), [Co] (2.5 mol %), additive 1 (10 mol %), additive 2 (2.0 equiv), TFE (2.5 mL), 80 °C, 18 h. [b] 25 °C. pym = pyrimydyl.

Received: September 15, 2015
Published: October 22, 2015

DOI: 10.1021/acs.orglett.5b02678
Org. Lett. 2015, 17, 5316−5319

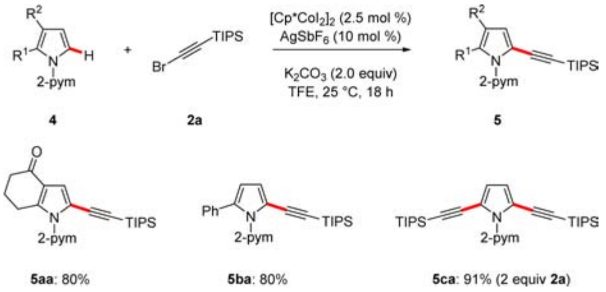
With an optimized catalytic system in hand, we probed its versatility in the C−H alkynylations of various indoles **1** (Scheme 1). The user-friendly cobalt catalyst displayed a notable chemoselectivity, in that important electrophilic functional groups, such as bromo or iodo substituents, were fully tolerated. Likewise, sterically hindered substrates **1g** and **1h** were also efficiently converted to the desired indoles **3ga** and **3ha**, respectively.

Scheme 1. Scope of Cobalt-Catalyzed C−H Alkynylation



The versatile cobalt(III) catalyst was not restricted to indole substrates **1**, but also enabled C−H alkynylations on pyrroles **4** in a site-selective fashion (Scheme 2).[20] Again, the C−H functionalization process was characterized by exceedingly mild reaction conditions at 25 °C, which, for instance, resulted in the tolerance of a valuable ketone in substrate **4a**.

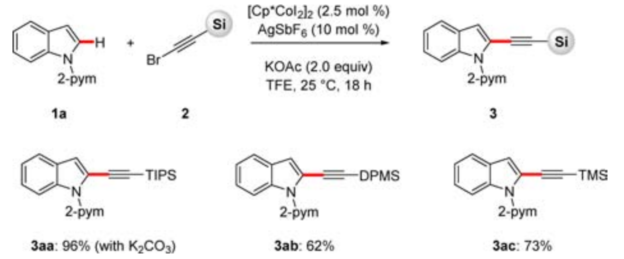
Scheme 2. C−H Alkynylation of Pyrroles 4



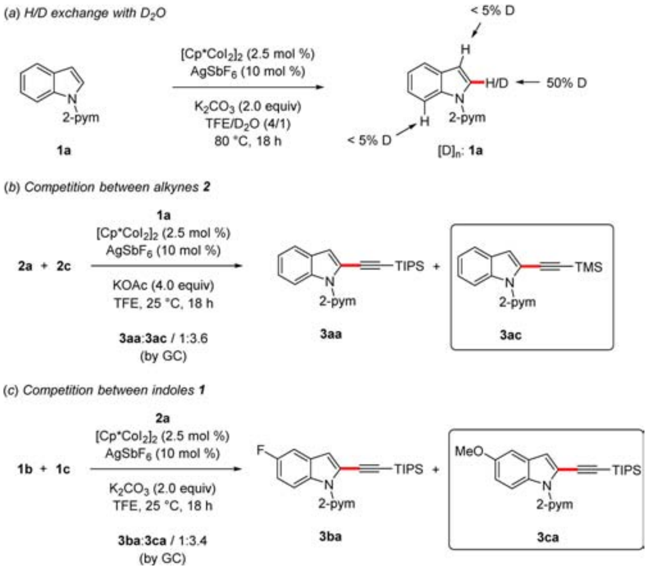
Differently silylated[20] bromoalkynes **2** proved to be viable starting materials for the cobalt(III)-catalyzed C−H alkynylation protocol given that KOAc was used as a mild base (Scheme 3). Again, the C−H transformation occurred efficiently at ambient temperature of 25 °C.

In consideration of the mild reaction conditions of the cobalt(III)-catalyzed C−H activation, we became attracted to unravelling its mode of action.[21] To this end, we observed a facile H/D exchange, solely occurring in the C-2 position of indole **1a** (Scheme 4a), indicating the importance of chelation assistance for the C−H activation step. Furthermore, competition experiments with differently substituted bromoalkynes **2** revealed that the TMS-decorated derivative reacted preferentially (b). As to the heteroarenes **1**, electron-rich indole **1c** was identified as the inherently more reactive substrate (c). This phenomenon can be rationalized in terms of an electrophilic-type C−H activation by the in situ generated cationic cobalt(III) complex.

Scheme 3. C−H Alkynylation with Bromoalkynes 2



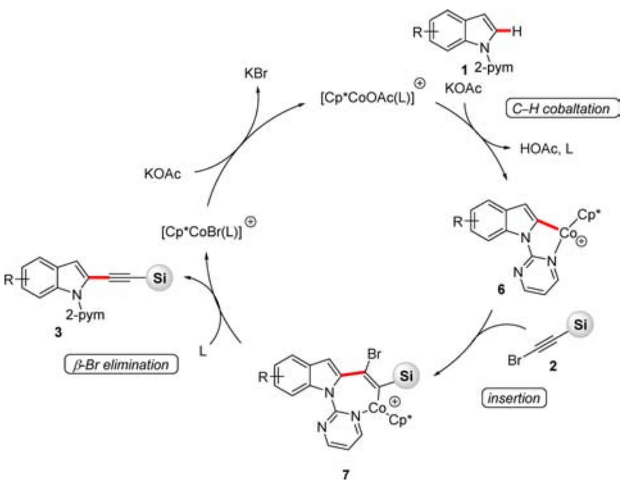
Scheme 4. Mechanistic Studies



Based on our mechanistic studies we propose a plausible catalytic cycle for the C−H alkynylation to be initiated by a reversible C−H cobaltation to generate metallacycle **6** (Scheme 5). A subsequent migratory insertion of bromoalkyne **2** delivers the key intermediate **7**, which finally undergoes *β*-bromo-elimination.

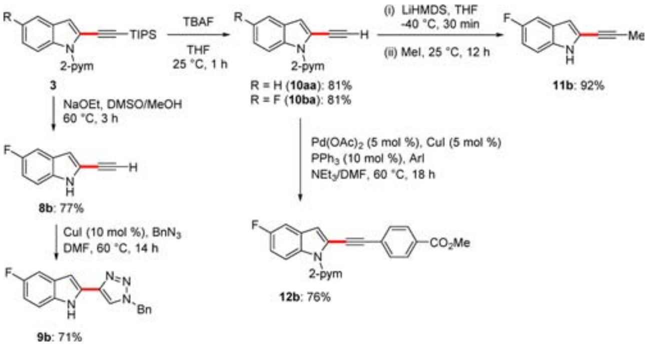
The synthetic utility of the cobalt(III)-catalyzed C−H alkynylation was illustrated by further diversification of the

Scheme 5. Plausible Catalytic Cycle



thus-obtained indoles **3** (Scheme 6). Hence, the chemoselective removal of the silyl-group was easily accomplished under mild reaction conditions, and further functionalizations proved viable to deliver products **8–12**.

Scheme 6. Diversification of Indoles 3



In summary, we have reported on cobalt-catalyzed C–H alkynylations under exceedingly mild reaction conditions. Thus, a versatile cobalt(III) catalyst allowed for direct functionalizations using 1-bromoalkynes with ample substrate scope. The most user-friendly catalyst proved amenable to C–H functionalizations on indoles and pyrroles at room temperature.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02678.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lutz.ackermann@chemie.uni-goettingen.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support by the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ ERC Grant agreement no. 307535, CaSuS (fellowship to N.S.), and the DAAD (fellowship to M.J.G.) is gratefully acknowledged.

■ REFERENCES

(1) (a) Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J. *Modern Heterocyclic Chemistry*; Wiley-VCH: Weinheim, 2011. (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. (c) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Commun.* **2004**, 2824–2825 and references cited therein..

(2) Select reviews on the preparation and functionalization of indoles and pyrroles: (a) Bandini, M. *Org. Biomol. Chem.* **2013**, *11*, 5206–5212. (b) Yoshikai, N.; Wei, Y. *Asian J. Org. Chem.* **2013**, *2*, 466–478. (c) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29–41. (d) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. React.* **2011**, *76*, 281–534. (e) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673–714. (f) Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153–2167. (g) Ackermann, L. *Synlett* **2007**, *2007*, 507–526. (h) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920 and references cited therein.

(3) Representative recent reviews on C–H activation: (a) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308–1318. (b) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040–1052. (c) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053–1064. (d) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 66–81. (e) Ackermann, L. *Org. Process Res. Dev.* **2015**, *19*, 260–269. (f) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843–895. (g) Kuhl, N.; Schroeder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443–1460. (h) Mesganaw, T.; Ellman, J. A. *Org. Process Res. Dev.* **2014**, *18*, 1097–1104. (i) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74–100. (j) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726–11743. (k) Schipper, D. J.; Fagnou, K. *Chem. Mater.* **2011**, *23*, 1594–1600. (l) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (m) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212–11222. (n) Daugulis, O. *Top. Curr. Chem.* **2009**, *292*, 57–84. (o) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (p) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (q) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115 and references cited therein.

(4) (a) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165–4179. (b) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096–2098.

(5) (a) Liu, Y.-H.; Liu, Y.-J.; Yan, S.-Y.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 11650–11653. (b) Yi, J.; Yang, L.; Xia, C.; Li, F. *J. Org. Chem.* **2015**, *80*, 6213–6221. (c) Kang, D.; Hong, S. *Org. Lett.* **2015**, *17*, 1938–1941. (d) Jin, N.; Pan, C.; Zhang, H.; Xu, P.; Cheng, Y.; Zhu, C. *Adv. Synth. Catal.* **2015**, *357*, 1149–1153. (e) Finkbeiner, P.; Kloeckner, U.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 4949–4952. (f) Liu, Y.-J.; Liu, Y.-H.; Yan, S.-Y.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 6388–6391. (g) Wu, Y.; Yang, Y.; Zhou, B.; Li, Y. *J. Org. Chem.* **2015**, *80*, 1946–1951. (h) Yang, X.-F.; Hu, X.-H.; Feng, C.; Loh, T.-P. *Chem. Commun.* **2015**, *51*, 2532–2535. (i) Feng, C.; Feng, D.; Luo, Y.; Loh, T.-P. *Org. Lett.* **2014**, *16*, 5956–5959. (j) Shang, M.; Wang, H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 11590–11593. (k) Feng, C.; Feng, D.; Loh, T.-P. *Chem. Commun.* **2014**, *50*, 9865–9868. (l) Collins, K. D.; Lied, F.; Glorius, F. *Chem. Commun.* **2014**, *50*, 4459–4461. (m) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780–4787. (n) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2722–2726. (o) Tolnai, G. N.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112–115. (p) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387–3390. (q) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354–357. (r) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984–12986. (s) Kim, S. H.; Yoon, J.; Chang, S. *Org. Lett.* **2011**, *13*, 1474–1477. (t) Yang, L.; Zhao, L.; Li, C.-J. *Chem. Commun.* **2010**, *46*, 4184–4186. (u) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522–2523. (v) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358–2361. (w) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346–9349. (x) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156–4159. (y) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250–3252. (z) Gu, Y.; Wang, X.-M. *Tetrahedron Lett.* **2009**, *50*, 763–766. (aa) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742–7743. (bb) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A.; Ushakov, I. A. *Tetrahedron Lett.* **2004**, *45*, 6513–6516.

(6) Recent reviews on the use of inexpensive first-row transition metal catalysts for C–H bond functionalization: (a) Nakamura, E.; Hatakeyama, T.; Ito, S.; Ishizuka, K.; Ilies, L.; Nakamura, M. *Org. React.* **2014**, *83*, 1–209. (b) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, *2013*, 19–30. (c) Yoshikai, N. *Synlett* **2011**, *2011*, 1047–1051. (d) Nakao, Y. *Chem. Rec.* **2011**, *11*, 242–251. (e) Kulkarni, A.; Daugulis, O. *Synthesis* **2009**, 4087–4109 and references cited therein.

(7) (a) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208–1219. (b) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948–8954.

(8) (a) Suzuki, Y.; Sun, B.; Sakata, K.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 9944–9947. (b) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 1491–1495. (c) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424–5431. (d) Yamamoto, S.;

Saga, Y.; Andou, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 401−405. (e) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Chem. - Eur. J.* **2013**, *19*, 9142−9146. (f) Andou, T.; Saga, Y.; Komai, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3213−3216. (g) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2207−2211.

(9) (a) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8551−8554. (b) Moselage, M.; Sauermann, N.; Koeller, J.; Liu, W.; Gelman, D.; Ackermann, L. *Synlett* **2015**, *26*, 1596−1600. (c) Ma, W.; Ackermann, L. *ACS Catal.* **2015**, *5*, 2822−2825. (d) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3635−3638.

(10) (a) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2015**, *17*, 1204−1207. (b) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209−10212.

(11) (a) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 4508−4511. (b) Gensch, T.; Vasquez-Cespedes, S.; Yu, D.-G.; Glorius, F. *Org. Lett.* **2015**, *17*, 3714−3717. (c) Yu, D.-G.; Gensch, T.; de Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722−17725.

(12) (a) Hummel, J. R.; Ellman, J. A. *Org. Lett.* **2015**, *17*, 2400−2403. (b) Hummel, J. R.; Ellman, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 490−498.

(13) (a) Pawar, A. B.; Chang, S. *Org. Lett.* **2015**, *17*, 660−663. (b) Patel, P.; Chang, S. *ACS Catal.* **2015**, *5*, 853−858.

(14) (a) Zhang, L.-B.; Hao, X.-Q.; Liu, Z.-J.; Zheng, X.-X.; Zhang, S.-K.; Niu, J.-L.; Song, M.-P. *Angew. Chem., Int. Ed.* **2015**, *54*, 10012−10015. (b) Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, Z.-J.; Zheng, X.-X.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *Angew. Chem., Int. Ed.* **2015**, *54*, 272−275.

(15) (a) Moselage, M.; Sauermann, N.; Richter, S. C.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 6352−6355. (b) Liu, W.; Zell, D.; John, M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 4092−4096. (c) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3868−3871. (d) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 2477−2480. (e) Punji, B.; Song, W.; Shevchenko, G. A.; Ackermann, L. *Chem. - Eur. J.* **2013**, *19*, 10605−10610.

(16) Zhang, Z.-Z.; Liu, B.; Wang, C.-Y.; Shi, B.-F. *Org. Lett.* **2015**, *17*, 4094−4097.

(17) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740−4761.

(18) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332−3335.

(19) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315−1345.

(20) Under otherwise identical reaction conditions, the use of 2-phenylpyridine and aryl- or alkyl-substituted alkynes gave thus far unsatisfactory results.

(21) For detailed information, see the Supporting Information.