C–H Activation Hot Paper

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C–H Alkenylations with Alkenyl Acetates, Phosphates, Carbonates, and Carbamates by Cobalt Catalysis at 23 °C**

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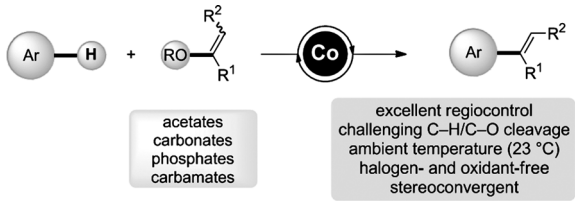
Abstract: *Inexpensive cobalt catalysts with N-heterocyclic carbene ligands enable direct arene alkenylations with easily accessible alkenyl acetates through regioselective C–H/C–O functionalizations in a stereoconvergent fashion. The versatile cobalt catalyst was broadly applicable and thus also allowed for the efficient conversion of alkenyl phosphates, carbonates, and carbamates at ambient temperature.*

Alkenylated arenes are key structural motifs in medicinal chemistry, crop protection, total synthesis, and material sciences.[1,2] Their most step-economic syntheses arguably involve metal-catalyzed C–H functionalizations.[3,4] Thus far, most catalyzed C–H functionalizations have been realized with relatively expensive 4d and 5d transition-metal complexes. Yet, in recent years, considerable success has been accomplished with naturally more abundant first-row transition-metal catalysts,[5] with particular progress achieved through versatile cobalt catalysis. Thus, for example, Nakamura, our group, Yoshikai, and Kanai have recently developed cobalt-catalyzed C–H functionalizations with organic electrophiles.[6,7] As of yet, cobalt-catalyzed C–H olefinations have been solely accomplished through hydroarylations[8] of alkynes.[7,9] Despite significant advances by Yoshikai and coworkers,[10,11] this approach continues to face considerable limitations, including the difficulty of controlling regioselectivity as well as the inherent limitation to the synthesis of acyclic alkenes.

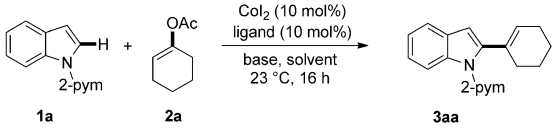
Within our program on sustainable C–H functionalizations,[12] we have developed a cobalt-catalyzed C–H olefination with easily accessible enol derivatives, which we report herein (Scheme 1). Notable features of our strategy are an excellent, predictable regiocontrol, challenging C–H/C–O functionalizations with unactivated alkenyl acetates, phosphates, carbonates, and carbamates in a stereoconvergent fashion, as well as oxidant-free olefinations under remarkably mild reaction conditions[13] at 23 °C. It is noteworthy that the only arene alkenylation of non-acidic C–H bonds[14] with alkenyl esters that has been reported thus far required the expensive ruthenium complex [Ru(cod)(cot)] and a reaction temperature of 120 °C.[15]



Scheme 1. Selective cobalt-catalyzed C–H alkenylation.

We initiated our studies by probing various reaction conditions for the envisioned C–H alkenylation of indole **1a**[16] with alkenyl acetate **2a** (Table 1). The use of phosphine ligands did not lead to significant conversion of the starting

Table 1: Optimization of the cobalt-catalyzed C–H alkenylation with acetate **2a**.[a]



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

Entry	Ligand (precursor)	Base	Solvent	Yield [%]
1	–	CyMgCl	DMPU	–
2	PPh_3	CyMgCl	DMPU	–
3	PCy_3	CyMgCl	DMPU	–
4	dppe	CyMgCl	DMPU	< 5
5	ICyHCl (**4a**)	CyMgCl	DMPU	11
6	IMesHCl (**4b**)	CyMgCl	DMPU	32
7	*IPrHCl (**4c**)*	*CyMgCl*	*DMPU*	*88*
8	$IAdHBF_4$ (**4d**)	CyMgCl	DMPU	8[b]
9	**4e**	CyMgCl	DMPU	5
10	**4f**	CyMgCl	DMPU	10
11	**4g**	CyMgCl	DMPU	3[b]
12	IPrHCl (**4c**)	*i*PrMgCl	DMPU	62
13	IPrHCl (**4c**)	*t*$BuCH_2MgCl$	DMPU	69
14	IPrHCl (**4c**)	*t*BuMgCl	DMPU	20
15	IPrHCl (**4c**)	MeMgCl	DMPU	–
16	IPrHCl (**4c**)	LiHMDS	DMPU	–
17	IPrHCl (**4c**)	CyMgCl	THF	21
18	IPrHCl (**4c**)	CyMgCl	NMP	11
19	IPrHCl (**4c**)	CyMgCl	toluene	< 5
20	IPrHCl (**4c**)	CyMgCl	DMPU	–[c]

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), CoI_2 (10 mol%), ligand (10 mol%), base (2.0 equiv), solvent (1.5 mL), 23 °C, 16 h; yields of isolated products. [b] GC conversion. [c] In the absence of CoI_2. DMPU = 1,3-dimethylhexahydro-2-pyrimidinone, dppe = 1,2-bis(diphenylphosphanyl)ethane, py(m) = pyri(mi)dyl.

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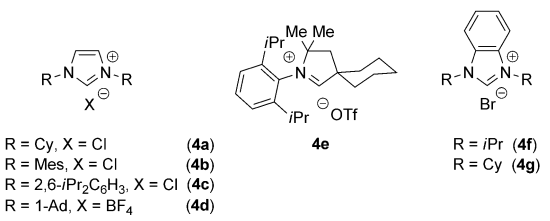
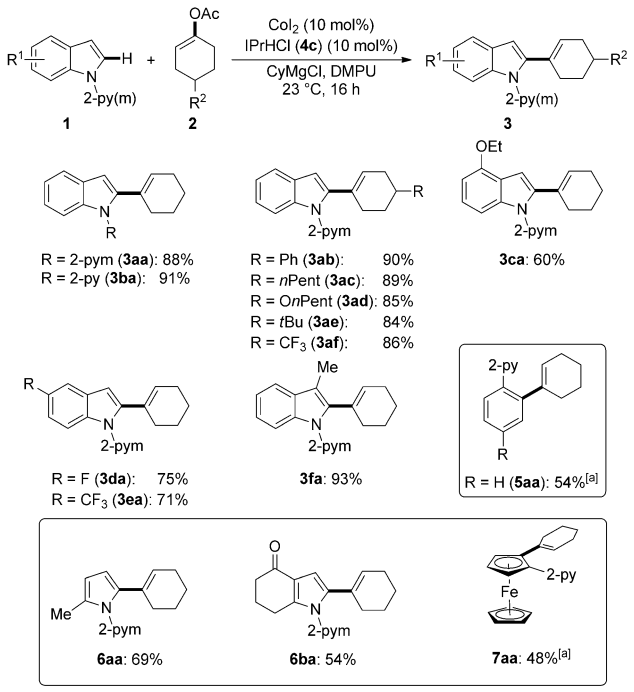


Figure 1. NHC precursors employed for C–H alkenylation. 1-Ad = 1-adamantyl, Cy = cyclohexyl, Mes = mesityl, Tf = trifluoromethanesulfonyl.

materials (entries 1–4). To our delight, in situ generated N-heterocyclic carbenes (NHCs) derived from inexpensive imidazolium salts (Figure 1) facilitated the desired transformation even at an ambient reaction temperature of 23 °C (entries 5–12), with optimal results being obtained with the preligand IPrHCl (**4c**; entry 7). Among a variety of representative bases and solvents, CyMgCl and DMPU, respectively, were found to be ideal (entries 11–19). Importantly, the reaction did not proceed in the absence of the NHC ligand or the cobalt complex (entries 1 and 20). It is also noteworthy that cycloalkenylated indoles of type **3** cannot be prepared through alkyne hydroarylations.

With the optimized cobalt catalyst in hand, we tested its generality with differently substituted heteroarenes and arenes **1** using cyclic alkenyl acetates **2** (Scheme 2).

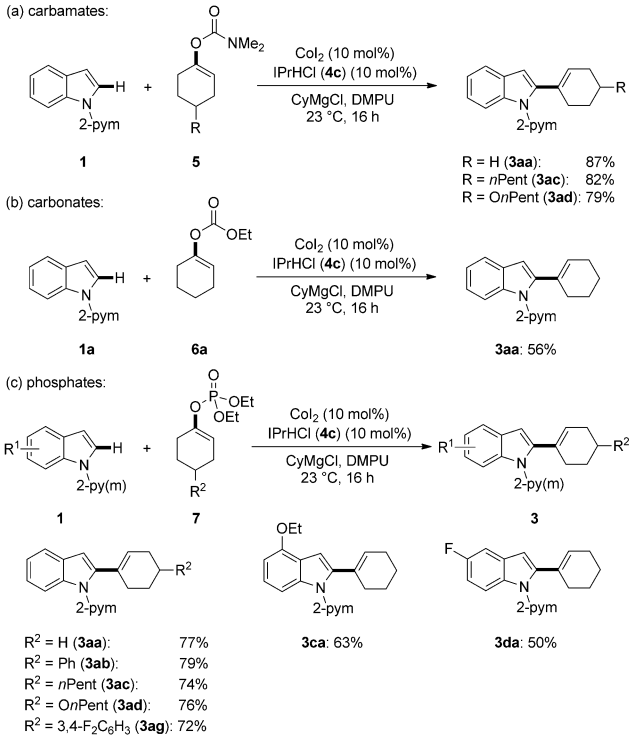
The low-valent cobalt catalyst was found to be broadly applicable and hence enabled the efficient conversion of indoles **1a** and **1b**, which bear *N*-pyridyl (py) and *N*-pyrimidyl (pym) substituents, respectively. Alkenyl acetates **2a–e** with different substituents proved to be viable substrates as well,



Scheme 2. Cobalt-catalyzed C–H alkenylation with cyclic enol acetates **2**. [a] **4a** (10 mol%) as the ligand.

and indole derivatives with substituents in the 4-, 5-, or even the sterically congested 3-position furnished the desired products **3ca–ea**. Likewise, aromatic substrates underwent the C–H alkenylation with excellent site selectivity (**5aa–ab**). Intriguingly, the versatile cobalt catalyst was not restricted to indole heterocycles, but also allowed for the efficient preparation of the alkenylated pyrroles **6aa** and **6ab**. Considering the potential of ferrocene derivatives for asymmetric catalysis and rational ligand design,[17,18] we were pleased to observe that the cobalt catalyst could be successfully employed for the difficult functionalization of ferrocene derivatives, furnishing alkenylated product **7aa**. Even though this direct alkenylation proceeded with a somewhat reduced efficacy, to the best of our knowledge, it represents the first example of a cobalt-catalyzed C–H functionalization of ferrocene derivatives.

In recent years, metal-catalyzed C–O functionalizations have received increasing attention.[19] Therefore, we became attracted by exploring different ketone-derived alkenyl derivatives for the C–H olefination of indoles **1** (Scheme 3). Interestingly, the versatility of the cobalt catalyst was



Scheme 3. C–H olefination with a) alkenyl carbamates **5**, b) alkenyl carbonates **6**, and c) alkenyl phosphates **7**.

reflected by the synthesis of the desired products **3** in high yields using substituted carbamates **5** (a), carbonates **6** (b), or phosphates **7** (c) at a temperature of 23 °C.

The optimized catalyst also proved applicable to acyclic acetates **2** and phosphates **7** under otherwise identical reaction conditions (Scheme 4). Interestingly, the alkenylations proceeded in a stereoconvergent fashion,[20] furnishing the *E* diastereomers **3ah–ak** as the sole products. It is

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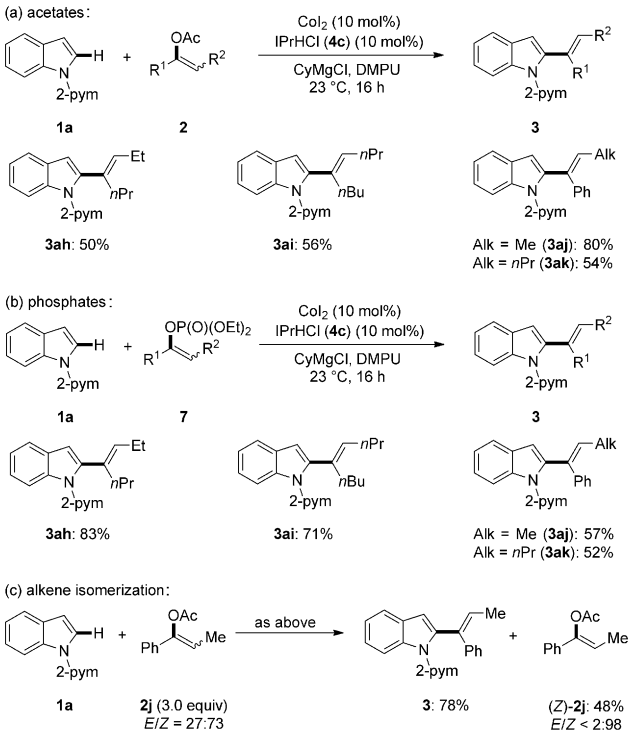
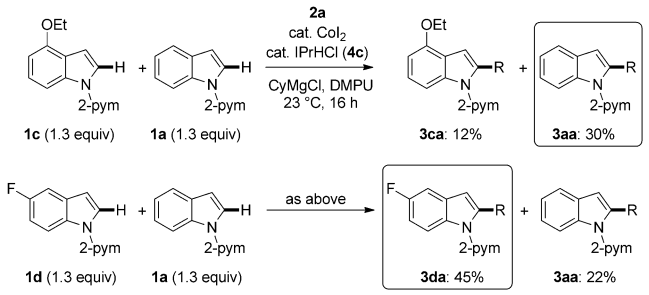
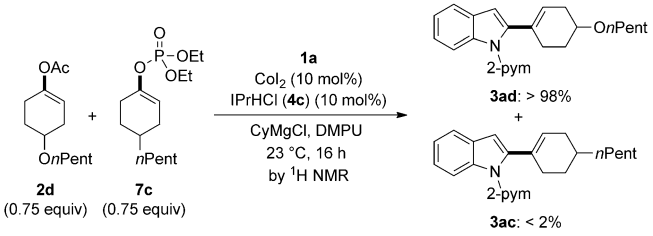


Scheme 4. C–H alkenylation with acyclic acetates **2** and phosphates **7**.[20]



Scheme 5. Intermolecular competition experiments with indoles **1** (R = 1-cyclohexenyl).



Scheme 6. Intermolecular competition experiments with different electrophiles.

noteworthy that the regioselectively substituted products **3** cannot be accessed through oxidative alkenylations or alkyne hydroarylations. Therefore, a mechanistic scenario based on initial β-elimination and subsequent hydroarylation could be ruled out.

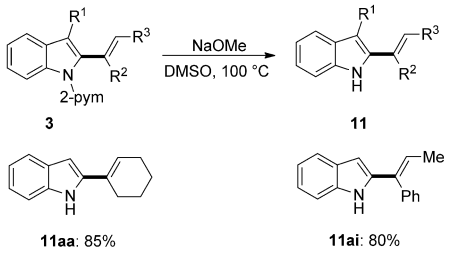
To probe the stereoconvergent nature of the cobalt-catalyzed C–H alkenylation, we performed a reaction with an excess of a diastereomeric mixture of alkenyl acetate **2j** (Scheme 4c). The alkenyl acetate was reisolated as its pure isomer (*Z*)-**2j**, which is indicative of an olefin isomerization process.

Given the unusual stereoconvergent nature of the novel cobalt-catalyzed C–H functionalization reaction, we were intrigued by its working mode. To this end, competition experiments between differently substituted indoles **1** highlighted the inherently higher reactivity of electron-deficient derivatives (see Scheme 5 and Scheme S1 in the Supporting Information).

A series of intermolecular competition experiments between enol derivatives with different leaving groups revealed the comparable reactivities of acetates and carbamates.[21] In contrast, alkenyl phosphates **7** were found to be significantly less reactive than the corresponding acetates **2** (see Scheme 6 and Schemes S4–S9).[21]

Therefore, the following order of reactivity was established for the alkenyl electrophiles, which is interestingly not in line with the C–O bond dissociation energies: $OAc \approx OC(O)NMe_2 > OP(O)(OEt)_2$. Based on our mechanistic studies and the stereoconvergent nature of the novel cobalt catalysis, we propose that the catalytic cycle begins with a C–H metalation step.[22] Thereafter, migratory insertion of the alkenyl ester generates an intermediate that is suggested to undergo β-acetoxy elimination to form the desired olefinated product while the cobalt catalyst is regenerated by transmetalation with the organomagnesium reagent.

Finally, the directing group on products **3** could be removed in a traceless fashion to deliver the desired free indoles **11** in high yields (Scheme 7).



Scheme 7. Removal of the directing group.

In summary, we have reported on the first cobalt-catalyzed direct alkenylation of unactivated C–H bonds with easily accessible enol derivatives. Thus, an NHC/cobalt catalyst allowed for olefinations of arenes, indoles, pyrroles, and ferrocenes with unactivated alkenyl acetates, phosphates, carbonates, and carbamates. The versatile cobalt-catalyzed C–H activation process occurred through a conceptually novel mechanism with high regiocontrol in a stereoconvergent fashion. The inexpensive cobalt catalyst proved to be widely applicable and displayed a high catalytic efficacy even at a reaction temperature of 23 °C.

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Angew. Chem. **2015**, *127*, 6450–6453

[1] For selected references, see: a) A. C. Grimsdale, K. L. Chan, R. E. Martin, P. G. Jokisz, A. B. Holmes, *Chem. Rev.* **2009**, *109*, 897–1091; b) A. R. Murphy, J. M. J. Fréchet, *Chem. Rev.* **2007**, *107*, 1066–1096.

[2] M. Oestreich, *The Mizoroki–Heck Reaction*, Wiley-VCH, Weinheim, **2009**.

[3] For representative recent reviews on C–H activation, see: a) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100; *Angew. Chem.* **2014**, *126*, 76–103; b) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461–1479; c) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375; d) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009; *Angew. Chem.* **2012**, *124*, 9092–9142; e) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788–802; f) O. Daugulis, *Top. Curr. Chem.* **2010**, *292*, 57–84; g) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; *Angew. Chem.* **2009**, *121*, 9976–10011; h) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238.

[4] For recent reviews that feature C–H olefinations, see: a) L. Zhou, W. Lu, *Chem. Eur. J.* **2014**, *20*, 634–642; b) S. I. Kozhushkov, L. Ackermann, *Chem. Sci.* **2013**, *4*, 886–896; c) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918; d) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170–1214; e) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; f) T. Satoh, M. Miura, *Synthesis* **2010**, 3395–3409.

[5] For recent reviews on first-row transition-metal catalysts for C–H bond functionalization, see: a) N. Yoshikai, K. Gao, *Pure Appl. Chem.* **2014**, *86*, 419–424; 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. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087–4109, and references cited therein.

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

[7] For representative examples of cobalt-catalyzed C–H functionalizations, see: a) J. R. Hummel, J. A. Ellman, *J. Am. Chem. Soc.* **2015**, *137*, 490–498; b) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 3635–3638; *Angew. Chem.* **2015**, *127*, 3706–3709; c) D.-G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17722–17725; d) L. Grigorjeva, O. Daugulis, *Org. Lett.* **2014**, *16*, 4684–4687; e) L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.* **2014**, *53*, 10209–10212; *Angew. Chem.* **2014**, *126*, 10373–10376; f) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2014**, *136*, 5424–5431; g) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 1491–1495; h) K. Gao, R. Paira, N. Yoshikai, *Adv. Synth. Catal.* **2014**, *356*, 1486–1490; i) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2013**, *135*, 9279–9282; j) Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.* **2013**, *52*, 8574–8578; *Angew. Chem.* **2013**, *125*, 8736–8740; k) B. Punji, W. Song, G. A. Shevchenko, L. Ackermann, *Chem. Eur. J.* **2013**, *19*, 10605–10610; l) T. Andou, Y. Saga, H. Komai, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 3213–3216; *Angew. Chem.* **2013**, *125*, 3295–3298; m) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 2207–2211; *Angew. Chem.* **2013**, *125*, 2263–2267; n) W. Song, L. Ackermann, *Angew. Chem. Int. Ed.* **2012**, *51*, 8251–8254; *Angew. Chem.* **2012**, *124*, 8376–8379; o) Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428–429; p) K. Gao, P.-S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2010**, *132*, 12249–12251; q) C. P. Lenges, M. Brookhart, *J. Am. Chem. Soc.* **1997**, *119*, 3165–3166; r) G. Halbritter, F. Knoch, A. Wolski, H. Kisch, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1603–1605; *Angew. Chem.* **1994**, *106*, 1676–1678 and references cited therein. For a cobalt-catalyzed alkenylation by reductive cross-coupling, see: s) M. Amatore, C. Gosmini, J. Périchon, *Eur. J. Org. Chem.* **2005**, 989–992.

[8] For recent reviews on catalyzed hydroarylations, see: a) Y. Yamamoto, *Chem. Soc. Rev.* **2014**, *43*, 1575–1600; b) T. Kitamura, *Eur. J. Org. Chem.* **2009**, 1111–1125.

[9] K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208–1219.

[10] K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2011**, *133*, 400–402.

[11] P.-S. Y. Lee, N. Yoshikai, *Angew. Chem. Int. Ed.* **2013**, *52*, 1240–1244; *Angew. Chem.* **2013**, *125*, 1278–1282.

[12] For reviews, see: a) L. Ackermann, *Org. Process Res. Dev.* **2015**, *19*, 260–269; b) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281–295; c) L. Ackermann, *Pure Appl. Chem.* **2010**, *82*, 1403–1413.

[13] J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740–4761.

[14] For palladium- and nickel-catalyzed functionalizations of C–H acidic azoles at 100 and 130–135 °C, see: a) L. Meng, Y. Kamada, K. Muto, J. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2013**, *52*, 10048–10051; *Angew. Chem.* **2013**, *125*, 10232–10235; b) L. Ackermann, S. Barfüßer, J. Pospech, *Org. Lett.* **2010**, *12*, 724–726.

[15] a) Y. Ogiwara, M. Tamura, T. Kochi, Y. Matsuura, N. Chatani, F. Kakiuchi, *Organometallics* **2014**, *33*, 402–420; b) Y. Matsuura, M. Tamura, T. Kochi, M. Sato, N. Chatani, F. Kakiuchi, *J. Am. Chem. Soc.* **2007**, *129*, 9858–9859.

[16] L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332–3335.

[17] For recent representative examples, see: a) D.-W. Gao, Q. Yin, Q. Gu, S.-L. You, *J. Am. Chem. Soc.* **2014**, *136*, 4841–4844; b) C. Kornhaaß, C. Kuper, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1619–1624; c) C. Pi, Y. Li, X. Cui, H. Zhang, Y. Han, Y. Wu, *Chem. Sci.* **2013**, *4*, 2675–2679; d) J.-B. Xia, S.-L. You, *Organometallics* **2007**, *26*, 4869–4871 and references cited therein.

[18] A. Togni, T. Hayashi, *Ferrocenes: Homogeneous Catalysis. Organic Synthesis. Materials Science*, Wiley-VCH, Weinheim, **2008**.

[19] For recent reviews on challenging arylations through C–O bond cleavages, see: a) J. Cornella, C. Zarate, R. Martin, *Chem. Soc. Rev.* **2014**, *43*, 8081–8097; b) S. I. Kozhushkov, H. K. Potukuchi, L. Ackermann, *Catal. Sci. Technol.* **2013**, *3*, 562–571; c) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346–1416; d) D.-G. Yu, B.-J. Li, Z.-J. Shi, *Acc. Chem. Res.* **2010**, *43*, 1486–1495; e) L. J. Gooßen, K. Gooßen, C. Stanciu, *Angew. Chem. Int. Ed.* **2009**, *48*, 3569–3571; *Angew. Chem.* **2009**, *121*, 3621–3624.

[20] The *E*/*Z* ratios of the substrates **2** and **7** ranged from 4:96 to 37:63. For detailed information, see the Supporting Information.

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

[22] H.-F. Klein, S. Camadanli, R. Beck, D. Leukel, U. Floerke, *Angew. Chem. Int. Ed.* **2005**, *44*, 975–977; *Angew. Chem.* **2005**, *117*, 997–999.

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