JOC The Journal of Organic Chemistry

JOCSynopsis

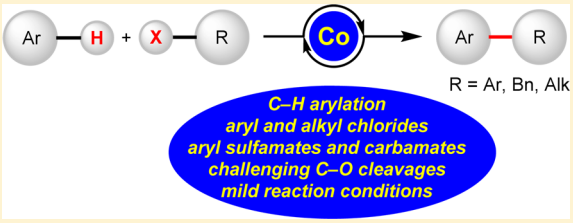
pubs.acs.org/joc

Cobalt-Catalyzed C–H Arylations, Benzylations, and Alkylations with Organic Electrophiles and Beyond

Lutz Ackermann*

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

ABSTRACT: Catalytic C–H functionalizations are increasingly viable tools for sustainable syntheses. In recent years, inexpensive cobalt complexes were identified as powerful catalysts for C–H arylations with challenging organic electrophiles. In particular, cobalt complexes of N-heterocyclic carbenes enabled high catalytic efficacy under exceedingly mild reaction conditions. This strategy set the stage for challenging direct alkylations with primary and sterically hindered secondary alkyl halides. Herein, the recent rapid evolution of cobalt-catalyzed C–H transformations with organic electrophiles is reviewed until summer 2014.



Substituted arenes are integral structural motifs in a wide range of bioactive compounds of importance to inter alia pharmaceutical industries or crop protection (Figure 1).[1−3]

Inspired by the early pioneering work of Ullmann and Goldberg,[4,5] the regioselective preparation of bi(hetero)aryls was in large part achieved via transition-metal-catalyzed cross-coupling reactions between organic electrophiles and organometallic reagents (Scheme 1a).[6] In particular, palladium-catalyzed cross-coupling reactions with aryl halides as the electrophiles have thus been established as indispensable tools for the synthesis of substituted biaryls. However, recent focus has shifted toward achieving catalytic arylations with phenol-derived arylating reagents, since these electrophiles are readily accessible, inexpensive, and can be implemented as directing groups in arene functionalization strategies.[7] The high C–O dissociation energy in phenols calls for an activation of these substrates,[8] which was predominantly achieved with very costly fluorine-containing reagents.[9] In this regard, a notable recent advance in cross-coupling chemistry was accomplished by challenging C–C formations with more difficult to activate, fluorine-free electrophiles, such as aryl tosylates, mesylates, phosphates, sulfamates or carbamates (Scheme 1b), with significant recent progress being achieved by Dankwardt, Garg, Shi, Chatani, and Snieckus among others.[7,10,11] While these cross-coupling methods are highly versatile, they inherently rely on the use of prefunctionalized organometallic starting materials as the nucleophiles, leading to undesired byproduct formation and inconvenient, lengthy reaction sequences.

The recent decade has witnessed remarkable progress in the development of step-economical[12] direct functionalizations of ubiquitous C–H bonds as latent functional groups, which served as the stimulus for the development of environmentally sound and economically attractive arylation strategies.[13] Until very recently, C–H arylations of heteroarenes with fluorine-free phenol-derived electrophiles were solely accomplished with the aid of palladium complexes,[14] while nickel catalysts were utilized by Itami and co-workers for recent direct arylations and alkenylations of C–H acidic azoles.[15,16] Direct arene arylations with tosylates or mesylates were restricted to complexes of the rare-transition-metals ruthenium[17,18] or palladium (Scheme 2a,b).[19] In stark contrast, protocols that exploit more abundant first-row transition-metal catalysts for direct arene arylations unfortunately continue to be scarce (Scheme 2c).[20]

Pioneering findings by Kharasch and Fields indicated the notable power of cobalt salts as effective catalysts for homocouplings of Grignard reagents.[21] Moreover, Murahashi and Horiie described in 1956 the chelation-assisted direct metalation of azobenzene **1**, which by carbonylative cyclization furnished indazolone **2** (Scheme 3).[22]

On the basis of these early contributions, considerable progress was thereafter made in cobalt-catalyzed cross-couplings and direct functionalizations.[23−25] In particular, the research groups of Yoshikai,[26] Nakamura,[27−29] and Kanai[30] devised methods for chelation-assisted hydroarylations of C–C multiple bonds, providing step-economical access to alkylated arenes.[23] In addition, oxidative C–H functionalizations with nucleophilic Grignard reagents were recently accomplished by means of cobalt catalysis.[31] Contrarily, the synthesis of biaryls through most user-friendly cobalt-catalyzed direct arylations of arenes with easily accessible, inexpensive organic electrophiles had proven elusive until 2012. In this Synopsis, the remarkable recent progress in cobalt-catalyzed C–H arylations of arenes is reviewed through summer 2014, along with advances in mechanistically related direct alkylations with organic halides.

C–H ARYLATIONS

Phenol-Derived Electrophiles. In consideration of the limitations in catalyzed direct arene arylations with stable, inexpensive phenol derivatives using user-friendly cobalt

Received: June 18, 2014
Published: August 7, 2014

   dx.doi.org/10.1021/jo501361k | J. Org. Chem. 2014, 79, 8948−8954

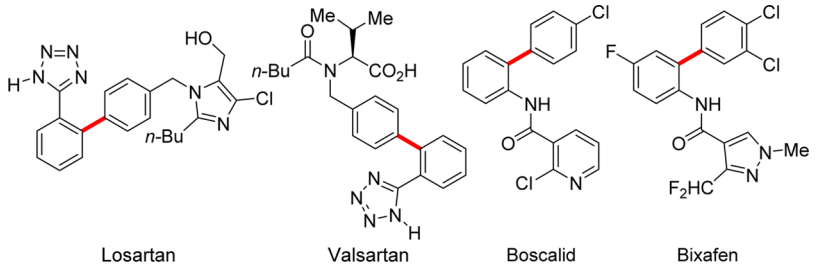
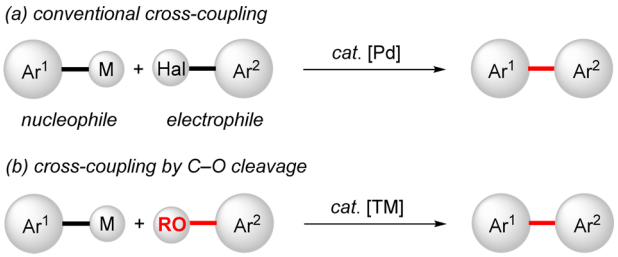
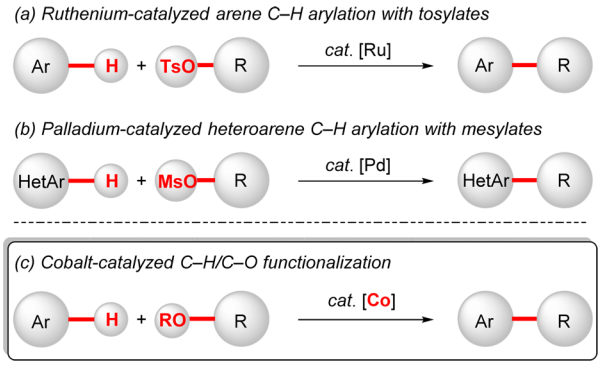


Figure 1. Representative bioactive biaryls.

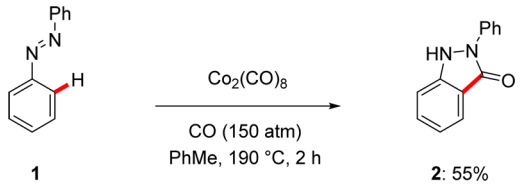
Scheme 1. Organic Electrophiles in Conventional Cross-Coupling Reactions



Scheme 2. Evolution of Catalyzed C−H/C−O Functionalizations

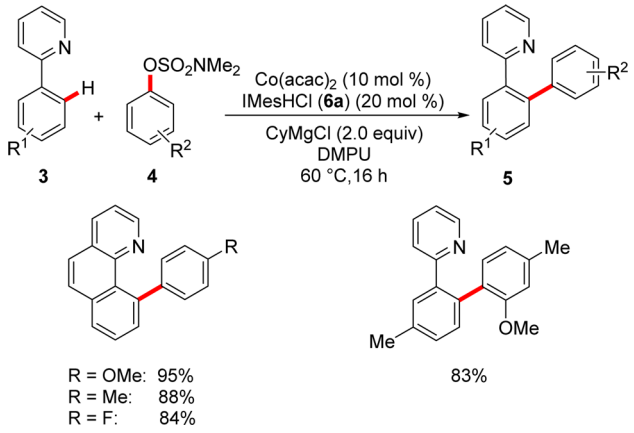


Scheme 3. Cobalt-Mediated Direct Functionalization of Azobenzene 1



catalysts, the Ackermann group initially set out to devise reaction conditions for C−H arylations of arenes **3** with electronically deactivated sulfamates **4** (Scheme 4).[32] In this context it is noteworthy that direct arene arylations with unactivated aryl sulfamates **4** have proven elusive and have not even been viable with otherwise broadly applicable palladium or ruthenium catalysts. Initial optimization studies revealed that among a set of representative (pre)ligands, including mono- or bidentate phosphines, optimal results were obtained with in situ generated N-heterocyclic carbene (NHC)[33,34] precursors bearing sterically hindered *N*,*N*′-substituents. Specifically, a catalytic system comprising $Co(acac)_2$ and IMesHCl (**6a**, Figure 2) proved to be highly effective, especially when

Scheme 4. Cobalt-Catalyzed C−H Arylations with Aryl Sulfamates 4



performing the C−H arylations with CyMgCl as the base in DMPU, a solvent previously utilized by Nakamura and co-workers.[29] As to the nature of the cobalt source, cobalt(II) and cobalt(III) compounds displayed comparable catalytic efficacies.[32] The optimized catalytic system was found to be widely applicable in the chelation-assisted C−H arylation with aryl sulfamates **4** (Scheme 4), even when employing electron-rich, and hence deactivated, substrates **4**.

The versatile cobalt catalyst was not limited to aryl sulfamates **4** but also set the stage for unprecedented arene C−H functionalizations with challenging aryl carbamates **7** (Scheme 5).[32] Notably, electron-rich as well as electron-deficient carbamates **7** were converted with high catalytic efficacy under exceedingly mild reaction conditions,[35] namely even at ambient reaction temperature.[32] Notably, the direct functionalizations chemoselectively delivered the monoarylated products **5**. Aryl carbamates **7** with sterically hindered substituents in the *ortho* position furnished the desired products **5**, highlighting the potential of aryl carbamates **7** for strategies that merge directed *ortho*-metalation (DoM)[36] and catalytic C−H activation.[32] As to the reaction mechanism (vide infra), it is noteworthy that intramolecular competition experiments with *meta*-fluoro-substituted arenes[37] site-selectively delivered the biaryls through functionalization of the kinetically more acidic C−H bond, which can be rationalized in terms of a deprotonative-type C−H metalation.[32] In accordance with this rationale, intermolecular competition experiments between differently substituted substrates **3** revealed the higher inherent reactivity of electron-deficient arenes **3**.

N-Heteroaromatic scaffolds are key structural motifs in a variety of bioactive compounds.[38] Thus, we were pleased to find that heteroarenes **8** also served as useful substrates for cobalt-catalyzed C−H arylations with aryl sulfamates **4** and

dx.doi.org/10.1021/jo501361k | J. Org. Chem. 2014, 79, 8948−8954

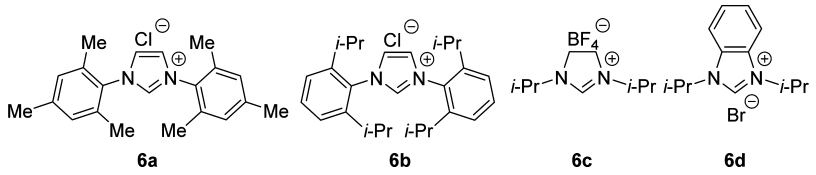
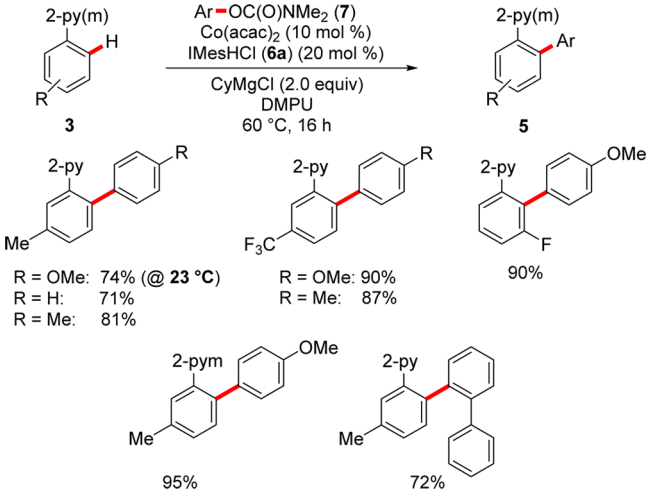


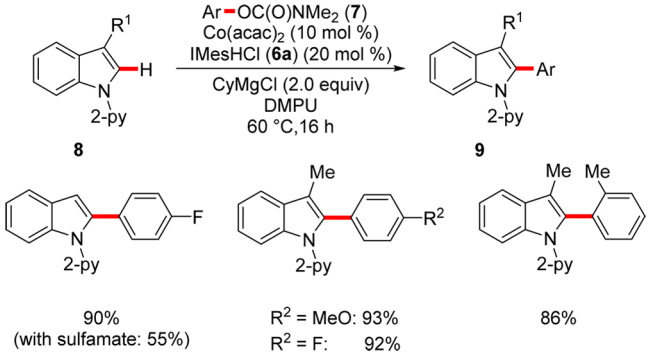
Figure 2. Preligands **6** utilized for cobalt-catalyzed C−H functionalizations.

Scheme 5. Cobalt-Catalyzed C−H Arylations with Carbamtes 7 (py = Pyridyl, pym = Pyrimidyl)



carbamates **7** (Scheme 6).[32] Indeed, *N*-substituted indoles[39] **8** were site-selectively functionalized at position C-2, which also

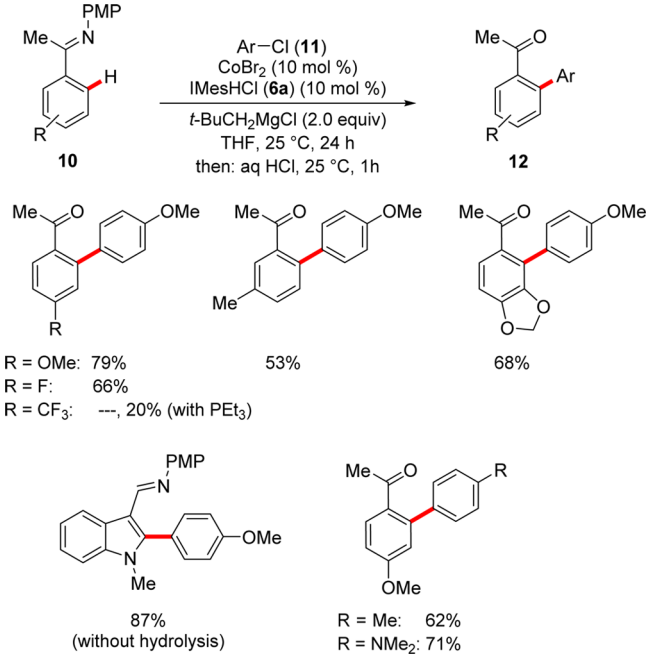
Scheme 6. Cobalt-Catalyzed C−H Arylations of Indoles 8 with Carbamates 7



enabled the synthesis of sterically congested tri-*ortho*-substituted heterobiaryls **9**.[32]

Aryl Chlorides. Aryl chlorides are the most attractive single class of aryl halides for biaryl syntheses since they are cost-effective while being widely available.[40,41] Subsequent to the development of first cobalt-catalyzed direct arylations with phenol derivatives (vide supra),[32] two protocols for cobalt-catalyzed direct arylations with aryl chlorides were independently disclosed by the groups of Yoshikai and Ackermann.[42,43] Hence, Yoshikai and co-workers found that a catalytic system consisting of $CoBr_2$ and HIMesCl (**6a**) allowed for C−H arylations of ketimines **10** (Scheme 7).[42] Interestingly, the direct arylations proceeded most efficiently at 25 °C, and a sterically hindered neopentyl Grignard reagent (*t*-$BuCH_2MgBr$) proved to be the optimal base by minimizing

Scheme 7. C−H Arylations of Aromatic Imines 10 with Aryl Chlorides 11 (PMP = *p*-Methoxyphenyl)

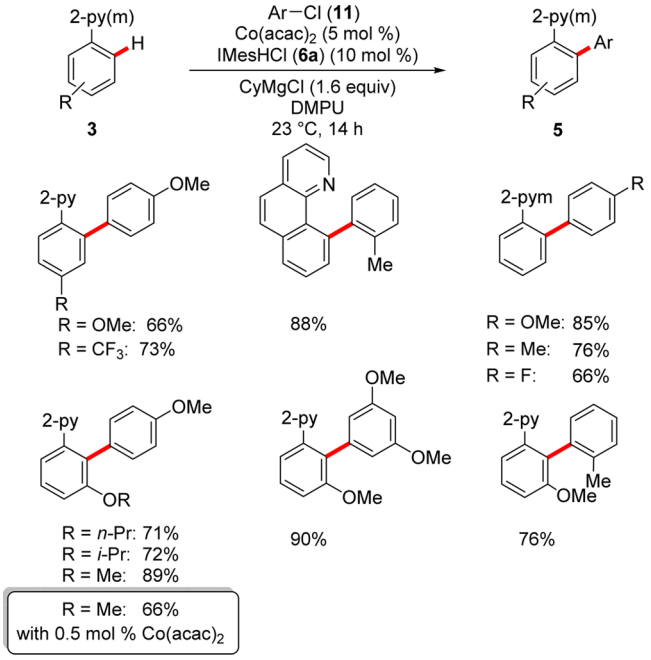


byproduct formation through undesired Kumada−Corriu cross-coupling reactions. The thus-optimized catalytic system displayed a broad substrate scope, delivering the arylated acetophenone derivatives **12** after acidic hydrolysis. A variety of arenes was functionalized by chelation-assisted cobalt catalysis. However, trifluoro-substituted arenes provided unsatisfactorily low yields of the desired products. The site-selectivity of the C−H arylations was largely governed by steric interactions, unless substituents displaying a secondary directing group were present. Interestingly, the catalytic system was also successfully applied to an imine derived from a heteroaromatic carbaldehyde.

On the basis of their previous findings on cobalt-catalyzed C−H arylations with phenol-derived electrophiles,[32] the Ackermann group developed expedient cobalt-catalyzed direct arylations with aryl chlorides through pyridine assistance (Scheme 8).[43] We were pleased to observe that the catalytic system originally designed for direct arylations with aryl sulfamates **4**[32] was also optimal for direct functionalizations with aryl chlorides **11**, which readily occurred at ambient reaction temperature.[43] Indeed, the catalytic system comprising of $Co(acac)_2$ and IMesHCl (**6a**) allowed for chelation-assisted arylations with ample substrate scope and excellent mono-selectivities (Scheme 8). The power of the cobalt catalyst was among others illustrated by efficient direct arylations with a low catalyst loading of only 0.5 mol % $Co(acac)_2$. We were particularly delighted by the outstanding site-selectivity with *m*-alkoxy-substituted arenes, which delivered the sterically more congested biaryls **5** as the sole products, highlighting a

dx.doi.org/10.1021/jo501361k | J. Org. Chem. 2014, 79, 8948−8954

Scheme 8. Site-Selective C−H Arylations with Chlorides 11

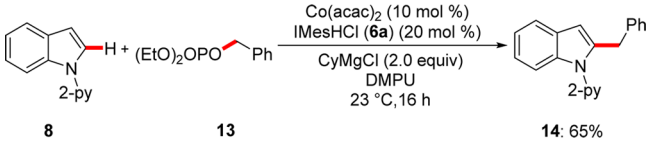


considerable secondary directing group effect. Intriguingly, this observation was exploited for the preparation of tri-*ortho*-substituted biaryls, which indicated the great potential for the future development of asymmetric[44,45] cobalt-catalyzed C−H arylations.

C−H BENZYLATIONS

The inexpensive cobalt catalyst was not restricted to C(sp^2)−C(sp^2)-forming processes but also enabled effective C−H benzylation[46] reactions on indoles **8** (Scheme 9).[32] Thus, the C(sp^2)−C(sp^3) formation was realized with benzyl phosphates **13** at a remarkably mild reaction temperature of 23 °C.

Scheme 9. C−H Benzylations of Heteroarenes 8 with Phosphates 11

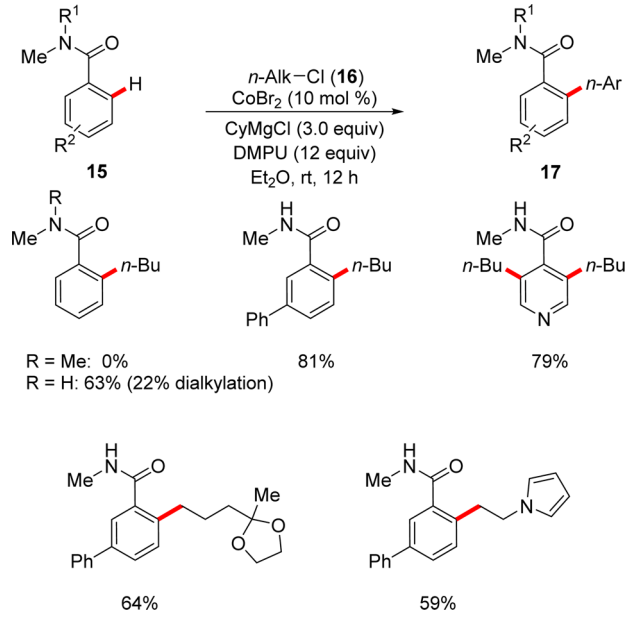


C−H ALKYLATIONS

While direct arylation chemistry has witnessed major progress during the past decade, C−H functionalizations with alkyl halides as the organic electrophiles continue to be scarce.[46] In particular, direct alkylations with secondary alkyl halides are extremely challenging because oxidative addition is often difficult and because β-hydride elimination of the thus-formed transition-metal alkyl complexes frequently outcompetes the desired reductive elimination.

In this regard, it is notable that Nakamura and co-workers elegantly devised effective cobalt-catalyzed direct *n*-alkylations with primary alkyl halides **16** (Scheme 10).[29] Interestingly, the C−H *n*-alkylation proceeded with synthetically useful secondary amides **15** in the absence of any additional NHC ligand. While primary alkyl chlorides **16** were efficiently converted, a

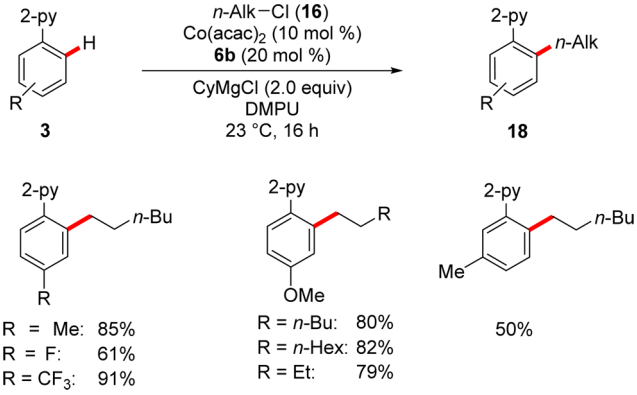
Scheme 10. C−H Alkylations of Benzamides 15 with Primary Alkyl Chlorides 16



secondary alkyl chloride gave an unsatisfactorily low conversion of only 15%. The versatile *n*-alkylation strategy was applicable to aromatic and heteroaromatic substrates **15** and allowed for the use of differently decorated alkyl chlorides **16**.

Based on our previous findings on cobalt-catalyzed direct arylations (vide supra)[32] and our continued interest in catalyzed C−H alkylations,[46−49] we examined cobalt catalysts for C−H transformations with alkyl halides **16**. Notably, the cobalt catalyst derived from NHC precursor HIMesCl (**6a**) enabled pyridine-assisted C−H alkylations,[43] yet the most effective catalysis was achieved here when the sterically hindered NHC derivative **6b** was used (Scheme 11). Therefore,

Scheme 11. C−H Alkylations with Alkyl Chlorides 16

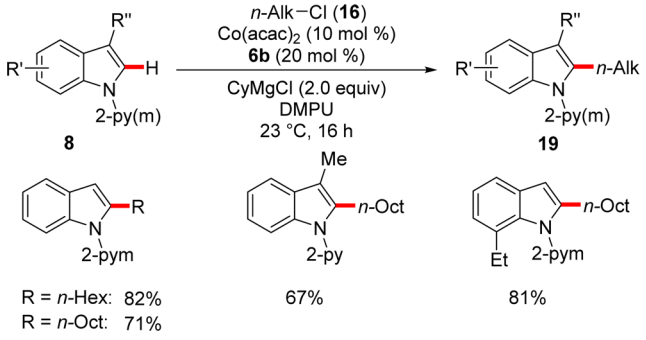


chelation-assisted direct alkylations were accomplished with various alkyl chlorides **16**. The C−H functionalizations efficiently occurred on various arenes displaying a set of electron-donating or electron-withdrawing substituents with excellent site-selectivities.

Likewise, the inexpensive cobalt catalyst proved applicable to the direct alkylation of indoles **8** (Scheme 12).[43] *N*-Pyridyl- and *N*-pyrimidyl-substituted heteroarenes **8** were identified as suitable starting materials, the latter of which set the stage for

dx.doi.org/10.1021/jo501361k | J. Org. Chem. 2014, 79, 8948−8954

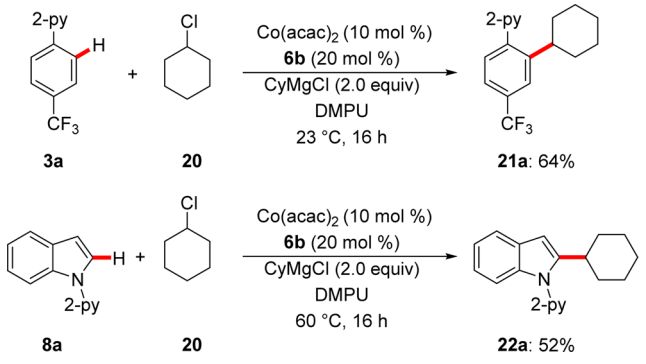
Scheme 12. C−H Alkylations of Indoles 8



a removable directing group strategy.[50,51] The catalytic system showed a wide substrate scope, as was among others illustrated by the successful use of various *n*-alkyl chlorides **16**.[43] Furthermore, substituted indoles **8** proved to be viable substrates, even with sterically congested substituents at the C-3 or C-7 position.

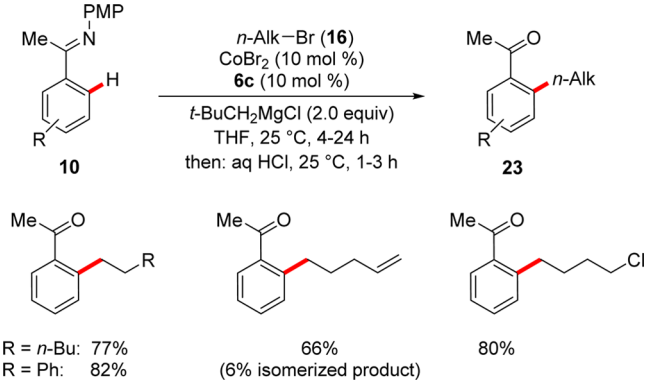
In consideration of the difficulties associated with the use of sterically hindered secondary alkyl halides **20**,[46] we were particularly pleased to find that the in situ generated cobalt catalyst allowed for C−H functionalizations with these challenging organic electrophiles **20** as well (Scheme 13).[43] The C−H alkylations proceeded with excellent *ortho*-selectivity[48] and proved amenable to functionalizations on arenes **3** as well as heteroarenes **8**.[43]

Scheme 13. Secondary C−H Alkylations



Based on their previous findings on C−H arylations with aryl chlorides,[42] Yoshikai and co-workers developed cobalt-catalyzed direct alkylations of ketimines **10** (Scheme 14).[52,53]

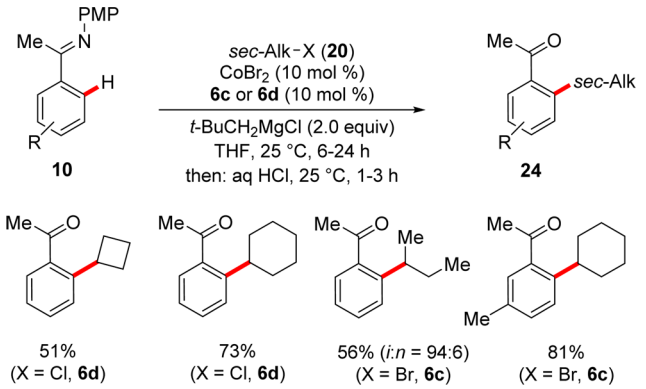
Scheme 14. C−H Alkylation of Ketimines 10



In contrast to their previous report, cobalt catalysts derived from the *N*,*N*-dialkyl-substituted NHC precursor **6c** or its benzannulated analog **6d** proved ideal (Figure 2). Interestingly, the method was successfully applied to both alkyl bromides and alkyl chlorides, with the former generally furnishing improved yields.

Intriguingly, the cobalt catalyst also allowed for more challenging C−H alkylations with secondary alkyl halides **20** with ample substrate scope (Scheme 15).[52] The optimized

Scheme 15. Secondary C−H Alkylations of Ketimines 10

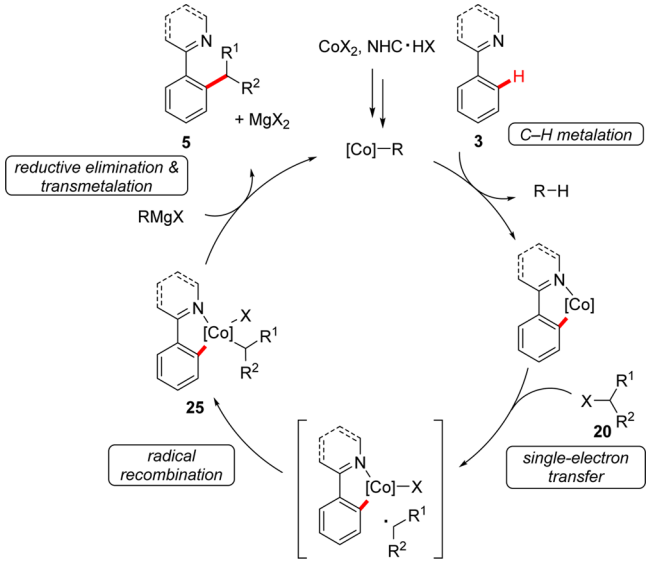


protocol was broadly applicable to cyclic secondary alkyl bromides and chlorides, and an unsymmetrical acyclic substrate reacted with a synthetically useful *iso*:*n* ratio of 94:6. However, heterocyclic substrates generally led to lower yields of the desired alkylated products.

Mechanistic Considerations. The novel cobalt-catalyzed direct C−H arylations represent rare examples of biaryl syntheses through cobalt-catalyzed functionalizations of unactivated aryl carbamates, sulfamates and chlorides.[24,25,54] In consideration of this unique reactivity profile, mechanistic studies were conducted to delineate the catalysts mode of action.[32,43,52] To this end, intermolecular competition experiments between differently substituted arenes generally highlighted more electron-deficient arenes to be significantly more reactive, both in C−H arylations as well as C−H alkylations. This observation is not in agreement with an electrophilic-type of C−H functionalization, but can be rationalized in terms of a deprotonative-type C−H cobaltation. While the full mechanistic scenario has hitherto to be unraveled, and the coordination chemistry of the individual intermediates has not been entirely elucidated, mechanistic studies suggest the cobalt-catalyzed C−H functionalizations to proceed by initial cyclometalation[55] (Scheme 16).[32] Further, reactions with isotopically labeled substrates highlighted a significant D/H-exchange reaction in the *ortho*-position and are thus suggestive of a reversible C−H metalation.[32,42,43,52] Thereafter, the activation of the organic electrophile is suggested to occur. On the basis of attempted cobalt-catalyzed direct arylations in the presence of typical radical scavengers[32] and alkylations with stereochemically well-defined secondary alkyl halides,[52] this C−X cleavage is proposed to proceed via a single-electron transfer.[32,43,52] However, further mechanistic studies are warranted to fully understand the catalytic activation of aromatic organic electrophiles within the C−H functionalization manifold. A subsequent radical rebound is put forward to generate intermediate **25**, which finally undergoes reductive elimination to furnish the desired product **5**, while trans-

dx.doi.org/10.1021/jo501361k | J. Org. Chem. 2014, 79, 8948−8954

Scheme 16. Plausible Catalytic Cycle for the Cobalt-Catalyzed C−H Functionalizations



metalation with the Grignard reagent regenerates the active cobalt catalyst.

CONCLUSION

During the past decade, C−H functionalization strategies using second-row transition-metal catalysts have revolutionized organic syntheses. However, less expensive first-row transition-metal complexes have in the past few years been established as increasingly viable alternatives for economically attractive C−H transformations. In particular, user-friendly cobalt salts were identified as versatile catalysts for step-economical chelation-assisted direct C−H arylations with user-friendly organic electrophiles. Hence, NHC-derived cobalt complexes proved to be the key to success for direct arene arylations with aryl chlorides as well as with stable, inexpensive phenol derivatives. The unique power of cobalt-catalyzed C−H activation was, for instance, illustrated by unprecedented direct arylations with unactivated aryl sulfamates or carbamates with low catalyst loadings and under exceedingly mild reaction conditions, namely at ambient reaction temperature. While direct benzylations were accomplished with benzyl phosphates, challenging direct alkylations proved viable with primary alkyl bromides and chlorides with pyridines, pyrimidines, amides, or imines as the site-selectivity ensuring entities. The C−H functionalization approach proved further amenable to the efficient conversion of challenging secondary alkyl halides. In consideration of these recent findings, along with examples of cobalt-catalyzed C−H functionalizations with alternative organic electrophiles containing C−N bonds,[56,57] further exciting developments, such as asymmetric C−H functionalizations, are expected in this rapidly evolving research area.

AUTHOR INFORMATION

Corresponding Author

*E-mail: lutz.ackermann@chemie.uni-goettingen.de. Fax: (+49) 551-39-6777. Tel: (+49)551-39-3202.

Notes

The authors declare no competing financial interest.

Biography

Lutz Ackermann studied Chemistry at the Christian-Albrechts-University Kiel, Germany, and performed his Ph.D. at the Max-Planck-Institut für Kohlenforschung in the laboratories of Prof. Alois Fürstner (Mülheim/Ruhr, 2001). After a postdoctoral stay at the University of California at Berkeley with Prof. Robert G. Bergman, he initiated his independent academic career in 2003 at the Ludwig Maximilians-University München. In 2007, he became Full Professor at the Georg-August-University Göttingen, and his research group develops catalytic methods for sustainable organic syntheses, with a current focus on C−H activation strategies.

ACKNOWLEDGMENTS

I sincerely thank all former and present co-workers involved in the C−H functionalization projects for their experimental work and intellectual contributions. Generous support by the European Research Council under the European Community's Seventh Framework Program (FP7 2007−2013)/ERC Grant Agreement No. 307535 is gratefully acknowledged.

REFERENCES

(1) Ackermann, L. *Modern Arylation Methods*; Wiley-VCH: Weinheim, 2009.
(2) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2004.
(3) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004
(4) Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174−2185.
(5) Goldberg, I. *Chem. Ber.* **1906**, *39*, 1691−1692.
(6) For a recent review on cross-coupling reactions, see: Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085 and references cited therein.
(7) For recent reviews on challenging arylations through C−O cleavages, see (a) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29−39. (b) Tobisu, M.; Chatani, N. *ChemCatChem.* **2011**, *3*, 1410−1411. (c) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346−1416 and references cited therein..
(8) For examples of biaryl syntheses directly using phenols, see: Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett.* **2012**, *14*, 2146−2149 and references cited therein.
(9) Högermeier, J.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747−2763.
(10) Littke, A. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009; pp 25−67.
(11) For selected representative examples, see: (a) Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352−6363. (b) Ackermann, L.; Sandmann, R.;

Song, W. *Org. Lett.* **2011**, *13*, 1784−1786. (c) Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428−2432 and references cited therein.
(12) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40−49.
(13) Representative recent reviews on catalyzed C−H activation: (a) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74−100. (b) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461−1479. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788−802. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238 and references cited therein.
(14) (a) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201−204. (b) Ackermann, L.; Barfüsser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724. (c) So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem.—Eur. J.* **2011**, *17*, 761−765.
(15) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169−172.
(16) Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10048−10051.
(17) Ruthenium-catalyzed C−H arylations with aryl tosylates: (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299−2302. (b) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619−2622.
(18) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211−229.
(19) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430−432.
(20) Authoritative reviews on the use of inexpensive first-row transition-metal catalysts for C−H 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**, 19−30. (c) Nakao, Y. *Chem. Rec.* **2011**, *11*, 242−251. (d) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087−4109.
(21) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316−2320.
(22) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816−4817.
(23) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208−1219.
(24) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435−1462.
(25) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537−3562.
(26) Selected representative examples: (a) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 8574−8578. (b) Tan, B.-H.; Dong, J.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 9610−9614. (c) Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283−17295. (d) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249−12251.
(27) Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2011**, *13*, 3232−3234.
(28) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221−5223.
(29) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428−429.
(30) Selected examples: (a) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424−5431. (b) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2207−2211.
(31) (a) Liu, W.; Cao, H.; Xin, J.; Jin, L.; Lei, A. *Chem.—Eur. J.* **2011**, *17*, 3588−3592. (b) To, C. T.; Chan, T. L.; Li, B. Z.; Hui, Y. Y.; Kwok, T. Y.; Lam, S. Y.; Chan, K. S. *Tetrahedron Lett.* **2011**, *52*, 1023−1026. (c) Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1109−1113. See also: (d) Tiecco, M. *Chem. Commun.* **1965**, 555−556.
(32) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251−8254.
(33) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309.
(34) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440−1449.
(35) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740−4761.
(36) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 330−367.
(37) Clot, E.; Megret, C.; Eisenstein, O.; Perutz, R. N. *J. Am. Chem. Soc.* **2009**, *131*, 7817−7827.
(38) Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J. *Modern Heterocyclic Chemistry*; Wiley-VCH: Weinheim, 2011.
(39) Selected reviews on the preparation and functionalization of indoles: (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. React.* **2012**, *76*, 281−534. (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875−2911 and references cited therein.
(40) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.
(41) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.
(42) Gao, K.; Lee, P.-S.; Long, C.; Yoshikai, N. *Org. Lett.* **2012**, *14*, 4234−4237.
(43) Punji, B.; Song, W.; Shevchenko, G. A.; Ackermann, L. *Chem.—Eur. J.* **2013**, *19*, 10605−10610.
(44) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242−3272.
(45) Herrmann, P.; Bach, T. *Chem. Soc. Rev.* **2011**, *40*, 2022−2038.
(46) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866−4877.
(47) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045−6048.
(48) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877−5884.
(49) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 2477−2480.
(50) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332−3335.
(51) Wang, C.; Huang, Y. *Synlett* **2013**, *24*, 145−149.
(52) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279−9282.
(53) Yoshikai, N.; Gao, K. *Pure Appl. Chem.* **2014**, *86*, 419−424.
(54) For recent examples, see: (a) Kuzmina, O. M.; Steib, A. K.; Markiewicz, J. T.; Flubacher, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 4945−4949. (b) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949−11963 and references cited therein.
(55) Klein, H.-F.; Camadanli, S.; Beck, R.; Leukel, D.; Floerke, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 975−977.
(56) Gao, K.; Paira, R.; Yoshikai, N. *Adv. Synth. Catal.* **2014**, *356*, 1486−1490.
(57) Gao, K.; Yoshikai, N. *Chem. Commun.* **2012**, *48*, 4305−4307.