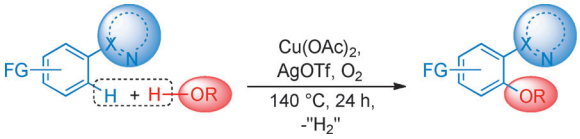
Communications

C–H Activation

S. Bhadra, C. Matheis, D. Katayev, L. J. Gooßen* ———— ■■■■–■■■■

Copper-Catalyzed Dehydrogenative Coupling of Arenes with Alcohols



What a couple! Arenes functionalized with donating groups undergo oxidative dehydrogenative coupling with alcohols in the presence of a copper/silver catalyst system. This intermolecular C–H alkoxylation provides a convenient synthetic route to the important class of aryl ethers. The catalyst system also allows the alkoxylation of benzylic C–H groups with formation of benzyl alkyl ethers.

C–H Activation

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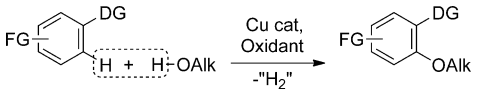
Copper-Catalyzed Dehydrogenative Coupling of Arenes with Alcohols**

*Sukalyan Bhadra, Christian Matheis, Dmitry Katayev, and Lukas J. Gooßen**

Dehydrogenative cross-couplings arguably represent the most attractive strategy to introduce carbon- or heteroatom-based groups into organic molecules.[1] Ideally, two different molecules are each selectively activated at one specific C–H or heteroatom–H group, and undergo regioselective cross-coupling with one another. The hydrogen formally produced is usually scavenged in an oxidative step, for example, with formation of water, which significantly contributes to the thermodynamic driving force of the reaction. Key advantages of this approach are that functionalization occurs within a single step rather than a resource- and waste-intensive synthetic sequence consisting of the prefunctionalization of substrates with leaving groups and traditional cross-coupling. Tremendous progress has been made in recent years in this field, and the feasibility of regioselective dehydrogenative cross-couplings has been demonstrated for various C–C,[1a,d] several C–N,[2] and a few C–O[3] bond-forming reactions. However, the practical utility of existing protocols is often limited by narrow substrate scopes, lack of selectivity or the use of expensive metal catalysts, e.g., Pd,[4] Rh,[5] or Ru.[6]

Owing to the abundance of aryl ether moieties in biologically active molecules and functional materials,[7] their synthesis by the dehydrogenative coupling of arenes and free alcohols is highly desirable (Scheme 1). It compares



Scheme 1. Dehydrogenative alkoxylation of arenes. DG = directing group, FG = functional group, Alk = alkyl.

favorably with traditional approaches[8] and modern aryl ether syntheses, for example, through Pd-catalyzed Buchwald–Hartwig[9] couplings and Cu-catalyzed Ullmann[10] or Chan–Evans–Lam[11] reactions. However, whereas efficient methods for direct hydroxylations,[12] acetoxylations,[13] and even a phenoxylation[13b] have been reported, the development of dehydrogenative alkoxylations of arenes is challenging. Alkanols easily dehydrate through cationic or radical mechanisms[14] and are sensitive towards oxidation to the corresponding ketones or carboxylic acids.[15] Moreover, metal alkoxide intermediates are prone to β-hydride elimination.[16] Pioneering direct dehydrogenative alkoxylations of arenes that involve the use of nitrogen-based directing groups and palladium catalysts have been disclosed by the groups of Sanford[17] and others.[18] A CuCl-catalyzed C2 alkoxylation of imidazoles has been reported by Kanai et al.[19] However, these methods have been applied only to a small number of simple alcohol substrates.

Based on the Cu-catalyzed phenoxylation of arenes developed by Yu and co-workers[13b] and the observation by Ribas and Stahl that a macrocyclic copper ligand was methoxylated on the addition of methanol,[20] we reasoned that a copper catalyst might promote the desired direct dehydrogenative cross-coupling between arenes and alcohols.[21,22] This was further supported by our recent discovery of decarboxylative *ipso*-[23] and *ortho*-alkoxylations[24] of benzoic acids with boron or silicon alkoxides.

To probe the viability of this approach, we investigated the reaction between 1-butanol and 2-phenylpyridine, a substrate widely employed for chelation-assisted C–H functionalizations.[25] Indeed, when a solution of 2-phenylpyridine in 1-butanol was treated with stoichiometric amounts of $Cu(OAc)_2$ under an O_2 atmosphere at 120 °C, the desired butoxyarene (**3ab**) was obtained in visible amounts, along with some doubly butoxylated product **4** (Table 1, entry 1).

As we had previously observed a beneficial effect of silver(I) salts on the alkoxylation step of decarboxylative Chan–Evans–Lam reactions, we next tested various silver salts as additives, including AgOTf, Ag_2CO_3, AgOAc, and Ag_2O (see also the Supporting Information, Table S1). Among them, silver(I) triflate proved to be particularly effective and its use led to a sharp increase in the yield (Table 1, entry 2). A reduction in the copper loading to 25 mol% and an increase in the temperature to 140 °C further enhanced the conversion and the selectivity for the monoalkoxylated product **3ab** (Table 1, entries 3 and 4). **3ab** was obtained exclusively when less 1-butanol was used (Table 1, entry 5). A reduction of the copper acetate loading to 10 mol% or the silver triflate loading to 1 equivalent led to decreased yields (Table 1, entries 6 and 7). Addition of various N or O donor and/or phosphine ligands to stabilize the copper catalyst did not substantially influence the yields (see the Supporting Information, Table S2). However, a combination of $Cu(OTf)_2$ with excess NaOAc is effective also at 10 mol% Cu loading. This is in agreement with findings by

[*] Dr. S. Bhadra, C. Matheis, Dr. D. Katayev, Prof. Dr. L. J. Gooßen
FB Chemie-Organische Chemie
Technische Universität Kaiserslautern
Erwin-Schrödinger-Strasse Geb. 54
67663 Kaiserslautern (Germany)
E-mail: goossen@chemie.uni-kl.de
Homepage: http://www.chemie.uni-kl.de/goossen

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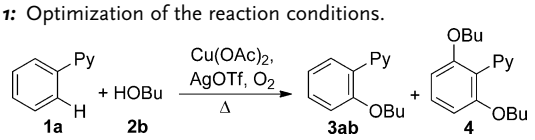
Table 1: Optimization of the reaction conditions.



1a 2b 3ab 4

Entry	**2b** [mL]	Cu salt [equiv]	Ag salt [equiv]	*T* [°C]	**3ab** [%]	**4** [%]
1	2	1	0	120	16	4
2	2	1	1.5	120	57	13
3	2	0.25	1.5	120	53	7
4	2	0.25	1.5	140	67	4
5	1	0.25	1.5	140	82	0
6	1	0.1	1.5	140	32	0
7	1	0.25	1	140	46	2
8[a]	1	0.1	1.5	140	61	5
9[b]	1	0.25	1.5	140	26	3
10	1	0.25	0.25	140	27	5
11	1	0	1.5	140	0	0

Reaction conditions: **1a** (0.3 mmol), **2** (1–2 mL), $Cu(OAc)_2$, AgOTf, 1 atm O_2, 24 h. Yields determined by GC analysis using *n*-tetradecane as internal standard. [a] $Cu(OTf)_2$ (0.1 equiv), NaOAc (1 mmol). [b] Under N_2 atmosphere. Py = 2-pyridyl, Tf = trifluoromethanesulfonyl.

Stahl and co-workers, who reported that copper(II) catalysts with non-coordinating anions can be activated by NaOAc.[26]

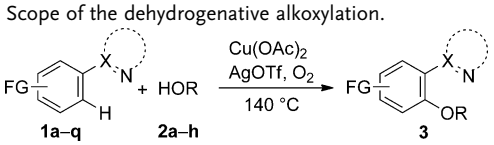
Control experiments revealed that an oxygen atmosphere is essential, even when a stoichiometric amount of silver triflate is used (Table 1, entries 9 and 10). Without copper acetate, no reaction takes place (Table 1, entry 11). This finding confirms that the main role of the silver is to transfer the alkoxy group to the copper catalyst. The presence of water in the alkoxylation reactions is tolerated but results in a decrease in the reaction rate. Even when the alcohols are completely replaced with water, no hydroxylation of the arene occurred (see Supporting Information, Table S3).

Having, thus, found an effective protocol for the dehydrogenative alkoxylation, we next investigated its scope and found that it has broad applications (Table 2). Both linear and branched alcohols were successfully coupled with 2-phenylpyridine to give products **3aa**–**3af**. Chiral alcohols reacted with retention of their configuration (see **3ag**–**3ah**). The reactions of methanol, as well as allylic and benzylic alcohols did not give good yields, presumably they are sensitive to oxidation.[15a] Phenols are also unsuitable as substrates because they undergo oxidative self-coupling under the reaction conditions. 2-(Hetero)arylpyridines with diversely substituted aryl/heteroaryl and pyridine rings were butoxylated in good to moderate yields to give products **3bb**–**3kb**, and **3mb**. Even bromide substituents remained largely intact (see **3eb**). As well as 2-pyridyl, other N-chelating directing groups, for example, pyrimidine, benzoquinoline, and pyrazole, can be used (see **3na**–**3qb**). The alkoxylation was regiospecific in all cases, and no bis(alkoxylation) product was obtained. The reactions proceeded cleanly with regard to the phenylpyridines. The differences between the isolated and expected product yields were due to incomplete conversion; by-products originating from these starting materials were detected only in trace amounts. Typical side reactions of the alcohols include the formation of symmetrical ethers (up to 30% based on the alcohol) and dialkyl acetals (ca. 2%). For the example of **3ab**, the alkoxylation reaction was successfully carried out also in the pesence of 10 mol% of $Cu(OTf)_2$ and 1 equivalent of NaOAc.[26]

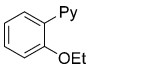
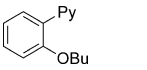
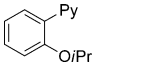
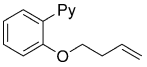
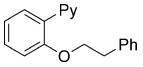
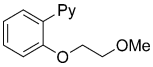
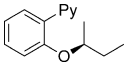
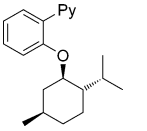
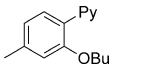
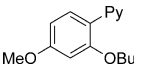
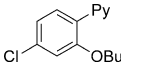
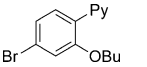
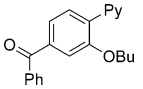
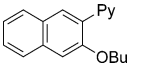
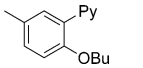
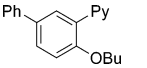
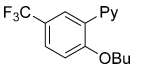
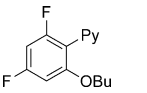
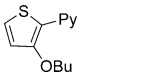
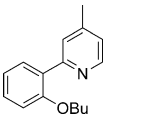
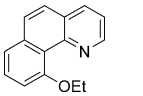
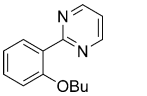
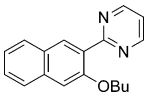
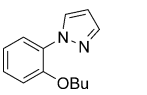
This strategy can also be used for the alkoxylation of benzylic C–H groups (Scheme 2). When 2-benzylpyridine (**1r**) was reacted with 1-butanol, the butoxy group was installed selectively in the benzylic position rather than on the aromatic ring. This shows that regioselective dehydrogenative alkoxylations are not limited to C_{sp^2}–H bonds.

Further studies were performed to obtain insight into mechanism of the dehydrogenative alkoxylation (see the

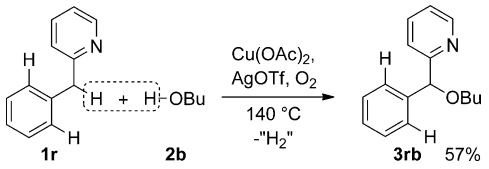
Table 2: Scope of the dehydrogenative alkoxylation.



1a–q 2a–h 3

Product		Yield [%]	Product		Yield [%]
	**3aa**	65		**3ab**	78 58[a] 76[b]
	**3ac**	53		**3ad**	57
	**3ae**	59		**3af**	65
	**3ag**	54[c]		**3ah**	32
	**3bb**	80		**3cb**	82
	**3db**	64		**3eb**	58[d]
	**3fb**	61		**3gb**	56
	**3hb**	68		**3ib**	54
	**3jb**	41		**3kb**	69
	**3lb**	58		**3mb**	76
	**3na**	51		**3ob**	62
	**3pb**	67		**3qb**	55

Reaction conditions: **1** (1.00 mmol), **2** (3 mL), $Cu(OAc)_2$ (0.25 mmol), AgOTf (1.50 mmol), 1 atm O_2, 140 °C, 24 h. [a] with 0.1 mmol of $Cu(OTf)_2$ and 1 mmol of NaOAc. [b] with 0.25 mmol of $Cu(OTf)_2$ and 1 mmol of NaOAc. [c] 1.8 mL of (*S*)-(+)-2-BuOH. [d] Along with 13% 2-(4-butoxyphenyl)pyridine.



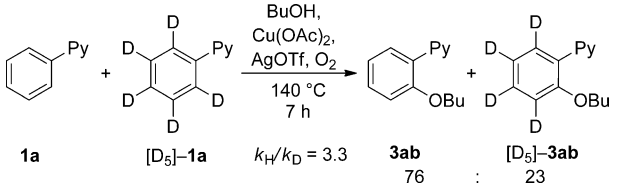
Scheme 2. Dehydrogenative alkoxylation of an C_{sp^3}–H bond.

Supporting Information). The presence of radical quenchers, such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or *p*-benzoquinone (1.5 equiv in each case), completely suppressed product formation; this finding suggests that the reaction involves radical steps. In the presence of TEMPO, the reaction exclusively produces butyraldehyde dibutyl acetal, whereas no reaction takes place in the presence of *p*-benzoquinone.

The intermediacy of alkoxy radicals is more likely than that of acyl radicals because no competing acylations[27] or hydroxyalkylations[28] were observed. Silver is likely to be involved in the formation of the alkoxy radicals because in the absence of silver, only low yields of the alkoxylated product **3ab** are obtained.[29] Treatment of 1-butanol with $Cu(OAc)_2$, AgOTf, and TEMPO affords butyraldehyde dibutyl acetal in high yield, whereas this product is formed at best in traces in the presence of only the copper catalyst.[15a] In GC–MS analyses of the copper/silver-catalyzed butoxylations of 2-phenylpyridine, traces of butyraldehyde dibutyl acetal were always detected. Moreover, the formation of metallic silver is observed in all reactions. These findings further support the intermediacy of alkoxy radicals, which would readily form from silver alkoxides. The generation of large quantities of di-*n*-butyl ether can be rationalized by the addition of butoxy radicals to 1-butene formed through thermal dehydration of 1-butanol.[14a]

Unfortunately, control experiments starting from preformed silver alkoxides, that would unambiguously prove their intermediacy, have so far been precluded by their instability.[30]

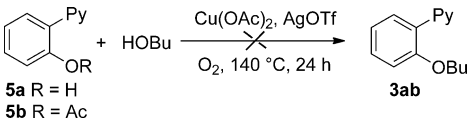
In the reaction of 2-phenylpyridine (**1a**) and 2-phenyl-[D_5]pyridine ([D_5]-**1a**) with 1-butanol, a high kinetic isotope effect of 3.3 was observed (Scheme 3). When 2-phenylpyridine was ethoxylated with ethanol-d_1, no proton scrambling in the starting material was detected. These findings indicate that the C–H activation of the arene is irreversible and rate limiting (see the Supporting Information). The process thus involves a directed C–H activation. Single-electron-transfer (SET) pathways as found by Yu and co-workers in copper-mediated chlorination reactions[13b] and mechanisms involving the attack of copper-coordinated oxide or peroxide onto



Scheme 3. Determination of the kinetic isotope effect.

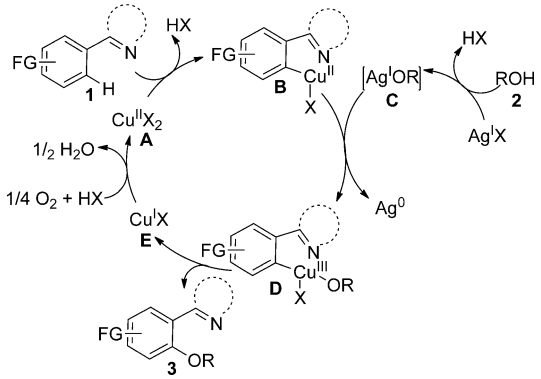
the arene ring[31] can be excluded, as they would have resulted in a low kinetic isotope effect. The possibility of a proton-coupled electron-transfer (PCET) mechanism cannot be excluded as it is also in agreement with the observed KIE value.[32]

The intermediacy of a hydroxy- or acetoxyarene resulting from an attack of (per)oxo/copper species to the arene ring was excluded on the basis that neither 2-(2-hydroxyphenyl)-pyridine nor 2-(2-acetoxyphenyl)pyridine were converted into **3ab** under the reaction conditions (Scheme 4).



Scheme 4. Evidence against the formation of hydroxyarene intermediates.

Based on the above mechanistic investigations, we tentatively propose the catalytic cycle outlined in Scheme 5. The arene **1** initially undergoes chelation-assisted C–H activation in the presence of the Cu^{II} catalyst to form intermediate **B**. The alcohol **2** is converted into the transient silver alkoxide species **C** by reaction with AgOTf.[30] In



Scheme 5. Proposed dehydrogenative alkoxylation mechanism.

a redox process, the alkoxy radical that is formed by fragmentation of **C** is transferred to the Cu^{II}/arene species **B** to give the Cu^{III}-intermediate **D** together with metallic silver. Reductive elimination of the alkoxyarene product furnishes Cu^{I}-species **E**, which is reoxidized in the presence of molecular oxygen to the initial Cu^{II}-species **A**.

In conclusion, a bimetallic copper/silver catalyst has been discovered that allows the regiospecific dehydrogenative cross-coupling of arenes substituted with donating groups and alcohols. This constitutes an expedient synthetic route to aryl and benzyl ethers. Ongoing research is directed towards extending this dehydrogenative alkoxylation to C_{sp^3}–H groups of aliphatic substrates.

Experimental Section

General procedure for the dehydrogenative alkoxylation: A 70 mL Schlenk tube was charged with the arene (**1a**–**r**, 1.00 mmol), copper(II) acetate (0.25 mmol) and silver triflate (1.5 mmol). Anhydrous alcohol (**2a**–**h**, 3 mL) was added, and the mixture was stirred at 140 °C for 24 h under an oxygen atmosphere. After cooling, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL), the organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by column chromatography on SiO_2 with an *n*-hexane/ethyl acetate gradient with 0.1 % triethylamine to give the corresponding alkyl aryl ether.

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[1] For reviews, see: a) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382 – 10401; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236 – 10254; b) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215 – 1292; c) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 – 1345; d) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335 – 344.

[2] a) L. D. Tran, J. Roane, O. Daugulis, *Angew. Chem.* **2013**, *125*, 6159 – 6162; *Angew. Chem. Int. Ed.* **2013**, *52*, 6043 – 6046; b) M.-L. Louillat, F. W. Patureau, *Org. Lett.* **2013**, *15*, 164 – 167; c) J. Pan, M. Su, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 8806 – 8810; *Angew. Chem. Int. Ed.* **2011**, *50*, 8647 – 8651; d) A. John, K. M. Nicholas, *J. Org. Chem.* **2011**, *76*, 4158 – 4162; e) Q. Shuai, G. Deng, Z. Chua, D. S. Bohle, C.-J. Li, *Adv. Synth. Catal.* **2010**, *352*, 632 – 636; f) T.-S. Mei, X. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806 – 10807; g) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 6552 – 6555; *Angew. Chem. Int. Ed.* **2008**, *47*, 6452 – 6455; h) W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560 – 14561.

[3] a) T. Wang, W. Zhou, H. Yin, J.-A. Ma, N. Jiao, *Angew. Chem.* **2012**, *124*, 10981 – 10984; *Angew. Chem. Int. Ed.* **2012**, *51*, 10823 – 10826; b) L. Chen, E. Shi, Z. Liu, S. Chen, W. Wei, H. Li, K. Xu, X. Wan, *Chem. Eur. J.* **2011**, *17*, 4085 – 4089; c) X. Wang, Y. Lu, H.-X. Dai, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12203 – 12205.

[4] For selected examples, see: a) F. Chen, Z. Feng, C.-Y. He, H.-Y. Wang, Y.-I. Guo, X. Zhang, *Org. Lett.* **2012**, *14*, 1176 – 1179; b) T. W. Lyons, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 4455 – 4464; c) X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 13864 – 13867; d) W. Han, P. Mayer, A. R. Ofial, *Angew. Chem.* **2011**, *123*, 2226 – 2230; *Angew. Chem. Int. Ed.* **2011**, *50*, 2178 – 2182; e) B. Haffemayer, M. Gulias, M. J. Gaunt, *Chem. Sci.* **2011**, *2*, 312 – 315; f) Y. Wei, W. Su, *J. Am. Chem. Soc.* **2010**, *132*, 16377 – 16379; g) X. Zhao, C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837 – 5844; h) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci.* **2010**, *1*, 331 – 336; i) B.-J. Li, S.-L. Tian, Z. Fang, Z.-J. Shi, *Angew. Chem.* **2008**, *120*, 1131 – 1134; *Angew. Chem. Int. Ed.* **2008**, *47*, 1115 – 1118; j) G. Brasche, J. García-Fortanet, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 2207 – 2210; k) A. Maehara, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1159 – 1162; l) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904 – 11905; m) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172 – 1175.

[5] For a review, see: a) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31 – 41; b) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212 – 11222.

[6] a) C. Gunanathan, D. Milstein, *Acc. Chem. Res.* **2011**, *44*, 588 – 602; b) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790 – 792.

[7] a) S. Enthaler, A. Company, *Chem. Soc. Rev.* **2011**, *40*, 4912 – 4924; b) J. J. Li, D. S. Johnson, *Modern Drug Synthesis*, Wiley, Hoboken, **2010**; c) J. J. Li, D. S. Johnson, D. R. Sliskovic, B. D. Roth, *Contemporary Drug Synthesis*, Wiley, Hoboken, **2004**; d) F. Müller, *Agrochemicals*, Wiley-VCH, Weinheim, **1999**; e) H.-G. Elias, *An Introduction to Polymer Science*, Wiley-VCH, Weinheim, **1997**.

[8] J. March, *Advanced Organic Chemistry*, Wiley-Interscience, Hoboken, **1992**.

[9] For reviews see: a) J. F. Hartwig, *Nature* **2008**, *455*, 314 – 322; b) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558 – 5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400 – 5449.

[10] For a review, see: F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088 – 7105; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954 – 6971.

[11] For a review, see: J. X. Qiao, P. Y. S. Lam, *Synthesis* **2011**, 829 – 856.

[12] a) Y. Yan, P. Feng, Q.-Z. Zheng, Y.-F. Liang, J.-F. Lu, Y. Cui, N. Jiao, *Angew. Chem.* **2013**, *125*, 5939 – 5943; *Angew. Chem. Int. Ed.* **2013**, *52*, 5827 – 5831; b) Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 14654 – 14655.

[13] a) W. Wang, F. Luo, S. Zhang, J. Cheng, *J. Org. Chem.* **2010**, *75*, 2415 – 2418; b) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790 – 6791.

[14] a) R. I. Khusnutdinov, A. R. Bayguzina, L. I. Gimaletdinova, U. M. Dzhemilev, *Russ. J. Org. Chem.* **2012**, *48*, 1191 – 1196; b) M. J. Fuchter, *Name Reactions for Functional Group Transformations* (Ed.: J. J. Li, E. J. Corey), Wiley, Hoboken, **2007**, pp. 334 – 342; c) T. Shibata, R. Fujiwara, Y. Ueno, *Synlett* **2005**, 152 – 154.

[15] a) J. M. Hoover, B. L. Ryland, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 2357 – 2367; b) E. T. T. Kumpulainen, A. M. P. Koskinen, *Chem. Eur. J.* **2009**, *15*, 10901 – 10911; c) P. Gamez, I. W. C. E. Arends, R. A. Sheldon, J. Reedijk, *Adv. Synth. Catal.* **2004**, *346*, 805 – 811; d) P. Gamez, I. W. C. E. Arends, J. Reedijk, R. A. Sheldon, *Chem. Commun.* **2003**, 2414 – 2415; e) M. F. Semmelhack, C. R. Schmid, D. A. Cortés, C. S. Chou, *J. Am. Chem. Soc.* **1984**, *106*, 3374 – 3376.

[16] a) X. Wu, B. P. Fors, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 10117 – 10121; *Angew. Chem. Int. Ed.* **2011**, *50*, 9943 – 9947; b) S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 11592 – 11598; c) K. E. Torraca, X. Huang, C. A. Parrish, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 10770 – 10771.

[17] a) L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett.* **2006**, *8*, 1141 – 1144; b) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300 – 2301.

[18] a) W. Li, P. Sun, *J. Org. Chem.* **2012**, *77*, 8362 – 8366; b) T.-S. Jiang, G.-W. Wang, *J. Org. Chem.* **2012**, *77*, 9504 – 9509; c) G.-W. Wang, T.-T. Yuan, *J. Org. Chem.* **2010**, *75*, 476 – 479.

[19] N. Takemura, Y. Kuninobu, M. Kanai, *Org. Lett.* **2013**, *15*, 844 – 847.

[20] a) L. M. Huffman, A. Casitas, M. Font, M. Canta, M. Costas, X. Ribas, S. S. Stahl, *Chem. Eur. J.* **2011**, *17*, 10643 – 10650; b) Z.-L. Wang, L. Zhao, M.-X. Wang, *Org. Lett.* **2011**, *13*, 6560 – 6563; c) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas, S. S. Stahl, *J. Am. Chem. Soc.* **2010**, *132*, 12068 – 12073.

[21] For reviews on copper-mediated C–H functionalizations see: a) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464 – 3484; b) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem.* **2011**, *123*, 11256 – 11283; *Angew. Chem. Int. Ed.* **2011**, *50*, 11062 – 11087; c) M. Zhang, *Appl. Organomet. Chem.* **2010**, *24*, 269 – 284.

[22] For related Cu-catalyzed C–C and C–N bond formations, see: a) C. Zhang, X. Zong, L. Zhang, N. Jiao, *Org. Lett.* **2012**, *14*,

3280 – 3283; b) T. Xiong, Y. Li, X. Bi, Y. Lv, Q. Zhang, *Angew. Chem.* **2011**, *123*, 7278 – 7281; *Angew. Chem. Int. Ed.* **2011**, *50*, 7140 – 7143; c) H. Richter, R. Rohlmann, O. G. Mancheño, *Chem. Eur. J.* **2011**, *17*, 11622 – 11627; d) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968 – 6969; e) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672 – 3673.

[23] S. Bhadra, W. I. Dzik, L. J. Gooßen, *J. Am. Chem. Soc.* **2012**, *134*, 9938 – 9941.

[24] S. Bhadra, W. I. Dzik, L. J. Gooßen, *Angew. Chem.* **2013**, *125*, 3031 – 3035; *Angew. Chem. Int. Ed.* **2013**, *52*, 2959 – 2962.

[25] For a review on chelation-assisted C–H activation processes, see: T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147 – 1169.

[26] A. E. King, B. L. Ryland, T. C. Brunold, S. S. Stahl, *Organometallics* **2012**, *31*, 7948 – 7957.

[27] a) F. Xiao, Q. Shuai, F. Zhao, O. Baslé, G. Deng, C.-J. Li, *Org. Lett.* **2011**, *13*, 1614 – 1617; b) Y. Yuan, D. Chen, X. Wang, *Adv. Synth. Catal.* **2011**, *353*, 3373 – 3379.

[28] a) Y. Li, X.-S. Zhang, K. Chen, K.-H. He, F. Pan, B.-J. Li, Z.-J. Shi, *Org. Lett.* **2012**, *14*, 636 – 639; b) B.-J. Li, Z.-J. Shi, *Chem. Sci.* **2011**, *2*, 488 – 493.

[29] T. Mitsudome, Y. Mikami, H. Funai, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem.* **2008**, *120*, 144 – 147; *Angew. Chem. Int. Ed.* **2008**, *47*, 138 – 141.

[30] a) A. Reisinger, D. Himmel, I. Krossing, *Angew. Chem.* **2006**, *118*, 7153 – 7156; *Angew. Chem. Int. Ed.* **2006**, *45*, 6997 – 7000; b) A. Reisinger, N. Trapp, I. Krossing, *Organometallics* **2007**, *26*, 2096 – 2105; c) R. S. Macomber, J. C. Ford, J. H. Wenzel, *Synth. React. Inorg. Met.-Org. Chem.* **1977**, *7*, 111 – 122.

[31] a) Q. Liu, P. Wu, Y. Yang, Z. Zeng, J. Liu, H. Yi, A. Lei, *Angew. Chem.* **2012**, *124*, 4744 – 4748; *Angew. Chem. Int. Ed.* **2012**, *51*, 4666 – 4670; b) D. Maiti, H. R. Lucas, A. A. Narducci Sarjeant, K. D. Karlin, *J. Am. Chem. Soc.* **2007**, *129*, 6998 – 6999; c) S. Hong, S. M. Huber, L. Gagliardi, C. C. Cramer, W. B. Tolman, *J. Am. Chem. Soc.* **2007**, *129*, 14190 – 14192.

[32] X. Ribas, C. Calle, A. Poater, A. Casitas, L. Gómez, R. Xifra, T. Parella, J. Benet-Buchholz, A. Schweiger, G. Mitrikas, M. Sola, A. Llobet, T. D. P. Stack, *J. Am. Chem. Soc.* **2010**, *132*, 12299 – 12306.

