Cross-Coupling

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Mild Cobalt-Catalyzed Negishi Cross-Couplings of (Hetero)arylzinc Reagents with (Hetero)aryl Halides

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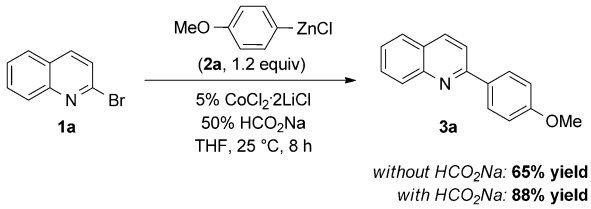
Abstract: *A catalytic system consisting of $CoCl_2$·2 LiCl (5 mol%) and HCO_2Na (50 mol%) enables the cross-coupling of various N-heterocyclic chlorides and bromides as well as aromatic halogenated ketones with various electron-rich and -poor arylzinc reagents. The reactions reached full conversion within a few hours at 25 °C.*

Transition-metal-catalyzed cross-coupling reactions are valuable approaches for the formation of $C(sp^2)$–$C(sp^2)$ bonds and are of great interest for the synthesis of biologically active molecules.[1] The Negishi cross-coupling, in particular, has attracted a lot of attention as a wide range of polyfunctional zinc reagents are available,[2] and transmetalations with transition-metal catalysts are fast and efficient. Mostly Pd and Ni catalysts have been used to perform such $C(sp^2)$–$C(sp^2)$ cross-couplings; however, price[3] and toxicity[4] issues have encouraged the search for alternative metal sources, such as cobalt[5,6] and iron.[7] Bedford and co-workers demonstrated that the use of iron(I) complexes in Negishi cross-couplings leads to great efficiency.[8] Gosmini and Bégouin showed that organozinc reagents can be generated in situ and cross-coupled with heteroaryl halides in a one-pot procedure.[9] Yoshikai and co-workers reported impressive organometallic cascade reactions, where arylzinc reagents were generated by Co catalysis and then underwent cross-coupling with aryl iodides in the presence of a Pd catalyst.[10] Furthermore, Hayashi and co-workers reported cobalt-catalyzed asymmetric $C(sp^2)$–$C(sp)$ couplings.[11]

Recently, we showed that arylzinc reagents that are prepared by directed metalation undergo smooth $C(sp^2)$–$C(sp^3)$ cross-couplings with primary and secondary alkyl halides.[12] Whereas this reaction proceeds under mild conditions, it suffers from a limited scope with respect to the arylzinc reagent, and the extension of this approach to $C(sp^2)$–$C(sp^2)$ couplings under the reported reaction conditions was difficult.

Herein, we report a new set of reaction conditions that enables smooth cross-couplings of various arylzinc reagents with (hetero)aryl chlorides or bromides within a few hours at room temperature. In a preliminary experiment, we treated 2-bromoquinoline (**1a**) with *para*-anisylzinc chloride (**2a**, 1.2 equiv) in the presence of $CoCl_2$·2 LiCl (5 mol%) and observed the formation of the desired cross-coupling product (**3a**) in 65% yield. However, aside from the desired cross-coupling, we observed extensive side reactions, including homocoupling. To improve the reaction outcome, we were inspired by the recent work of Miller and co-workers, who showed that the addition of potassium formate plays an important role in Suzuki reactions.[13] We anticipated that this salt could generate a more selective cobalt species with equal or superior catalytic activity.

To our delight, the addition of HCO_2Na (50 mol%) led to an improved yield of 88% of the isolated product (Scheme 1). Preliminary kinetic studies showed that the main effect of HCO_2Na is to considerably reduce the occurrence of side reactions, thus, as anticipated, leading to more selective cross-couplings.[14] This effect proved to be general, and a broader screen of reaction conditions using 2-bromopyridine (**1b**) showed that cobalt halides,[6f] $Co(acac)_2$, and $Co(acac)_3$[6c] gave good results (Table 1, entries 1–5). In particular, $CoCl_2$·2 LiCl,[15] which is conveniently soluble in THF, afforded product **3b** in excellent yield in the presence of HCO_2Na (entry 7). Interestingly, when sodium pivalate (tBuCO$_2$Na = PivONa) was used as an additive, the reaction was equally efficient, showing that HCO_2Na does not act as a reducing agent, but rather as a ligand.[16] Control experiments using ultrapure $CoCl_2$ (99.99%) confirmed that the Co salts are the active catalysts and that metal impurities do not play a role (compare with entry 2). Polar solvents, such as *N*,*N*′-dimethylpropylene urea (DMPU),[6b] or the use of a typical additive, such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA),[15] did not improve the reaction (entries 9 and 10). The use of $Co(acac)_3$ instead of $CoCl_2$·2 LiCl was not advantageous (entry 11). Furthermore, we confirmed that HCO_2Na alone did not catalyze this coupling by additional metal impurities (entry 12). Additional control experiments



Scheme 1. Cobalt-catalyzed cross-coupling of 2-bromoquinoline (**1a**) and *para*-anisylzinc chloride (**2a**) with and without sodium formate.

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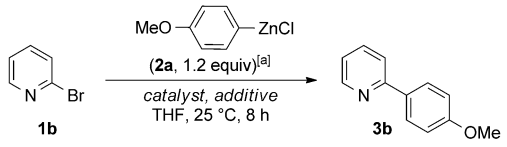
Table 1: Optimization of the reaction conditions for the cobalt-catalyzed $C(sp^2)$–$C(sp^2)$ cross-coupling of 2-bromopyridine (**1b**).



Entry	Catalyst	Additive	Homocoupling [%]	Yield [%][b]
1	$CoCl_2$	–	14	82
2	$CoCl_2$[c]	–	24	76
3	$CoBr_2$	–	14	78
4	$Co(acac)_2$	–	10	72
5	$Co(acac)_3$	–	14	80
6	$CoCl_2$·2 LiCl	–	13	83 (79)[d]
7	$CoCl_2$·2 LiCl	HCO_2Na	12	94 (87)[d]
8	$CoCl_2$·2 LiCl	PivONa	14	96
9	$CoCl_2$·2 LiCl	DMPU	12	84
10	$CoCl_2$·2 LiCl	TMEDA	7	51
11	$Co(acac)_3$	HCO_2Na	16	89
12	–	HCO_2Na	–	–
13	$CrCl_2$	–	traces	traces
14	$FeCl_2$	–	traces	17

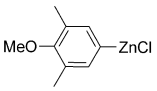
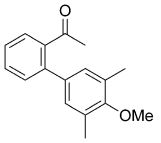
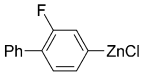
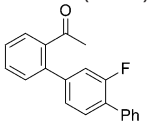
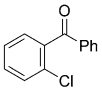
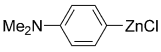
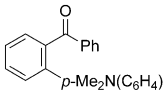
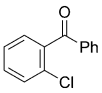
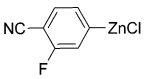
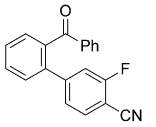
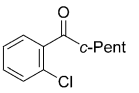
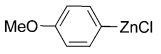
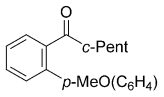
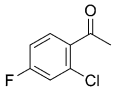
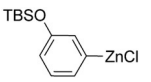
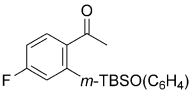
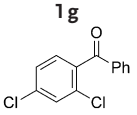
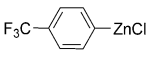
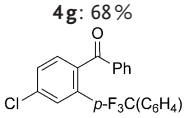
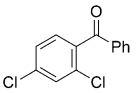
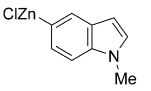
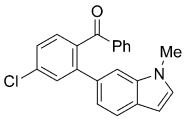
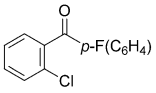
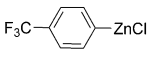
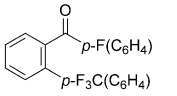
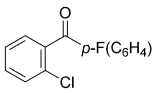
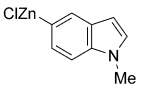
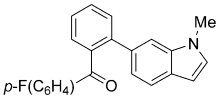
[a] $MgCl_2$ and LiCl were omitted for the sake of clarity. 5 mol% of the indicated catalyst and 50 mol% of the indicated additive were used. [b] Determined by GC analysis using undecane ($C_{11}H_{24}$) as an internal standard. [c] 99.99% purity. [d] Yield of isolated product.

indicated that Cr[17] and Fe[18] salts are not good catalysts for this reaction (entries 13 and 14).

The reaction scope of this cross-coupling proved to be quite broad. Thus, 2-halogenated, functionalized aceto- and benzophenones (**1c**–**1j**) underwent the cobalt-catalyzed cross-coupling with a range of aryl- and heteroarylzinc reagents (**2a**–**2h**), yielding the corresponding ketones (**4a**–**4k**) in 61–98% yield (Table 2). 2-Chloro- and 2-bromoacetophenone (**1c**, **1d**) reacted with zinc reagents bearing various functional groups, providing the expected products (**4a**–**4c**) in 65–74% yield (entries 1 and 2). Interestingly, zinc reagents with a dimethylamino substituent or a cyano group (**2d**, **2e**) were well tolerated as they reacted with 2-chlorobenzophenone (**1e**) to give **4d** and **4e** in 73 and 98% yield, respectively (entries 3 and 4). Remarkably, various other 2-chlorinated aromatic ketones (**1f**–**1j**) underwent the cross-coupling with both electron-rich and -poor arylzinc reagents, yielding the desired products in 61–89% yield (entries 5–10). Heterocyclic zinc reagents, such as **2h**, provided the new ketones **4i** and **4k** in 61 and 62% yield, respectively (entries 8 and 10).

Furthermore, a range of 2,3-disubstituted N-heterocyclic chlorides can also be readily employed in this reaction (Table 3, entries 1–4). *p*-$MeOC_6H_4ZnCl$ (**2a**) reacted smoothly with ethyl 2-chloronicotinate (**1k**), leading to the 2,3-disubstituted pyridine **3c** in 70% yield (entry 1). The coupling of the electron-rich arylzinc reagents **2i** and **2d** with methyl 2-chloronicotinate (**1l**) afforded pyridines **3d** and **3e** in 71 and 91% yield, respectively (entries 2 and 3). Similarly, the cross-coupling of 2-chloronicotinonitrile (**1m**) and an organozinc reagent bearing a OMOM group (MOM = methoxymethyl) led to the desired pyridine **3f** in 60% yield (entry 4). Furthermore, 2,5-disubstituted N-heterocyclic

Table 2: Cobalt-catalyzed cross-coupling reactions between 2-chlorinated aromatic ketones and arylzinc reagents.

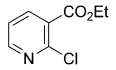
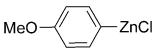
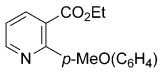
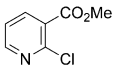
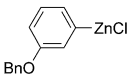
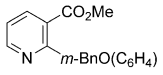
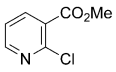
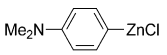
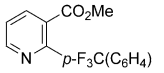
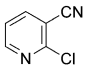
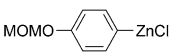
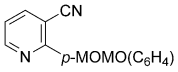
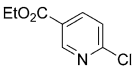
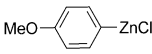
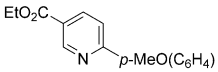
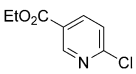
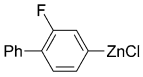
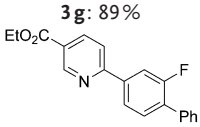
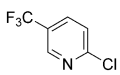
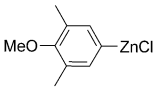
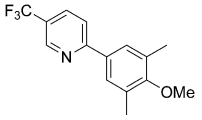
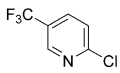
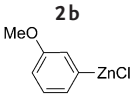
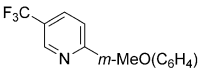
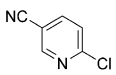
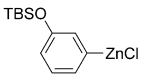
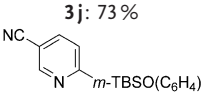
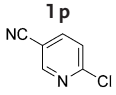
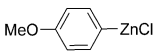
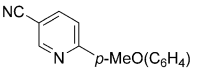
Entry	Electrophile	Zinc reagent	Product[a]
1	 **1c** (X = Cl) **1d** (X = Br)	 **2b**	 **4a**: 65% (X = Cl) **4b**: 74% (X = Br)
2	 **1c**	 **2c**	 **4c**: 67%
3	 **1e**	 **2d**	 **4d**: 73%
4	 **1e**	 **2e**	 **4e**: 98%
5	 **1f**	 **2a**	 **4f**: 76%
6	 **1g**	 **2f**	 **4g**: 68%
7	 **1h**	 **2g**	 **4h**: 89%
8	 **1h**	 **2h**	 **4i**: 61%
9	 **1i**	 **2g**	 **4j**: 73%
10	 **1i**	 **2h**	 **4k**: 62%

[a] Yield of isolated product. TBS = *tert*-butyldimethylsilyl.

chlorides were also good substrates, delivering the diarylated pyridines **3g**–**3l** in 73–89% yield (entries 5–10).

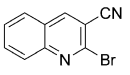
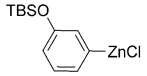
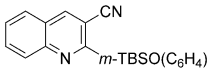
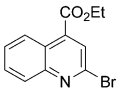
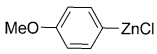
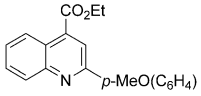
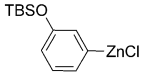
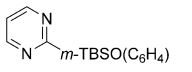
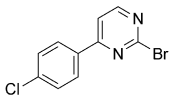
Moreover, halogenated quinolines, pyrimidines, and triazines also proved to be good substrates for this cross-coupling (Table 4). Substituted quinolines, such as 2-bromoquinoline-3-carbonitrile (**1q**) and ethyl 2-bromoquinoline-4-

Table 3: Cobalt-catalyzed cross-coupling reactions between 2-chloropyridines and arylzinc reagents.

Entry	Electrophile	Zinc reagent	Product[a]
1	 **1k**	 **2a**	 **3c**: 70%
2	 **1l**	 **2i**	 **3d**: 71%
3	 **1l**	 **2d**	 **3e**: 91%
4	 **1m**	 **2j**	 **3f**: 60%
5	 **1n**	 **2a**	 **3g**: 89%
6	 **1n**	 **2c**	 **3h**: 88%
7	 **1o**	 **2b**	 **3i**: 86%
8	 **1o**	 **2k**	 **3j**: 73%
9	 **1p**	 **2f**	 **3k**: 84%
10	 **1p**	 **2a**	 **3l**: 84%

[a] Yield of isolated product. Bn = benzyl.

Table 4: Cobalt-catalyzed cross-coupling reactions between N-heterocyclic halides and arylzinc reagents.

Entry	Electrophile	Zinc reagent	Product[a]
1	 **1q**	 **2f**	 **3m**: 92%
2	 **1r**	 **2a**	 **3n**: 65%
3	 **1s**	 **2f**	 **3o**: 92%
4	 **1t**	**2l**	**3p**: 86%
5	**1u**	**2c**	**3q**: 76%
6	**1v**	**2l**	**3r**: 65%
7	**1w**	**2m**	**3s**: 61%

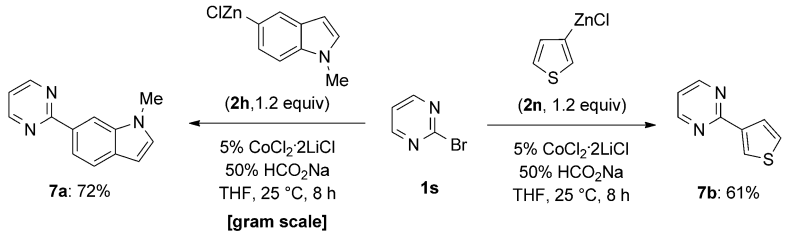
[a] Yield of isolated product.

Scheme 2. Cobalt-catalyzed cross-coupling reaction between 4,6-dichloropyrimidine (**5**) and *p*-MeOC$_6$H$_4$ZnCl (**2a**).

carboxylate (**1r**), can be rapidly coupled with the organozinc reagents **2f** and **2a** to provide the corresponding arylated quinolines in 92 and 65% yield, respectively (**3m** and **3n**; entries 1 and 2). Pyrimidines, which are common scaffolds of pharmaceuticals,[19] were readily obtained by the coupling of 2-chloro- or 2-bromopyrimidine (**1s**–**1v**) in 65–92% yield (entries 3–6). Triazines are also of great importance as building blocks for materials and agrochemicals.[20] The cross-coupling of 2-chloro-4,6-diphenyl-1,3,5-triazine (**1w**) with the arylzinc reagent **2m** led to the desired product **3s** in 61% yield (entry 7). The cross-coupling of 4,6-dichloropyrimidine (**5**) with *p*-MeOC$_6$H$_4$ZnCl (**2a**; 2.4 equiv) afforded the arylated compound **6** in 73% yield on gram scale (Scheme 2).

The synthesis of heteroaryl–heteroaryl cross-coupling products is a challenge. When Pd or Ni catalysts are used, catalyst deactivation is often observed owing to chelation of the reagents with the catalyst.[21] However, in the presence of THF-soluble $CoCl_2$·2LiCl (5 mol%) and sodium formate (50 mol%), the cross-coupling of 2-bromopyrimidine (**1s**) with (1-methyl-1*H*-indol-5-yl)zinc chloride (**2h**) or thiophen-3-ylzinc chloride (**2n**) proceeded smoothly to afford the heteroaryl compounds **7a** and **7b** in 72 and 61% yield, respectively (Scheme 3).

In summary, we have developed a new, practical, cobalt-catalyzed, sodium formate promoted C(sp^2)–C(sp^2) cross-coupling reaction between N-heterocyclic chlorides and



Scheme 3. Heteroaryl–heteroaryl cross-coupling reactions between 2-bromopyrimidine (**1s**) and heteroarylzinc reagents.

bromides as well as halogenated aromatic ketones with various (hetero)arylzinc reagents. The use of sodium formate was the key to the success of these cobalt-catalyzed cross-couplings. Further studies, including mechanistic investigations, are currently underway in our laboratories.

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Keywords: cobalt · cross-coupling · heteroarenes · heterocycles · Negishi coupling

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Angew. Chem. **2016**, *128*, 3873–3877

[1] a) N. Miyaura, *Cross-Coupling Reactions. A Practical Guide*, Springer, Berlin, **2002**; b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, A. de Meijere), Wiley-VCH, Weinheim, **2004**; c) *Organotransition Metal Chemistry* (Ed.: J. F. Hartwig), University Science Books, Sausalito, California, **2010**.

[2] *Handbook of Functionalized Organometallics: Applications in Synthesis* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2004**.

[3] a) World market prices for Pd: $770 per pound; b) world market price for Co: $13 per pound; 11.02.2015.

[4] a) *Handbook on the Toxicology of Metals* (Eds.: L. Friberg, G. F. Nordberg, V. B. Vouk), Elsevier, Amsterdam, **1986**; b) M. N. Hughes, *Comprehensive Coordination Chemistry, Vol. 6* (Eds.: G. Wilkinson, R. D. Gillard, J. A. McCleverty), Pergamon Press, Oxford, **1987**, pp. 643–648; c) *Nickel and the Skin: Absorption, Immunology, Epidemology, and Metallurgy* (Eds.: J. J. Hostynek, H. I. Maibach), CRC, Boca Raton, FL, **2002**.

[5] For selected reviews on cobalt-catalyzed reactions, see a) C. Gosmini, J.-M. Bégouin, A. Moncomble, *Chem. Commun.* **2008**, 3221; b) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435.

[6] For representative examples, see: a) H. Ohmiya, H. Yorimitsu, K. Oshima, *Chem. Lett.* **2004**, *33*, 1240; b) T. J. Korn, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 2947; *Angew. Chem.* **2005**, *117*, 3007; c) T. Hatakeyama, S. Hashimoto, K. Ishizuka, M. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 11949; d) J.-M. Bégouin, M. Rivard, C. Gosmini, *Chem. Commun.* **2010**, *46*, 5972; e) O. M. Kuzmina, A. K. Steib, D. Flubacher, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 4945; *Angew. Chem.* **2013**, *125*, 5045; f) C. E. I. Knappke, S. Grupe, D. Gärtner, M. Corpet, C. Gosmini, A. Jacobi von Wangelin, *Chem. Eur. J.* **2014**, *20*, 6828; g) M. Corpet, X.-Z. Bai, C. Gosmini, *Adv. Synth. Catal.* **2014**, *356*, 2937; h) B. Barré, L. Gonnard, R. Campagne, S. Reymond, J. Marin, P. Ciapetti, M. Brellier, A. Guérinot, J. Cossy, *Org. Lett.* **2014**, *16*, 6160; i) O. M. Kuzmina, A. K. Steib, S. Fernandez, W. Boudot, J. T. Markiewicz, P. Knochel, *Chem. Eur. J.* **2015**, *21*, 8242; j) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 8551; *Angew. Chem.* **2015**, *127*, 8671; k) M. Moselage, N. Sauermann, S. C. Richter, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 6352; l) J. Wu, N. Yoshikai, *Angew. Chem. Int. Ed.* **2016**, *55*, 336; *Angew. Chem.* **2016**, *128*, 344.

[7] For selected reviews on iron-catalyzed reactions, see: a) C. Bolm, *Nat. Chem.* **2009**, *1*, 420; b) A. Fürstner, *Angew. Chem. Int. Ed.* **2009**, *48*, 1364; *Angew. Chem.* **2009**, *121*, 1390; c) W. M. Czaplik, M. Mayer, J. Cvengroš, A. Jacobi von Wangelin, *ChemSusChem* **2009**, *2*, 396; d) E. Nakamura, N. Yoshikai, *J. Org. Chem.* **2010**, *75*, 6061.

[8] For representative examples, see: a) C. J. Adams, R. B. Bedford, E. Carter, N. J. Gower, M. F. Haddow, J. N. Harvey, M. Huwe, M. Ángeles Cartes, S. M. Mansell, C. Mendoza, D. M. Murphy, E. Neeve, J. Nunn, *J. Am. Chem. Soc.* **2012**, *134*, 10333; b) R. B. Bedford, E. Carter, P. M. Cogswell, N. J. Gower, M. F. Haddow, J. N. Harvey, D. M. Murphy, E. C. Neeve, J. Nunn, *Angew. Chem. Int. Ed.* **2013**, *52*, 1285; *Angew. Chem.* **2013**, *125*, 1323.

[9] J.-M. Bégouin, C. Gosmini, *J. Org. Chem.* **2009**, *74*, 3221.

[10] B.-H. Tan, J. Dong, N. Yoshikai, *Angew. Chem. Int. Ed.* **2012**, *51*, 9610; *Angew. Chem.* **2012**, *124*, 9748.

[11] a) T. Sawano, K. Ou, T. Nishimura, T. Hayashi, *Chem. Commun.* **2012**, *48*, 6106; b) T. Sawano, K. Ou, T. Nishimura, T. Hayashi, *J. Org. Chem.* **2013**, *78*, 8986.

[12] J. M. Hammann, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 4478; *Angew. Chem.* **2015**, *127*, 4560.

[13] W. D. Miller, A. H. Fray, J. T. Quatroche, C. D. Sturgill, *Org. Process Res. Dev.* **2007**, *11*, 359.

[14] See the Supporting Information for details.

[15] a) J. M. Hammann, A. K. Steib, P. Knochel, *Org. Lett.* **2014**, *16*, 6500; b) G. Cahiez, C. Chaboche, C. Duplais, A. Giulliani, A. Moyeux, *Adv. Synth. Catal.* **2008**, *350*, 1484.

[16] We propose that the halide ligands in $CoCl_2$·2LiCl are replaced by carboxylate ligands (HCO_2^-), which provides a more selective cobalt catalyst. In fact, halide ligands mostly lead to tetrahedral coordination (see, for example: N. S. Gill, F. B. Taylor, *Inorg. Synth.* **1967**, *9*, 136), whereas carboxylate ligands lead to an octahedral coordination (see, for example: a) A. Kaufmann, C. Afshar, M. Rossi, D. E. Zacharias, J. P. Glusker, *Struct. Chem.* **1993**, *4*, 191; b) G. Aromí, A. S. Batsanov, P. Christian, M. Helliwell, A. Parkin, S. Parsons, A. A. Smith, G. A. Timco, R. E. P. Winpenny, *Chem. Eur. J.* **2003**, *9*, 5142). Furthermore, whereas $CoCl_2$·2LiCl in THF is a blue solution, the addition of HCO_2Na leads to a pink solution, which is typical for a coordination change.

[17] A. K. Steib, O. M. Kuzmina, S. Fernandez, D. Flubacher, P. Knochel, *J. Am. Chem. Soc.* **2013**, *135*, 15346.

[18] O. M. Kuzmina, A. K. Steib, D. Flubacher, P. Knochel, *Org. Lett.* **2012**, *14*, 4818.

[19] M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347.

[20] a) H. Zhong, H. Lai, Q. Fang, *J. Phys. Chem. C* **2011**, *115*, 2423; b) R. V. Patel, Y.-S. Keum, S. W. Park, *Mini-Rev. Med. Chem.* **2014**, *14*, 768.

[21] a) C. Kaes, A. Katz, M. W. Hosseini, *Chem. Rev.* **2000**, *100*, 3553; b) *Comprehensive Coordination Chemistry II*, *Vol. 1* (Eds.: J. A. McCleverty, T. J. Meyer), Elsevier, Oxford, **2004**.

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