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Iron and Copper Salts in the Synthesis of Benzo[*b*]furans

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Abstract: Intramolecular C–O bond forming reactions of aryl 2-bromobenzyl ketones lead to benzo[*b*]furans. The cyclizations can be catalyzed by 10 mol% of iron trichloride (of 98% or of 99.995% purity) or sub-mol% quantities of copper(II) chloride (of 99.995% purity).

Keywords: benzofurans; copper; cross-coupling; iron

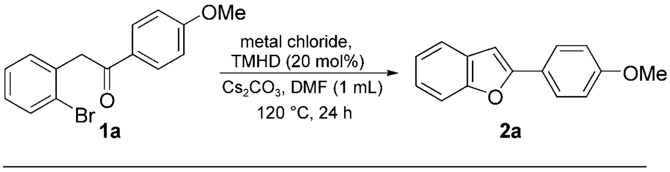
Benzo[*b*]furans are widely distributed in nature,[1] and many derivatives, in particular, 2-aryl-substituted ones, exhibit biological activities.[2–7] Consequently, various synthetic approaches towards benzo[*b*]furans have been developed,[8] including, for example, electrophilic cyclizations of the corresponding alkynyl- or *o*-alkenylphenols.[9] Many of those processes are palladium-[10] or copper-catalyzed.[11] Furthermore, metal-free reactions, such as cycloadditions starting from *ortho*-silylaryl triflates[12] or reactions between arynes and iodonium ylides[13] have been applied. Recently, Kim and co-workers reported low temperature boron trichloride-mediated cyclodehydrations for the synthesis of 3-arylbenzo[*b*]furan derivatives.[14] Finding an effective protocol that involves low cost materials and mild reaction conditions is a prevailing and scientifically interesting challenge.

Iron catalysts show promising properties in many synthetically valuable transformations,[15] and iron is generally regarded to be a cheap, benign and non-toxic metal.[16] Recently, Zhao and Li used iron trichloride in oxidative syntheses of functionalized benzo[*b*]furans,[17] but the required large quantity of the metal salt (2.5 equiv.) or the presence of strong oxidants renders these aromatic ring closures by intramolecular C–O bond formations synthetically less attractive. In our group, various C–S, C–N, C–O and C–C cross-couplings in the presence of catalytic amounts of $FeCl_3$ have been studied.[18] Recent results revealed that parts per million (ppm) quantities of copper (present in the iron salt) can influence such reactions.[19,20] Because our previous studies had included the synthesis of benzoxazoles by intramolecular C–O cross-coupling,[18d] we decided to focus our attention on a related ring closure reaction and to investigate the catalytic effects of iron and copper salts in intramolecular cyclizations of aryl 2-bromobenzyl ketones to give 2-arylbenzo[*b*]furans.

Atom absorption spectroscopy (AAS) of a sample of $FeCl_3$ (98% from Merck) (Table 1) showed the presence of nickel (190 ppm), palladium (13.2 ppm), copper (344 ppm) and manganese (1720 ppm). This finding prompted us to verify the importance of each of these metals in a given test reaction.

Using 2-(2-bromophenyl)-1-(4-methoxyphenyl)-ethanone (**1a**)[21] as starting material and 10 mol% of the $FeCl_3$ described above in combination with 20 mol% of 2,2,7,7-tetramethylhepta-2,5-dione (TMHD) and an excess of Cs_2CO_3 (2 equiv.) in DMF at 120 °C for 24 h afforded the 2-arylbenzo[*b*]furan **2a**

Table 1. Effects of metal dichlorides in cyclizations of **1a**.



Entry	Metal	ppm	Mol%	Yield [%][a]
1	$FeCl_3$ (98%)		10	79
2	–	–	–	8
3	$CuCl_2$	344	0.0088	60
4	$MnCl_2 \cdot 4H_2O$	1720	0.0510	8
5	$PdCl_2$	13.2	0.0002	8
6	$NiCl_2 \cdot 6H_2O$	190	0.0053	8

[a] Yield of the isolated product after flash chromatography.

in 79% yield (Table 1, entry 1).[22] In the absence of the metal salt, **2a** was obtained in only 8% yield indicating the positive effect of the metal salt. Next, all metals found by AAS were applied in their respective quantities. Considering that they were present in a sample of $FeCl_3$ (an oxidant and chlorinating agent) the corresponding chloride salts in oxidation state 2+ were applied. With the exception of $CuCl_2$ none of the other metal salts showed any effect. Noteworthy, even with only 344 ppm of copper salt (corresponding to 0.0088 mol%) the product was obtained in 60% yield (Table 1, entry 3).

Apparently, copper showed a very high activity in this intramolecular C−O bond formation. In order to elucidate its role further, the effects of mixtures of high purity iron trichloride and copper dichloride (both from Aldrich with purities of 99.995%) on cyclizations of **1a** to give 2-(*p*-methoxyphenyl)benzo[*b*]furan (**2a**) were tested. The results are summarized in Table 2.

The intramolecular ring closure of **1a** with 10 mol% of $FeCl_3$ and 0.0088 mol% of $CuCl_2$ gave **2a** in 79% yield (Table 2, entry 1), which mirrored the earlier result with $FeCl_3$ (from Merck having a purity of 98%). When the loading of $FeCl_3$ was lowered to 0.1 and 0.0088 mol% (at a constant $CuCl_2$ amount of 0.0088 mol%), the yield of **2a** decreased to 68% and 65%, respectively (entries 2 and 3). By a stepwise increase of the amount of $CuCl_2$ (in the absence of iron) from 0.0088 to 0.05 mol% a yield of 79% for **2a** could finally be reached (entries 4–8). A comparison of all results obtained in catalyses with 0.0088 mol% of $CuCl_2$ (entries 1–4) revealed the predominant effect of the copper salt. However, at high catalyst loading $FeCl_3$ showed an impact. While in the absence of the iron salt **2a** was obtained in 60% yield (entry 4), it increased to 79% upon addition of 10 mol% of $FeCl_3$ (entry 1).

Table 2. Effect of $FeCl_3$/$CuCl_2$ mixtures on the synthesis of **2a** starting from **1a**.

Entry	Mol% of $FeCl_3$[a]	Mol% of $CuCl_2$[a]	Yield [%][b]
1	10	0.0088	79
2	0.1	0.0088	68
3	0.0088	0.0088	65
4	0	0.0088	60
5	0	0.02	63
6	0	0.03	67
7	0	0.04	77
8	0	0.05	79
9	0.0088	0	8
10[c]	10	0	79

[a] With a purity of 99.995% (Aldrich).
[b] Yield of the isolated product after flash chromatography.
[c] Using a stock solution of $FeCl_3$ in DMF.

Finally, important experiments were performed *without* added copper. There, the product was obtained in only 8% yield, when 0.0088 mol% of $FeCl_3$ was applied (Table 2, entry 9). However, using 10 mol% of $FeCl_3$ (with a purity of 99.995%) led to 79% of **2a** (entry 10), which clearly indicated a catalytic effect of $FeCl_3$ at high catalyst loading.

Next, the substrate scope was evaluated. Considering that the highest yield of **2a** was obtained in the catalysis with the standard $FeCl_3$ obtained from Merck (98% purity; Table 1, entry 1) and knowing the impact of the metal contaminants in this sample, this salt was selected for subsequent studies. As before, TMHD served as ligand,[22] and 10 mol% of $FeCl_3$ was applied. In order to avoid formation of cyclized products by uncatalyzed intramolecular nucleophilic substitution the reaction temperature was kept at 120 °C.[23]

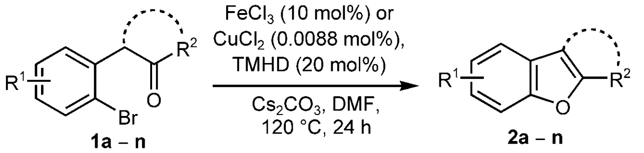
Good yields (up to 87%) were obtained in catalyzed *O*-arylations of substrates with electron-donating groups in the *para* position of the carbonyl-substituted arene (Table 3, entries 1–5). An electron-withdrawing chloro group hampered the cyclizations and the yield of the resulting benzo[*b*]furan **2f** was only 25% (entry 6). Steric hinderance appeared to support the reactions as indicated by the cyclization of mesityl-substituted **1e**, which gave the corresponding product **2e** in 89% yield (entry 5). 2,3-Disubstituted benzo[*b*]furans **2g** and **2h** were obtained from cyclic ketones **1g** and **1h** in 33% and 76% yield, respectively (entries 7 and 8). Also, aryl benzyl ketones with methoxy substituents *para* to the bromo group in the benzyl fragment (**1k–n**) cyclized to the corresponding benzo[*b*]furans, but generally the yields were lower compared to the ones observed in reactions with the related unsubstituted educts (Table 3, entries 11–14).

Knowing that the $FeCl_3$ applied in the substrate scope screening had a purity of 98% and that it contained *ca.* 0.0088 mol% of copper, all experiments were repeated under identical conditions using as catalyst the appropriate amount of $CuCl_2$ (with a purity of 99.995% obtained from Aldrich) instead of $FeCl_3$. These results are also shown in Table 3.

In general, the same trend was observed with respect to the substitution pattern. In all cases, product formation occurred, but the yields were significantly lower than in the reactions catalyzed by the iron salt. The best results were achieved in cyclizations of compounds **1b** and **1e**, which afforded the corresponding benzo[*b*]furans in yields of 67% and 69%, respectively (Table 3, entries 2 and 5).

In summary, we have demonstrated that benzo[*b*]furans can be obtained by metal-catalyzed cyclizations starting from appropriately substituted aryl 2-bromobenzyl ketones. The reactions proceed well in the presence of 10 mol% of $FeCl_3$ having a purity of 98%. Although generally lower yields are observed, $CuCl_2$

Table 3. Substrate scope in the benzo[*b*]furan syntheses.



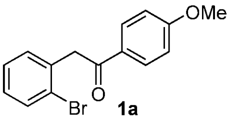
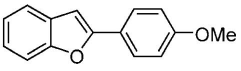
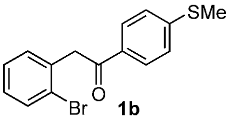
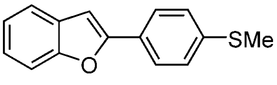
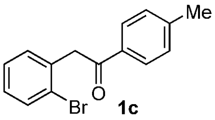
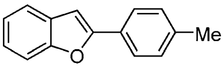
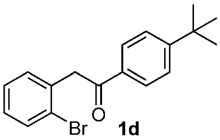
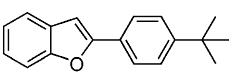
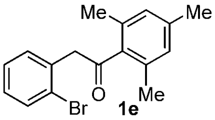
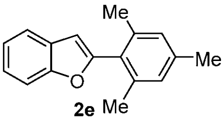
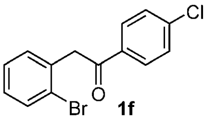
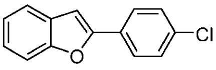
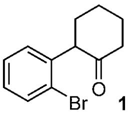
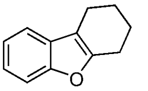
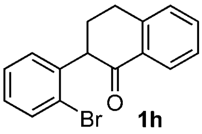
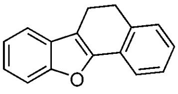
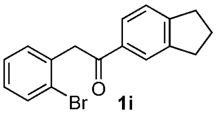
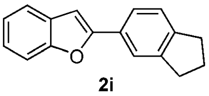
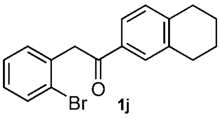
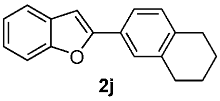
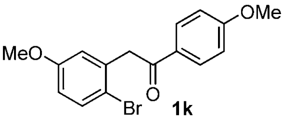
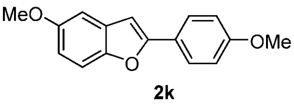
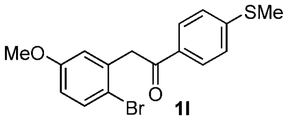
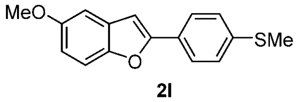
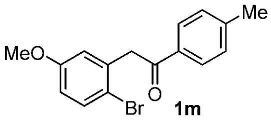
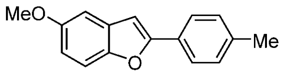
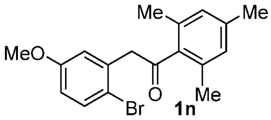
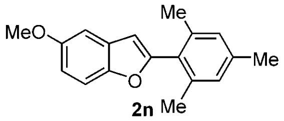
Entry	Substrate	Product	Yield [%][a]
1	 **1a**	 **2a**	79 (60)
2	 **1b**	 **2b**	72 (67)
3	 **1c**	 **2c**	59 (50)
4	 **1d**	 **2d**	54 (42)
5	 **1e**	 **2e**	87 (69)
6	 **1f**	 **2f**	25 (16)
7	 **1g**	 **2g**	33 (30)
8	 **1h**	 **2h**	76 (60)
9	 **1i**	 **2i**	75 (45)
10	 **1j**	 **2j**	81 (36)
11	 **1k**	 **2k**	47 (42)

Table 3. (Continued)

Entry	Substrate	Product	Yield [%][a]
12	 **1l**	 **2l**	30 (10)
13	 **1m**	 **2m**	36 (31)
14	 **1n**	 **2n**	66 (59)

[a] Yield of the isolated product after flash chromatography; in parentheses, results from experiments performed with 0.0088 mol% of $CuCl_2$ (99.995%; Aldrich).

(with a purity of 99.995%) shows a remarkable activity, and even 0.0088 mol% of this salt are sufficient to provide products with up to 69% yield. Further investigations to study these effects are in progress in our laboratories.

Experimental Section

General Procedure for Intramolecular *O*-Arylation to give Benzo[*b*]furans

A sealed tube equipped with a magnetic bead bar was charged with the 2-(2-bromophenyl) ketone (1.0 equiv., 0.32 mmol), Cs_2CO_3 (2.0 equiv., 0.64 mmol) and $FeCl_3$ (0.1 equiv, 0.03 mmol). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. 2,2,6,6-Tetramethyl-3,5-heptanedione (TMHD, 0.2 equiv., 0.06 mmol) and DMF (1 mL) were added *via* syringe. The septum was replaced by a teflon-coated screw cap, and the reaction vessel was heated to 120 °C. The reaction mixture was stirred at this temperature for 24 h, then the heterogeneous mixture was allowed to cool to room temperature, diluted with dichloromethane and filtered through a pad of celite. The solution was concentrated under vacuum to give the product, which was purified by silica gel chromatography to yield the benzo[*b*]furan. The identity and the purity of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopy and exact mass determination. For details see Supporting Information.

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References

[1] a) B.-H Lipshutz, *Chem. Rev.* **1986**, *86*, 795; b) D. E. Fuerst, B. M. Stoltz, J. L. Wood, *Org. Lett.* **2000**, *2*, 3521.

[2] L. De Luca, G. Nieddu, A. Porcheddu, G. Giacomelli, *Curr. Med. Chem.* **2009**, *16*, 1.

[3] For antiproliferative activity, see: a) E. Navarro, S. J. Alonso, J. Trujillo, E. Jorge, C. J. Perez, Nat. Prod. **2001**, 64, 134; b) J. D. Lambert, R. O. Meyers, B. N. Timmermann, R. T. Dorr, *Cancer Lett.* **2001**, *171*, 47; c) M. T. Takasaki, K. Komatsu, H. Tokuda, H. Nishino, *Cancer Lett.* **2000**, *158*, 53; d) A. Banskota, Y. Tezuka, K. Midorikawa, K. Matsushige, S. J. Kadota, *Nat. Prod.* **2000**, *63*, 1277.

[4] For antiviral activity, see: a) G. A. Kraus, I. Kim, *Org. Lett.* **2003**, *5*, 1191; b) J. Craigo, M. Callahan, R. C. C. Huang, A. L. DeLucia, *Antiviral Res.* **2000**, *47*, 19; c) C. Leung, J. L. Charlton, C. Cow, *Can. J. Chem.* **2000**, *78*, 553.

[5] For antioxidative activity, see: D. H. S. Silva, F. C. Pereira, M. V. B. Zanoni, M. Yoshida, *Phytochemistry* **2001**, *57*, 437.

[6] For anti-inflammatory activity, see: a) M. Sun, C. Zhao, G. A. Gfesser, C. Thiffault, T. R. Miller, K. Marsh, J. Wetter, M. Curtis, R. Faghih, T. A. Esbenshade, A. A. Hancock, M. Cowart, *J. Med. Chem.* **2005**, *48*, 6482; b) M. Inoue, M. W. Carson, A. J. Frontier, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 1878.

[7] For cancer inhibitory activity, see: a) I. den Tonkelaar, L. Keinan-Boker, P. Van't Veer, C. J. M. Arts, H. Adlercreutz, J. H. H. Thijssen, P. H. M. Peeters, *Cancer Epidemiol. Biomark. Prev.* **2001**, *10*, 223; b) P. Knekt, H. Adlercreutz, H. Rissanen, A. Aromaa, L. Teppo, M. Heliovaara, *Br. J. Cancer* **2000**, *82*, 1107; c) M. Hirose, C. Lin, N. Kimoto, M. Futakuchi, T. Kono, S. Nishibe,

T. Shirai, T. Yamaguchi, *Cancer Lett.* **2000**, *155*, 79; d) S. I. Oikannen, A. M. Pajari, M. Mutanen, *Cancer Lett.* **2000**, *159*, 183.

[8] a) D. Yue, T. Yao, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 10292; b) C.-L. Kao, J.-W. Chern, *J. Org. Chem.* **2002**, *67*, 6772; c) A. R. Katritzky, Y. Ji, Y. Fang, I. J. Prakash, *J. Org. Chem.* **2001**, *66*, 5613; d) K. C. Nicolaou, S. A. Snyder, A. Bigot, J. A. Pfefferkorn, *Angew. Chem.* **2000**, *112*, 3615; *Angew. Chem. Int. Ed.* **2000**, *39*, 3473.

[9] a) M. C. Willis, D. Taylor, A. T. Gillmore, *Org. Lett.* **2004**, *6*, 4755; b) M. Yoshida, Y. Morishita, M. Fujita, M. Ihara, *Tetrahedron Lett.* **2004**, *45*, 1861; c) Y. Hu, Z. Yang, *Org. Lett.* **2001**, *3*, 1387.

[10] a) C. Martinex, R. Alvarez, J. M. Aurrecoechea. *Org. Lett.* **2009**, *11*, 1083; b) J. Faragó, A. Kotschy, *Synthesis* **2009**, 85; c) for a review on palladium-catalyzed syntheses of benzofurans, see: S. Cacchi, G. Fabrizi, A. Goggiamani, *Curr. Org. Chem.* **2006**, *10*, 1423.

[11] a) A. C. Tadd, M. R. Fielding, M. C. Willis, *Tetrahedron Lett.* **2007**, *48*, 7578; b) M. Carril, R. SanMartin, I. Tellitu, E. Dominguez, *Org. Lett.* **2006**, *8*, 1467; c) C. Y. Chen, P. G. Dormer, *J. Org.Chem.* **2005**, *70*, 6964; P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul, T. Punniyamurthy, *J. Org.Chem.* **2009**, *74*, 8719.

[12] a) Z. Liu, F. Shi, P. D. G. Martinez, C. Paminelli, R. C. Larock, *J. Org. Chem.* **2008**, *73*, 219; b) Y. K. Ramtohul, A. Chartrand, *Org. Lett.* **2007**, *9*, 1029; c) C. Xie, Y. Zhang, *Org. Lett.* **2007**, *9*, 781.

[13] X.-C. Huang, Y.-L. Liu, Y. Liang, S.-F. Pi, F. Wang, J.-H. Li, *Org. Lett.* **2008**, *10*, 1525.

[14] I. Kim, S.-H. Lee, S. Lee, *Tetrahedron Lett.* **2008**, *49*, 6579.

[15] a) J. Bonnamour, C. Bolm, *Chem. Eur. J.* **2009**, *15*, 4543; b) C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez, P. Knochel, *Angew. Chem.* **2004**, *116*, 3028; *Angew. Chem. Int. Ed.* **2004**, *43*, 2968; c) A. Guérinot, S. Reymond, J. Cossy, *Angew. Chem.* **2007**, *119*, 6641; *Angew. Chem. Int. Ed.* **2007**, *46*, 6521; d) Z. Lu, G. Chai, S. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 14546; e) C. M. Rao Volla, P. Vogel, *Angew. Chem.* **2008**, *120*, 1325; *Angew. Chem. Int. Ed.* **2008**, *47*, 1305; f) A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992; g) C. Sui-Seng, F. Freutel, A. J. Lough, R. H. Morris, *Angew. Chem.* **2008**, *120*, 954; *Angew. Chem. Int. Ed.* **2008**, *47*, 940. Reviews: h) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; i) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624; j) A. Correa, O. Garcia Mancheño, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108; k) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500; l) S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 3363; *Angew. Chem. Int. Ed.* **2008**, *47*, 3317; m) E. B. Bauer, *Curr. Org. Chem.* **2008**, *12*, 1341; n) S. Gaillard, J.-L. Renaud, *ChemSusChem.* **2008**, *1*, 505; o) A. Fürstner, *Angew. Chem.* **2009**, *121*, 1390; *Angew. Chem. Int. Ed.* **2009**, *48*, 1364; p) W. M. Czaplik, M. Mayer, J. Cvengroc, A. Jacobi von Wangelin, *ChemSusChem.* **2009**, *2*, 396; q) A. A. O. Sarhan, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 2730.

[16] C. Bolm, *Nature Chem.* **2009**, *1*, 420.

[17] a) Z. Liang, W. Hou, Y. Du, Y. Zhang, Y. Pan, D. Mao, K. Zhao, *Org. Lett.* **2009**, *11*, 4978; b) for an access to substituted benzofurans by iron-catalyzed tandem oxidative coupling and annulation, see: X. Guo, R. Yu, H. Li, Z. Li, *J. Am. Chem. Soc.* **2009**, *131*, 17387.

[18] a) A. Correa, C. Bolm, *Angew. Chem.* **2007**, *119*, 9018; *Angew. Chem. Int. Ed.* **2007**, *46*, 8862; b) A. Correa, C. Bolm, *Adv. Synth. Catal.* **2008**, *350*, 391; c) O. Bistri, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 596; *Angew. Chem. Int. Ed.* **2008**, *47*, 586; d) J. Bonnamour, C. Bolm, *Org. Lett.* **2008**, *10*, 2665; e) A. Correa, M. Carril, C. Bolm, *Angew. Chem.* **2008**, *120*, 2922; *Angew. Chem. Int. Ed.* **2008**, *47*, 2880; f) M. Carril, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 4940; *Angew. Chem. Int. Ed.* **2008**, *47*, 4862; g) A. Correa, S. Elmore, C. Bolm, *Chem. Eur. J.* **2008**, *14*, 3527; h) A. Correa, M. Carril, C. Bolm, *Chem. Eur. J.* **2008**, *14*, 10919.

[19] a) S. L. Buchwald, C. Bolm, *Angew. Chem.* **2009**, *121*, 5694; *Angew. Chem. Int. Ed.* **2009**, *48*, 5586; b) P.-F. Larsson, A. Correa, M. Carril, P.-O. Norrby, C. Bolm, *Angew. Chem.* **2009**, *121*, 5801; *Angew. Chem. Int. Ed.* **2009**, *48*, 5691.

[20] For a kinetic analysis of Castro-Stephens-type cross-couplings catalyzed by sub-mol% quantities a copper complex, see: E. Zuidema, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 4181.

[21] Compounds of this type can easily be prepared by Friedel–Crafts acylation reactions. For example, 2-(2-bromophenyl)-1-(4-methoxyphenyl)ethanone (**1a**) was obtained starting from 2-(2-bromophenyl)acetyl chloride and anisole.

[22] For details of the optimization by base, solvent and ligand screening, see the Supporting Information.

[23] Control experiments with **1a** revealed that in the absence of a catalyst no product was formed at 120 °C. However, performing the reaction under the same conditions at 130 °C gave **2a** in 51% yield.