

An Improved Protocol for Palladium-Catalyzed Alkoxycarbonylations of Aryl Chlorides with Alkyl Formates

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Abstract: The palladium-catalyzed alkoxycarbonylation of aryl and heteroaryl halides using butyl formate has been investigated. In the presence of palladium(II) acetate/*n*-butylbis(1-adamantyl)phosphine (**L1**), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base for the first time non-activated chloroarenes can be conveniently carbonylated in good yields.

Keywords: alkoxycarbonylation; aryl chlorides; carbon monoxide-free conditions; catalysis; palladium

Palladium-catalyzed carbonylation reactions of aryl halides and related compounds leading to carboxylic acid derivatives have become a versatile tool in organic synthesis.^[1] Nowadays various aromatic carboxylic acid derivatives, which are of interest for pharmaceuticals and agrochemicals (Figure 1), are accessible by this methodology. In general, aromatic halides are

reacted with different nucleophiles under a carbon monoxide atmosphere in the presence of palladium catalysts. Thereby, the halide is formally replaced by the nucleophile with incorporation of carbon monoxide. Typically, the reactions take place at 60–140 °C and 5–60 bar of carbon monoxide and require a stoichiometric amount of base to regenerate the catalyst. Clearly, carbon monoxide is an inexpensive and industrially widely used feedstock; however its toxic nature, gaseous form, and flammability render its handling on a laboratory scale inconvenient. Often additional safety measurements and special waste treatment are needed.

Although alkoxycarbonylations using CO at low and ambient pressure are known,^[2] there exists a significant interest in the use of more easy to handle and less toxic synthetic equivalents of carbon monoxide.^[3] In this respect especially formic acid derivatives are promising alternatives due to their low price and good availability.

Based on our previous work in palladium-catalyzed carbonylations,^[4] we became interested in the use of alkyl formates in alkoxycarbonylations of inexpensive aryl chlorides under practical conditions.

The first successful carbonylation reactions of aryl bromides and chromium complexes of aryl chlorides with alkyl formates have been achieved by Carpentier and Mortreux et al.^[5] Later on, Jenner and Bentaleb demonstrated carbonylations towards benzoic acid salts.^[6] With respect to aryl chlorides it should be noted that aminocarbonylations have also been achieved with Mo(CO)₆ under microwave activation.^[7]

Despite these studies, a more general method for the alkoxycarbonylation of aryl chlorides without using carbon monoxide is still desirable.

Initial studies focused on the alkoxycarbonylation of 4-chloro-*o*-xylene with butyl formate in NMP, which constitutes a challenging model reaction due to the deactivation of the chloroarene by the methyl

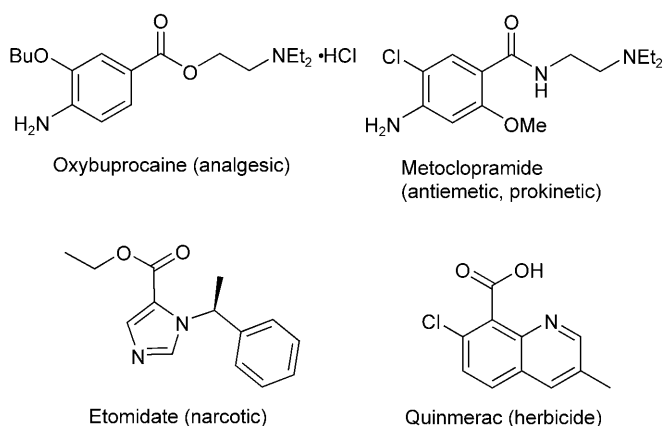


Figure 1. Examples for aromatic acid derivatives as active compounds.

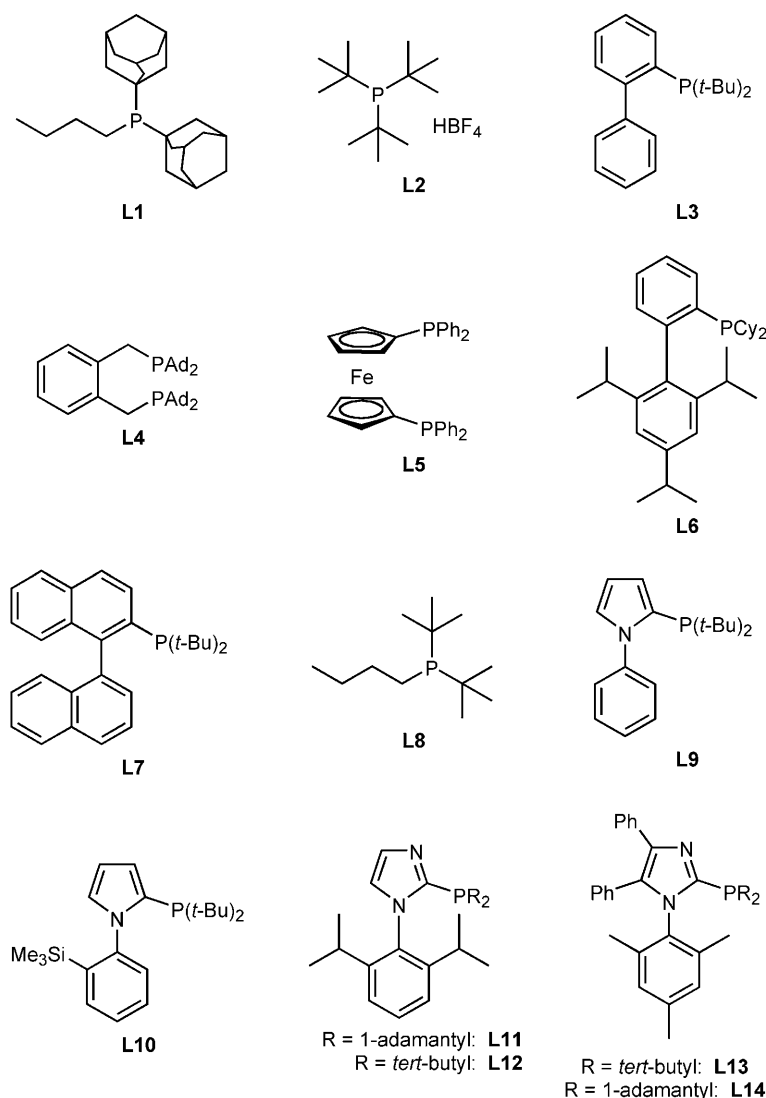


Figure 2. Tested ligands in the model reaction.

groups. Noteworthy, butyl formate allows for a convenient coupling protocol in standard glassware.

In previous work the addition of ruthenium co-catalysts to the reaction mixture was claimed to be beneficial for the product yield, since the ruthenium complex should activate the corresponding formic acid ester.^[3,6] Therefore, a mixture of 0.5 mol% Pd(OAc)₂ and 0.07 mol% Ru₃(CO)₁₂ was tested in the presence of various ligands (Figure 2) and DBU as base.

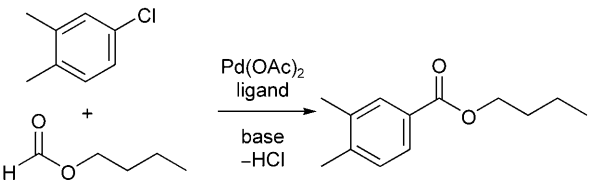
As shown in Table 1 the choice of ligand is crucial for the success of the model reaction. The best activity is found for ligand **L1** [*n*-butylbis(1-adamantyl)phosphine, cataCXium® A], which gave 87% conversion and 52% yield of butyl 3,4-dimethylbenzoate. It should be noted that this ligand induced also improved activities in reductive carbonylations and alkoxycarbonylations of aryl bromides using gaseous CO.^[8,9] In addition, in the presence of dpfp some activity and excellent selectivity was obtained.

In a further series of experiments, the choice of base was investigated in more detail (Table 2). Among the various amines and inorganic salts tested, DBU provided the highest yield. Interestingly, a significantly lower yield was obtained in the case of DBN, which is structurally similar to DBU.

To the best of our knowledge such a highly specific behavior has not been noted in carbonylation reactions before. In common polar and non-polar solvents the model reaction gave yields in a range between 30 to 52% (Table 3). To our delight applying acetonitrile as solvent provided the desired product in >80% yield! Other nitriles were also more effective compared to standard solvents.

Advantageously, in the presence of acetonitrile the addition of ruthenium co-catalysts is also not necessary. Hence, no difference in product yield is observed in the presence or absence of Ru. Having defined an optimized set of conditions, the scope of the aryl chlo-

Table 1. Alkoxy-carbonylation of 3,4-dimethyl-1-chlorobenzene – influence of ligands.^[a]



Entry	T [°C]	Ligand (mol%)	Conv. [%]	Yield [%]
1	160	L1 (2)	87	52
2	160	L2 (2)	23	15
3	160	L3 (2)	2	1
4	160	L4 (1)	7	4
5	140	L5 (2)	18	18
6	160	L6 (2)	1	0
7	160	L7 (2)	1	0
8	160	L8 (2)	3	1
9	160	L9 (2)	1	0
10	160	L10 (2)	1	0
11	160	L11 (2)	1	1
12	160	L12 (2)	1	0
13	140	L13 (2)	0	0
14	140	L14 (2)	0	0

^[a] *Reaction conditions:* 1 mmol 3,4-dimethyl-1-chlorobenzene, 1 mL butyl formate, 0.5 mol% Pd(OAc)₂, 0.07 mol% Ru₃(CO)₁₂, ligand as given, 120 mol% DBU (DBU = 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine), 1 mL NMP (NMP = 1-methylpyrrolidin-2-one), temperature as given, 16 h, closed vessel. GC yields.

Table 2. Optimization of reaction conditions – base.^[a]

Entry	Base (mol%)	Conv. [%]	Yield [%]
1	DBU (120)	87	52
2	K ₃ PO ₄ (120)	99	27
3	DMAP ^[b] (120)	29	18
4	DBN ^[b] (120)	5	3
5	1,1,3,3-tetramethylguanidine (120)	85	6
6	DBU (20) + K ₃ PO ₄ (100)	27	11

^[a] *Reaction conditions:* 1 mmol 4-chloro-*o*-xylene, 1 mL butyl formate, 0.5 mol% Pd(OAc)₂, 0.07 mol% Ru₃(CO)₁₂, 2 mol% **L1**, 1 mL NMP, 160 °C, 16 h, closed vessel. GC yields.

^[b] Abbreviations: DMAP = 4-dimethylaminopyridine, DBN = 2,3,4,6,7,8-hexahydropyrrolo[1,2-*a*]pyrimidine.

ride coupling reaction with butyl formate was explored next. Highlighted in Table 4, a number of neutral and electron-rich chloroarenes, which are in general less reactive in coupling reactions than electron-deficient chlorobenzenes, were successfully reacted to give the substituted benzoates in moderate to good yields. While *ortho* substituents on the aryl chloride were well tolerated (Table 4, entry 2), 2,6-disubstitu-

Table 3. Optimization of reaction conditions – influence of solvents.^[a]

Entry	Solvent	T [°C]	Conv. [%]	Yield [%]
1	NMP	160	87	52
2	DMAc ^[b]	160	66	42
3	dioxane	160	71	43
4	diglyme	160	60	39
5	toluene	160	55	35
6	acetonitrile	140	88	81

^[a] *Reaction conditions:* 1 mmol 4-chloro-*o*-xylene, 1 mL butyl formate, 0.5 mol% Pd(OAc)₂, 0.07 mol% Ru₃(CO)₁₂, 2 mol% **L1**, 1 mL solvent, 16 h, closed vessel. GC yields.

^[b] Abbreviations: DMAc = *N,N*-dimethylacetamide.

tion led to lower yields (Table 4, entry 3). As shown by GC-MS in all cases the main side product is the corresponding dehalogenated arene.

Compared to electron-rich arenes, for example, 4-chloroanisole, which performed well (69%, Table 4, entry 4), arenes with electron-withdrawing substituents gave low yields. This observation is in agreement with other CO-free carbonylation reactions.^[10a] Apparently, oxidative addition of the metal complex is not the rate-determining step, but more likely insertion of the carbonyl compound or reductive elimination.

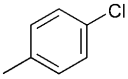
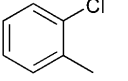
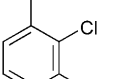
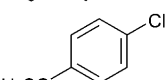
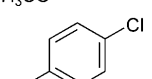
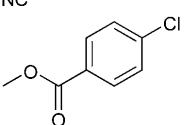
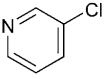
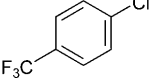
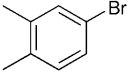
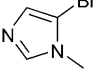
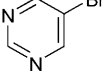
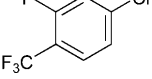
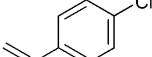
On further optimization, we discovered that the use of butyl formate as both solvent and reagent considerably improved the yields for electron-poor substrates (see method C in Table 4, entries 5–8). Aryl bromides reacted with higher yields than the corresponding chlorides. For example, 4-bromo-*o*-xylene gave 91% of the target compound (Table 4, entry 9). Notably, alkoxy-carbonylation of 5-bromo-*N*-methylimidazole provided the backbone of the narcotic etomidate in one step (Table 4, entry 10).^[11]

Starting from methyl 4-chlorobenzoate, the isolated product turned out to be dibutyl terephthalate. During the course of the reaction 1-butanol is formed, which reacted with the methyl group of the ester. This supports the assumption that the mechanism of this alkoxy-carbonylation is similar to the one reported previously.^[10]

Finally, 1-chloro-4-vinylbenzene was used as substrate in order to study chemoselectivity issues. Here, carbonylation of the double bond is observed only to a minor amount (Table 4, entry 13), resulting in *ca.* 15% of the side product butyl 3-(4-chlorophenyl)acrylate.

In addition, some other formates were tested in the alkoxy-carbonylation of 3,4-dimethylchlorobenzene (Figure 3). Here, ethyl formate gave a reasonably good result of 56% yield. The isopropyl ester was formed in lower yield presumably because of steric reasons.

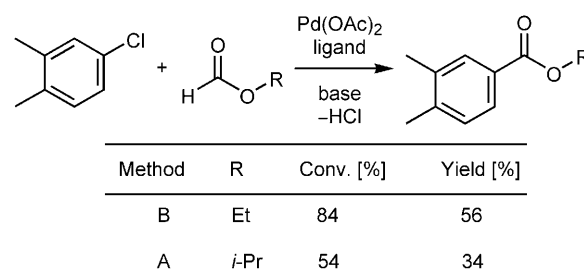
Table 4. Palladium-catalyzed alkoxy carbonylations with butyl formate – scope and limitations.^[a]

Entry	Substrate	Method	Conv. [%]	Yield [%]
1		B	67	57
2		B	82	51
3		B	33	16
4		B	80	69
5		C	100	69
6		C	100	53 ^[b]
7		C	99	56
8		C	90	63
9		B	100	91
10		B	100	69
11		C	100	56
12		A	100	45
13		B	100	51

^[a] Reaction conditions: 1 mmol aryl halide, 0.5 mol% Pd(OAc)₂, 2 mol% **L1**, 120 mol% DBU, 16 h, closed vessel. Method A: 1 mL butyl formate, 0.07 mol% Ru₃(CO)₁₂, 1 mL NMP, 160 °C. Method B: 0.5 mL butyl formate, 140 °C, 1 mL acetonitrile. Method C: 1 mL butyl formate, 140 °C. GC yields.

^[b] Product is dibutyl terephthalate.

In summary, an improved protocol for the palladium-catalyzed alkoxy carbonylation of aryl and heteroaryl halides using alkyl formates has been developed. For the first time non-activated chloroarenes have been successfully carbonylated using alkyl formates.

**Figure 3.** Alkoxy carbonylation with different formates.

Advantageously compared to previous work, it has been shown that the presented catalyst system does not need the presence of ruthenium co-catalysts. Notably, the reactions can be conveniently carried out and performed in standard equipment.

Experimental Section

General Remarks

NMP (*N*-methylpyrrolidone) was dried over CaH₂, distilled at reduced pressure and stored under argon. Butyl formate was fractionally distilled and stored under argon. Acetonitrile was distilled from phosphorus pentoxide and stored under argon. Ligands **L1–L7** and **L9** are commercially available. Ligands **L8**,^[12] **L10**,^[13] **L11–L14**^[14] were available as samples from our group. All other chemicals are commercially available and were used without further purification.

Standard Reaction Procedure

All solid ingredients were weighed into a pressure-proof glass tube with a PTFE-lined cap. The tube was flushed with argon for at least 1 min, then the liquid compounds were introduced by syringe under a constant flow of argon (stock solutions of palladium acetate in the respective solvent were used if appropriate), with the formate ester always as the last addition. Hexadecane was used as internal GC standard. The tube was sealed and heated with magnetic stirring for the time and at the temperature given in the Tables. After cooling to room temperature ethyl acetate (5 mL) was added and the reaction mixture was analyzed by GC. Conversion and yield were calculated as average of 2 parallel runs. The products can be isolated by column chromatography (silica gel, hexane/ethyl acetate) after washing the organic phase with water, drying over sodium sulfate and distilling off the solvents.

Butyl 3,4-dimethylbenzoate (product of model reaction):

¹H NMR (300 MHz, CDCl₃): δ = 7.8 (bs, 1 H), 7.77 (dd, *J* = 2 Hz, 8 Hz, 1 H), 7.18 (d, *J* = 8 Hz, 1 H), 4.30 (t, *J* = 6.3 Hz, 2 H), 2.32 (s, 6 H), 1.75 (m, 2 H), 1.45 (m, 2 H), 0.98 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 167.0, 142.1, 136.7, 130.6, 129.6, 128.1, 127.1, 64.6, 30.9, 20.0, 19.7, 19.3, 13.8; IR (ATR, neat): ν = 2959 (m), 2934 (sh), 2873 (m), 1713 (s, C=O), 1289 (s), 1259 (s), 1218 (s), 1178 (s), 1124 (m), 1101 (s), 759 cm⁻¹ (s); elemental analysis: calculated for C₁₃H₁₈O₂: C 75.69, H 8.80; found: C 75.65, H 8.71; MS

(EI, 70 eV): m/e (%) = 206 (9) M^+ , 150 (100), 133 (99), 105 (41).

Acknowledgements

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References

- [1] For reviews on palladium-catalyzed carbonylations see: a) A. Brennfürer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176–4196; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133; b) A. Brennfürer, H. Neumann, M. Beller, *ChemCatChem* **2009**, *1*, 28–41; c) M. Beller, *Carbonylation of Benzyl- and Aryl-X Compounds*, in: (Eds.: B. Cornils, W. A. Herrmann), *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd edn., Wiley-VCH, **2002**, Weinheim, pp 145–156; d) M. Beller, W. Mägerlein, A. F. Indolese, C. Fischer, *Synthesis* **2001**, 1098–1109; e) H. M. Colquhoun, D. J. Thompson, M. V. Twigg, *Carbonylation: Direct Synthesis of Carbonyl Compounds*, Plenum, New York, **1991**; f) M. Beller, B. Cornils, C. D. Frohning, C. W. Kohlpaintner, *J. Mol. Catal. A*: **1995**, *104*, 17–85.
- [2] a) D. A. Watson, X. X. Fan, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7096–7101; b) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 8612–8615; *Angew. Chem. Int. Ed.* **2007**, *46*, 8460–8463; c) C. Jimenez-Rodriguez, G. R. Eastham, D. J. Cole-Hamilton, *Dalton Trans.* **2005**, 1826–1830; d) W. Mägerlein, A. F. Indolese, M. Beller, *J. Organomet. Chem.* **2002**, *641*, 30–40; e) M. Beller, W. Mägerlein, A. F. Indolese, C. Fischer, *Synthesis* **2001**, 1098–1109; f) D. Najiba, J. F. Carpentier, Y. Castanet, C. Biot, J. Brocard, A. Mortreux, *Tetrahedron Lett.* **1999**, *40*, 3719–3722.
- [3] For an excellent review see: T. Morimoto, K. Kakiuchi, *Angew. Chem.* **2004**, *116*, 5698–5706; *Angew. Chem. Int. Ed.* **2004**, *43*, 5580–5588.
- [4] a) W. Mägerlein, A. Indolese, M. Beller, *Angew. Chem.* **2001**, *113*, 2940–2943; *Angew. Chem. Int. Ed.* **2001**, *40*, 2856–2859; b) W. Mägerlein, A. F. Indolese, M. Beller, *J. Organomet. Chem.* **2002**, *641*, 30–40; c) A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431–440.
- [5] a) J. F. Carpentier, Y. Castanet, J. Brocard, A. Mortreux, F. Petit, *Tetrahedron Lett.* **1991**, *32*, 4705–4708; b) J. F. Carpentier, Y. Castanet, J. Brocard, A. Mortreux, F. Petit, *Tetrahedron Lett.* **1992**, *33*, 2001–2004; c) J. F. Carpentier, F. Petit, A. Mortreux, V. Dufaud, J. M. Basset, J. Thivollecizat, *J. Mol. Catal. A*: **1993**, *81*, 1–15; d) J. F. Carpentier, E. Finet, Y. Castanet, J. Brocard, A. Mortreux, *Tetrahedron Lett.* **1994**, *35*, 4995–4998.
- [6] G. Jenner, A. Bentaleb, *J. Organomet. Chem.* **1994**, *470*, 257–261.
- [7] a) P. Appukkuttan, L. Axelsson, E. Van der Eycken, M. Larhed, *Tetrahedron Lett.* **2008**, *49*, 5625–5628; b) O. Lagerlund, M. Larhed, *J. Comb. Chem.* **2006**, *8*, 4–6.
- [8] A. G. Sergeev, A. Spannenberg, M. Beller, *J. Am. Chem. Soc.* **2008**, *130*, 15549–15563.
- [9] a) H. Neumann, A. Brennfürer, M. Beller, *Chem. Eur. J.* **2008**, *14*, 3645–3652; b) H. Neumann, A. Sergeev, M. Beller, *Angew. Chem.* **2008**, *120*, 4965–4969; *Angew. Chem. Int. Ed.* **2008**, *47*, 4887–4891; c) H. Neumann, A. Brennfürer, P. Groß, T. Riermeier, J. Almerna, M. Beller, *Adv. Synth. Catal.* **2006**, *348*, 1255–1261.
- [10] a) Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*, 6232–6235; b) J.-F. Carpentier, Y. Castanet, A. Mortreux, F. Petit, *J. Organomet. Chem.* **1994**, *482*, 31–38.
- [11] L. F. C. Roevens, J. J. P. Heykants, W. A. M. Heisen, (Janssen Pharmaceutica, N. V.), German Patent DE 2,609,573, **1976**.
- [12] a) A. Ehrentaut, A. Zapf, M. Beller, *J. Mol. Catal. A*: **2002**, *182–183*, 515–523; b) A. Tewari, M. Hein, A. Zapf, M. Beller, *Tetrahedron* **2005**, *61*, 9705–9709; c) A. Ehrentaut, A. Zapf, M. Beller, *Synlett* **2000**, 1589–1592; d) A. Zapf, A. Ehrentaut, M. Beller, *Angew. Chem.* **2000**, *112*, 4315–4317; *Angew. Chem. Int. Ed.* **2000**, *39*, 4153–4155; e) A. Tewari, M. Hein, A. Zapf, M. Beller, *Synthesis* **2004**, *6*, 935–941; f) A. Köllhofer, T. Pullmann, H. Plenio, *Angew. Chem.* **2003**, *115*, 1086–1088; *Angew. Chem. Int. Ed.* **2003**, *42*, 1056–1058; g) A. Ehrentaut, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 209–217.
- [13] T. Schareina, R. Jackstell, T. Schulz, A. Zapf, A. Cotte, M. Gotta, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 643–648.
- [14] a) T. Schulz, C. Torborg, B. Schöffner, J. Huang, A. Zapf, R. Kadyrov, A. Börner, M. Beller, *Angew. Chem.* **2009**, *121*, 936–939; *Angew. Chem. Int. Ed.* **2009**, *48*, 918–921; b) A. G. Sergeev, T. Schulz, C. Torborg, A. Spannenberg, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 7731–7735; *Angew. Chem. Int. Ed.* **2009**, *48*, 7595–7599; c) T. Hu, T. Schulz, C. Torborg, X. Chen, J. Wang, M. Beller, J. Huang, *Chem. Commun.* **2009**, 7330–7332.