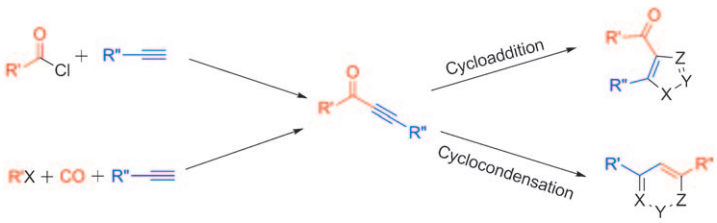
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201001864

A General and Convenient Palladium-Catalyzed Carbonylative Sonogashira Coupling of Aryl Bromides

Xiao-Feng Wu, Helfried Neumann, and Matthias Beller*[a]

Alkynones represent an interesting structural motif found in numerous biologically active molecules.[1] Notably, this class of compounds play a crucial role as key intermediates in the synthesis of natural products[2] and in the efficient formation of several heterocycles.[3] In the past alkynones have been typically synthesised by transition-metal-catalyzed cross-coupling reactions of acid chlorides and terminal alkynes (Scheme 1).[4] However, the stability of the respective acid chlorides is limited and a lack of functional tolerance is another problem of this methodology.



Scheme 1. Selected synthesis and applications of alkynones.

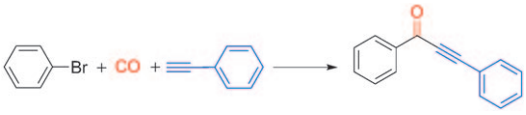
Within the last two decades, palladium-catalyzed carbonylations of aryl halides have become a powerful toolbox for the synthesis of all kinds of (hetero)aromatic carboxylic acid derivatives.[5] In this respect, it has also been shown that palladium-catalyzed carbonylative Sonogashira reactions represent a viable alternative and efficient methodology for the synthesis of alkynones. Advantageously, numerous such starting materials are easily available and good functional group compatibility has been demonstrated.[6] Since the first report by Kobayashi and Tanaka in 1981,[6a] significant improvements applying this methodology have been achieved. For example, Ahmed and Mori described room temperature reactions in the presence of 1 bar of CO.[6c] The groups of Xia[6b] and Ryu[6j] developed a recyclable reaction system with the assistance of Fe_3O_4 or in the presence of ionic liquids. More recently, Ryu and co-workers also published the synthesis of alkynones from iodoalkenes by applying a combination of Pd/*hv*.[6m] In addition to palladium-based catalysts copper was also described as an active metal for carbonylative Sonogashira reactions.[6n] Unfortunately, to date most carbonylative Sonogashira reactions are strictly limited to aryl iodides or iodoalkenes. So far, only a few exceptions exist that require higher CO pressure (20–80 bar) and do not proceed commonly in good yields.[6a] Clearly, aryl bromides offer considerable advantages with regard to availability and costs compared with aryl iodides. Thus, a general protocol for carbonylative Sonogashira couplings of aryl bromides is of significant interest for both industrial and academic communities.

Based on our recently developed palladium-catalyzed alkoxycarbonylation with phenols,[7] we investigated the carbonylative Sonogashira reaction of bromobenzene and phenyl acetylene with a catalyst system consisting of $[(cinnamyl)PdCl]_2$ (1 mol%) and $BuPAd_2$ (di-1-adamantyl-n-butylphosphine; cata*CX*ium A; 6 mol%) in the presence of NEt_3. Unfortunately, only 13% of the desired carbonylative product at 45% conversion was obtained (Table 1, entry 1). As a major side-product the Hay/Glaser product (1,4-diphenylbutadiyne) was observed. Notably, the product of the competing Sonogashira coupling (1,2-diphenylethyne) is not formed under these conditions. Hence, we investigated the benchmark reaction further. To our delight simple variation of base showed that inexpensive carbonates led to much improved selectivity (Table 1, entries 2–4). For example, by employing simple K_2CO_3 a 71% yield with 100% selectivity is obtained (Table 1, entry 2). In the presence of this base, we tested several mono- and bidentate ligands to improve the yield further; however $BuPAd_2$ appeared to be the best ligand in this reaction (Table 1, entries 7–12). Remarkably, the reaction temperature has a pronounced influence on this

[a] X.-F. Wu, Dr. H. Neumann, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V. an der Universität Rostock
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
Fax: (+49) 381-1281-5000
E-mail: matthias.beller@catalysis.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001864.

Table 1. Variation of the reaction conditions.[a]



Entry	Ligand [mol %]		Base	Conv. [%][b]	Yield [%][b]
1	$BuPAd_2$	6	NEt_3	45 %	13 %
2	$BuPAd_2$	6	K_2CO_3	71 %	71 %
3	$BuPAd_2$	6	$NaHCO_3$	30 %	23 %
4	$BuPAd_2$	6	Na_2CO_3	50 %	46 %
5	$BuPAd_2$	6	K_3PO_4	20 %	7 %
6	$BuPAd_2$	6	Cy_2NEt	23 %	6 %
7	PPh_3	6	K_2CO_3	69 %	14 %
8	PCy_3	6	K_2CO_3	19 %	9 %
9	$HPAd_2$	6	K_2CO_3	26 %	12 %
10	$BzPAd_2$	6	K_2CO_3	63 %	7 %
11	DPPF	6	K_2CO_3	30 %	0 %
12	$P(tBu)_3$	6	K_2CO_3	90 %	42 %
13[c]	$BuPAd_2$	12	K_2CO_3	82 %	52 %
14[c]	$BuPAd_2$	6	K_2CO_3	97 %	83 %
15[c]	$BuPAd_2$	4	K_2CO_3	87 %	71 %
16[c]	$BuPAd_2$	6	K_2CO_3	84 %	47 %[d]

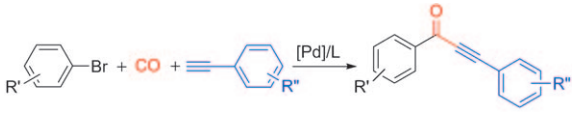
[a] Bromobenzene (1 mmol), phenyl acetylene (1 mmol), [(cinnamyl)PdCl]$_2$ (1 mol %), ligand, base (2 equiv), DMF (2 mL), CO (10 bar), 100 °C, 20 h. [b] Conversion and yield were determined by GC based on bromobenzene with hexadecane as an internal standard. [c] [(Cinnamyl)PdCl]$_2$ (2 mol %). [d] CO (5 bar).

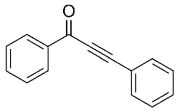
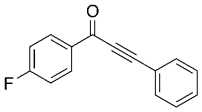
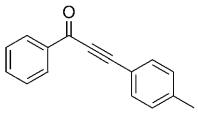
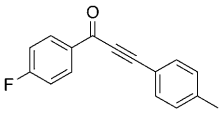
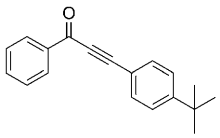
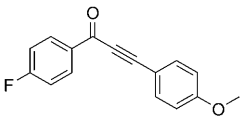
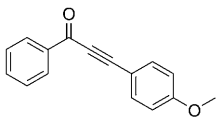
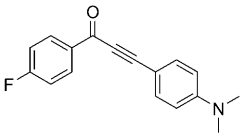
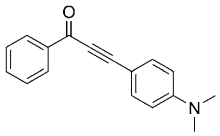
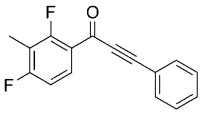
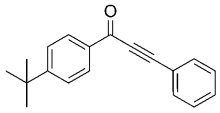
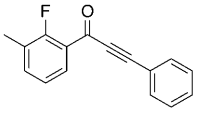
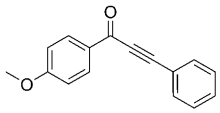
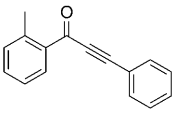
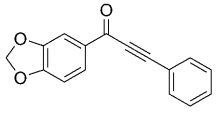
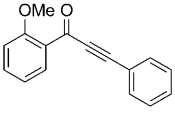
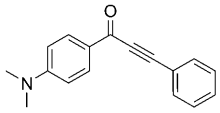
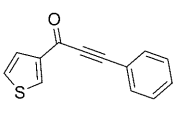
model reaction: increasing the temperature to 120 °C led to the selective formation of (undesired) 1,2-diphenylethyne! On the other hand, when we decreased the Pd/L ratio from 1:3 to 1:1.5 the yield of the carbonylative Sonogashira reaction increased to 83 % (Table 1, entry 14).

With suitable conditions in hand (Table 1, entry 14), we next employed different terminal alkynes and aryl bromides in 18 carbonylative Sonogashira reactions. As shown in Table 2 in general good to very good yields (47–88 %) were achieved. With respect to functional group tolerance, ether, amino, alkyl and fluoride substituents were tolerated without problems both in the alkyne and aryl part. *ortho*-Substituted aryl bromides also resulted in the corresponding alkynones with moderate to good yields (Table 2, entries 14–17; 47–79 %). In addition, 3-bromothiophene (as an example of a heterocyclic bromide) also worked in our system (Table 2, entry 18). However, in this case a higher CO pressure (30 bar CO) had to be applied. On the other hand *p*-CF_3-, *p*-CHO- and *p*-CN-substituted bromoarenes were not successfully carbonylated under these conditions. Here, apart from traces of the alkynones, a large amount of the respective Sonogashira coupling product was formed. 4-Chloroacetophone did not show any conversion.

Müller and co-workers[8] as well as other groups[9] have elegantly demonstrated the potential of alkynones in heterocycle syntheses. Hence, we performed exemplarily one-pot syntheses of isoxazolines and pyrazoles starting from inexpensive aryl bromides (Scheme 2). Here, methylhydrazine, phenylhydrazine, or hydroxylamine was added at the end of the carbonylative Sonogashira reaction. After additional stirring at room temperature for 1 hour, the corresponding pyrazole and isoxazole products were successfully isolated in high yield (75–81 %).

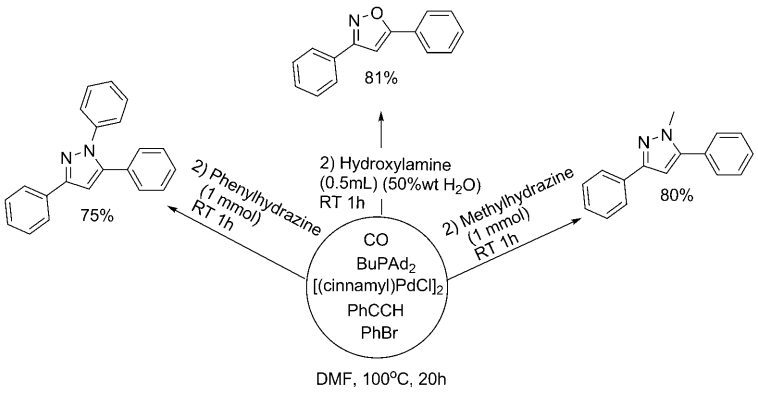
Table 2. Carbonylative Sonogashira reaction of various aryl bromides.[a]



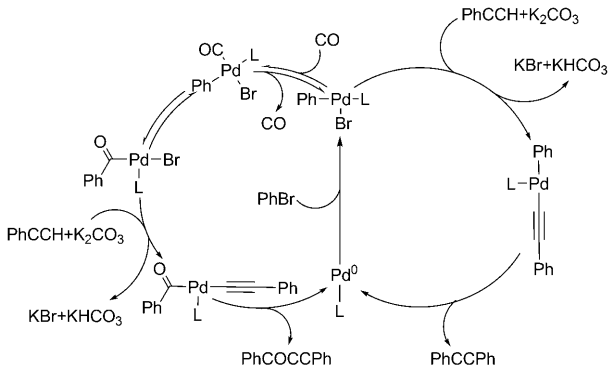
Entry	Product	Yield [%][b]	Entry	Product	Yield [%][b]
1		81 %	10		57 % 88 %[c]
2		65 %	11		85 %[c]
3		66 %	12		80 %[c]
4		75 %	13		81 %[c]
5		88 %	14		79 %
6		61 %	15		62 %
7		76 %	16		55 %[d]
8		62 %	17		47 %[d]
9		68 %	18		53 %[d]

[a] Aryl bromide (1 mmol), alkyne (1 mmol), [(cinnamyl)PdCl]$_2$ (2 mol %), $BuPAd_2$ (6 mol %), K_2CO_3 (2 equiv), DMF (2 mL), CO (10 bar), 100 °C, 20 h. [b] Yield of the isolated product. [c] 1.5 equiv of alkyne. [d] 115 °C, CO (30 bar).

With regard to the mechanism, we propose an initial oxidative addition of the aryl bromide to the LPd^0 species to give the corresponding arylpalladium(II) complex (Scheme 3). Subsequent formation of the benzoylpalladium complex takes place by CO insertion. Supported by K_2CO_3 an exchange of the bromide by phenyl acetylide occurs and



Scheme 2. One-pot synthesis of heterocycles.



Scheme 3. Proposed reaction mechanism.

the desired product is formed by reductive elimination. It is worth mentioning that CO migration and insertion are considered to be reversible steps within this system. Since at higher temperature (120 °C) decarbonylation[10] is favoured and only 1,2-diphenylethyne is formed, whereas at lower temperature (80 °C) the carbonylation dominates and only the alkynone is observed as product.

In conclusion, a novel chemoselective protocol for the carbonylative Sonogashira coupling of aryl bromides at low pressure has been developed. The key to success is the application of a palladium/$BuPAd_2$ catalyst system[11] in the presence of potassium carbonate as base.

Experimental Section

General procedure for carbonylative Sonogashira reactions: $[(Cinnamyl)PdCl]_2$ (10.3 mg, 2 mol %), $BuPAd_2$ (22 mg, 6 mol %) and K_2CO_3 (276 mg, 2 equiv) were transferred into a vial (12 mL reaction volume) equipped with a septum, a small cannula and a stirring bar. After the vial was purged with argon, bromobenzene (105 μL, 1 mmol), phenyl acetylene (111 μl, 1 mmol), DMF (2 mL) and hexadecane (0.1 mL, internal GC standard) were injected into the vial by syringe. Then, the vial was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments under an argon atmosphere. After flushing the autoclave three times with CO, a pressure of 10 bar was adjusted and the reaction was performed for 20 h at 100 °C. After the reaction, the autoclave was cooled down to room temperature and the pressure was released carefully. To the reaction mixture 6 mL water was added and the solution was extracted 3–5 times with 2–3 mL of ethyl acetate. The extracts were evaporated with adsorption on silica gel and the crude product was purified by column chromatography using *n*-heptane and *n*-heptane/AcOEt (50:1) as eluent. The product was obtained in 81 % yield (167 mg) as a yellow oil.

General procedure for the one-port heterocyclic formation: After the carbonylation reaction, the reaction mixture was cooled to room temperature and the pressure was released carefully. Next, 1 mmol of methylhydrazine was added and stirring was continued at room temperature for 1 h. Water (2 mL) was added to the reaction solution and the organic layer was extracted 3–5 times with of ethyl acetate (2 mL). The extracts were evaporated with adsorption on silica gel and the crude product was purified by column chromatography using *n*-heptane and *n*-heptane/AcOEt (50:1) as eluent.

Acknowledgements

The authors thank the state of Mecklenburg-Vorpommern and the Bundesministerium für Bildung und Forschung (BMBF) for financial support. We also thank S. Leiminger, K. Mevius, Dr. W. Baumann, Dr. C. Fischer and S. Buchholz (LIKAT) for analytical support.

Keywords: alkynones · aryl bromides · carbonylation · palladium · Sonogashira reaction

[1] a) C. H. Faweett, R. D. Firu, D. M. Spencer, *Physiol. Plant Pathol.* **1971**, *1*, 163–166; b) K. Imai, *J. Pharm. Soc. Jpn.* **1956**, *76*, 405–408; c) C. A. Quesnelle, P. Gill, M. Dodier, D. St. Laurent, M. Serrano-Wu, A. Marinier, A. Martel, C. E. Mazzucco, T. M. Stickle, J. F. Barrett, D. M. Vyas, B. N. Balasubramanian, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 519–524.

[2] a) A. S. Karpov, E. Merkul, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2005**, *117*, 7112–7117; *Angew. Chem. Int. Ed.* **2005**, *44*, 6951–6956; b) D. M. D'Souza, T. J. J. Müller, *Nat. Protoc.* **2008**, *3*, 1660–1665; c) J. Marco-Contelles, E. de Opazo, *J. Org. Chem.* **2002**, *67*, 3705–3717; d) C. J. Forsyth, J. Xu, S. T. Nguyen, I. A. Samdai, L. R. Briggs, T. Rundberget, M. Sandvik, C. O. Miles, *J. Am. Chem. Soc.* **2006**, *128*, 15114–15116; e) L. F. Tietze, R. R. Singidi, K. M. Gericke, H. Bockemeier, H. Laatsch, *Eur. J. Org. Chem.* **2007**, 5875–5878.

[3] a) B. Willy, T. J. J. Müller, *Arkivoc* **2008**, 195–208; b) A. Arcadi, M. Aschi, F. Marinelli, M. Verdecchia, *Tetrahedron* **2008**, *64*, 5354–5361; c) P. Bannwarth, A. Valleix, D. Gree, R. Gree, *J. Org. Chem.* **2009**, *74*, 4646–4649.

[4] a) K. Y. Lee, M. J. Lee, J. N. Kim, *Tetrahedron* **2005**, *61*, 8705–8710; b) H. A. Stefani, R. Cella, F. A. Dorr, C. M. P. de Pereira, F. P. Gomes, G. Zeni, *Tetrahedron Lett.* **2005**, *46*, 2001–2003; c) S. S. Palimkar, P. H. Kumar, N. R. Jogdand, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *Tetrahedron Lett.* **2006**, *47*, 5527–5530; d) S. J. Yim, C. H. Kwon, D. K. An, *Tetrahedron Lett.* **2007**, *48*, 5393–5395; e) M. M. Jackson, C. Leverett, J. F. Toczko, J. C. Roberts, *J. Org. Chem.* **2002**, *67*, 5032–5035; f) D. A. Alonso, C. Nájera, M. C. Pacheco, *J. Org.*

Chem. **2004**, *69*, 1615–1619; g) B. Wang, M. Bonin, L. Micouin, *J. Org. Chem.* **2005**, *70*, 6126–6128; h) L. Chen, C. Li, *Org. Lett.* **2004**, *6*, 3151–3153; i) N. Kakusawa, K. Yamaguchi, J. Kurita, T. Tsuchiya, *Tetrahedron Lett.* **2000**, *41*, 4143–4146.

[5] For reviews on palladium-catalyzed carbonylations, see: a) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176–4196; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133; b) A. Brennführer, H. Neumann, M. Beller, *ChemCatChem* **2009**, *1*, 28–41; c) M. Beller, *Carbonylation of Benzyl- and Aryl-X Compounds in B. Cornils in Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed. (Ed.: W. A. Herrmann), Wiley-VCH, Weinheim, **2002**, pp. 145–156; d) R. Skoda-Foldes, L. Kollár, *Curr. Org. Chem.* **2002**, *6*, 1097–1119; e) J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, New York, **1995**; f) M. Beller, B. Cornils, C. D. Frohning, C. W. Kohlpaintner, *J. Mol. Catal. A* **1995**, *104*, 17–85.

[6] a) T. Kobayashi, M. Tanaka, *J. Chem. Soc. Chem. Commun.* **1981**, 333–334; b) J. Liu, X. Peng, W. Sun, Y. Zhao, C. Xia, *Org. Lett.* **2008**, *10*, 3933–3936; c) M. S. Mohamed Ahmed, A. Mori, *Org. Lett.* **2003**, *5*, 3057–3060; d) J. Liu, J. Chen, C. Xia, *J. Catal.* **2008**, *253*, 50–56; e) S. Kang, K. Lim, P. Ho, W. Kim, *Synthesis* **1997**, 874–876; f) L. Delaude, A. M. Masdeu, H. Alper, *Synthesis* **1994**, 1149–1151; g) A. Arcadi, S. Cacchi, F. Marinelli, P. Pace, G. Sanzi, *Synlett* **1995**, 823–824; h) M. Iizuka, Y, Kondo, *Eur. J. Org. Chem.* **2007**, 5180–5182; i) V. Sans, A. M. Trzeciak, S. Luis, J. J. Ziólkowski, *Catal. Lett.* **2006**, *109*, 37–41; j) T. Fukuyama, R. Yamaura, I. Ryu, *Can. J. Chem.* **2005**, *83*, 711–715; k) M. T. Rahman, T. Fukuyama, N. Kamata, M. Sato, I. Ryu, *Chem. Commun.* **2006**, 2236–2238; l) B. Liang, M. Huang, Z. You, Z. Xiong, K. Lu, R. Fathi, J. Chen, Z. Yang, *J. Org. Chem.* **2005**, *70*, 6097–6100; m) A. Fusano, T. Fukuyama, S. Nishitani, T. Inouye, I. Ryu, *Org. Lett.* **2010**, *12*, 2410–2413; n) P. J. Tambade, Y. P. Patil, N. S. Nandurkar, B. M. Bhanage, *Synlett* **2008**, 886–888.

[7] X. Wu, H. Neumann, M. Beller, *ChemCatChem* **2010**, *2*, 509–513.

[8] a) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108; b) B. Willy, T. J. J. Müller, *Curr. Org. Chem.* **2009**, *13*, 1777–1790; c) E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Eur. J.* **2009**, *15*, 5006–5011; d) B. Willy, T. J. J. Müller, *Synthesis* **2008**, 293–303; e) A. V. Rotaru, I. D. Druta, T. Oeser, T. J. J. Müller, *Helv. Chim. Acta* **2005**, *88*, 1798–1812; f) B. Willy, T. J. J. Müller, *Eur. J. Org. Chem.* **2008**, 4157–4168; g) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581–2583; h) E. Merkul, T. J. J. Müller, *Chem. Commun.* **2006**, 4817–4819; i) A. S. Karpov, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2004**, 1502–1503.

[9] a) B. C. Bishop, K. M. J. Brands, A. D. Gibb, D. J. Kennedy, *Synthesis* **2004**, 43–52; b) M. S. Mohamed Ahmed, K. Kobayashi, A. Mori, *Org. Lett.* **2005**, *7*, 4487–4489; c) S. S. Palimkar, R. J. Lahoti, K. V. Srinivasan, *Green Chem.* **2007**, *9*, 146–152.

[10] a) F. Calderazzo F. A. Cotton, *Inorg. Chem.* **1962**, *1*, 30–36; b) L. J. Goossen, N. Rodriguez, K. Goossen, *Angew. Chem.* **2008**, *120*, 3144–3164; *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120.

[11] For some other applications of this catalyst system, see: a) S. Klaus, H. Neumann, A. Zapf, D. Strübing, S. Hübner, J. Almena, T. Riermeier, P. Groß, M. Sarich, W.-R. Krähnert, K. Rossen, M. Beller, *Angew. Chem.* **2006**, *118*, 161–165; *Angew. Chem. Int. Ed.* **2006**, *45*, 154–158; b) A. Brennführer, H. Neumann, S. Klaus, T. Riermeier, J. Almena, M. Beller, *Tetrahedron* **2007**, *63*, 6252–6258; c) A. G. Sergeev, A. Zapf, A. Spannenberg, M. Beller, *Organometallics* **2008**, *27*, 297–300; d) H. Neumann, A. Brennführer, P. Groß, T. Riermeier, J. Almena, M. Beller, *Adv. Synth. Catal.* **2006**, *348*, 1255–1261; e) H. Neumann, A. Brennführer, M. Beller, *Chem. Eur. J.* **2008**, *14*, 3645–3652; f) A. Tewari, M. Hein, A. Zapf, M. Beller, *Tetrahedron* **2005**, *61*, 9705–9709; g) A. Ehrentraut, A. Zapf, M. Beller, *Synlett* **2000**, 1589–1592; h) A. Zapf, A. Ehrentraut, M. Beller, *Angew. Chem.* **2000**, *112*, 4315–4317; *Angew. Chem. Int. Ed.* **2000**, *39*, 4153–4155; i) A. Tewari, M. Hein, A. Zapf, M. Beller, *Synthesis* **2004**, 935–941; j) A. Köllhofer, T. Pullmann, H. Plenio, *Angew. Chem.* **2003**, *115*, 1086–1088; *Angew. Chem. Int. Ed.* **2003**, *42*, 1056–1058; k) A. Ehrentraut, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 209–217; l) A. G. Sergeev, A. Spannenberg, M. Beller, *J. Am. Chem. Soc.* **2008**, *130*, 15549–15563.

Received: July 1, 2010
Published online: September 16, 2010

