Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201300687

Palladium-Catalyzed Methoxylation of Aromatic Chlorides with Borate Salts

Gergely L. Tolnai,[+a] Bálint Pethő,[+a] Péter Králl,[a] and Zoltán Novák[a,*]

[a] MTA-ELTE "Lendület" Catalysis and Organic Synthesis Research Group, Institute of Chemistry, Eötvös University, Pázmány Péter stny. 1/a, H-1117 Budapest, Hungary
E-mail: novakz@elte.hu

[+] These authors contributed equally to the present work.

Received: August 10, 2013; Revised: October 23, 2013; Published online: January 13, 2014

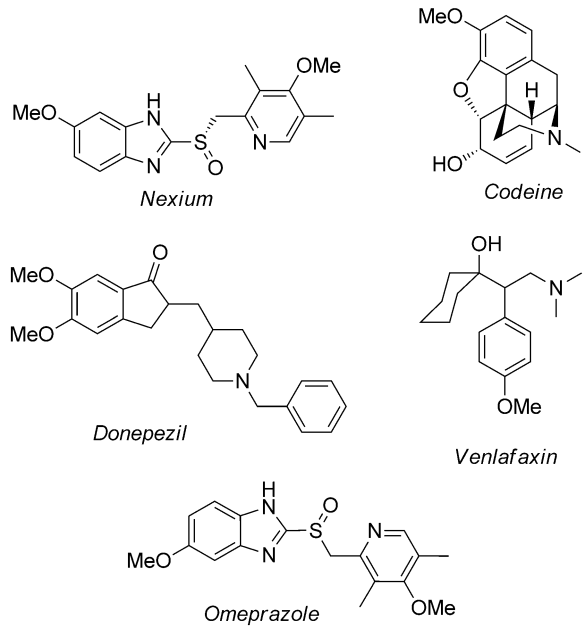
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300687.

Abstract: Herein we disclose a simple palladium-catalyzed transformation for the methoxylation of aromatic chlorides with tetramethoxyborate salts. The procedure provides a new and efficient synthetic tool for the introduction of a methoxy group into aromatic systems. In addition, the reaction can be achieved using a wide range of aromatic and heteroaromatic chlorides, the cheapest class of halides.

Keywords: borates; cross-coupling; Lewis acids; palladium

Aromatic ethers are in great interest of organic chemistry. They appear in many natural products and active pharmaceutical ingredients (Scheme 1). Due to the strong electron-donating property of the methoxy group, its presence significantly modifies the electronic properties of aromatic compounds to ensure unique properties in several materials.[1]

Besides the traditional Ullmann coupling,[2] in the last decades the Buchwald–Hartwig-type coupling has become a general tool for the construction of C–N and C–O bonds between the heteroatom and the aromatic ring. Despite the existence of versatile palladium-catalyzed C–N bond forming reactions,[3] the methodologies for the C–O coupling reaction between aryl halides and oxygen nucleophiles are still limited.[4] The main difficulty in these transformations is the presence of competing β-hydride elimination side reactions. The first report of Buchwald describes a convenient palladium-catalyzed method that only enables the coupling of *ortho*-substituted aryl bromides with primary alcohols containing at least four carbons.[5] Later improvements gave a more tuneable ligand system that is able to promote the coupling of primary and secondary alcohols with aromatic and heteroaromatic bromides.[6] However, the introduction of the simple methoxy group is still challenging. Beller and co-workers recently published the first palladium-catalyzed method for methoxylation based on the utilization of the adamantly-BiPyphos ligand.[7] Their catalyst system reduces the ratio of β-hydride elimination by accelerating the reductive elimination step. The described method works excellently with electron-deficient bromides in MeOH, in the presence of Cs_2CO_3 as base. It is of note that the methoxylation of chlorides, especially those which are functionalized with electron-donating groups, is still unprecedented.



Scheme 1. Selected biologically active methoxy compounds.

However, the application of chlorides is more beneficial than other halides or triflates.

Very recently, Gooßen demonstrated with a slightly different approach that the introduction of the methoxy group is possible using a copper/silver catalyst system *via* decarboxylative coupling with tetramethoxysilane.[8]

Boranes and borate salts are widely used in cross-coupling reactions due to the high importance of Suzuki reactions.[9] The only example for the utilization of methoxyborate salts instead of trifluoroborate salts in cross-coupling chemistry is Gooßen's copper-catalyzed trifluoromethylation of aryl iodides with trifluoromethyltrimethylborate salts.[10] To the best of our knowledge the approach based on alkoxyborates has never been used for carbon-oxygen bond formation.

Taking into consideration that the trialkoxyboranes can bind nucleophilic heteroatoms *via* the formation of Lewis acid–base adduct, we aimed to develop a catalytic method for the methoxylation of aromatic chlorides without the use of a large excess of strong base or methanol. The easily accessible air-stable tetramethoxyborates salts[11] could provide methoxy groups *via* transmetallation for a general palladium-catalyzed cross-coupling cycle in a Suzuki-type C–O bond forming reaction. However, this type of reaction is as yet not known.

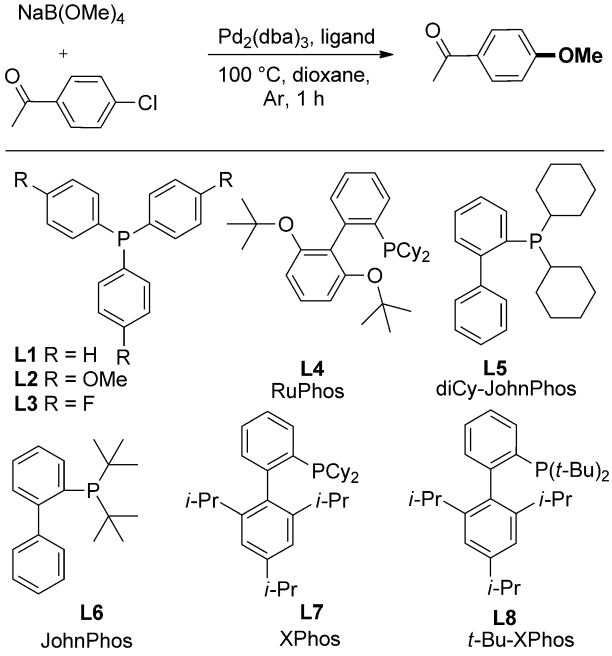
For preliminary optimization, we examined the methoxylation of 4-chloroacetophenone using sodium tetramethoxyborate salt in the presence of $Pd_2(dba)_3$ in dioxane at 100 °C Table 1).

We tested several phosphane ligands and, to our delight, we were able to achieve the desired coupling in the presence of several triarylphosphanes and Buchwald-type biphenyl-based ligands, but we found that 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (*t*-BuXPhos) was essential for the efficient coupling (Table 1). In the case of this electron-deficient aryl chloride the catalyst loading could be reduced to 0.5 mol%.[12]

Further optimization of the methoxylation with a less reactive chloride, 4-chloroanisole, and freshly prepared K[$B(OMe)_4$] demonstrated the real synthetic power of the method (Table 2). We found that the reaction is even more sensitive to the choice of the ligands, and only *t*-BuXPhos provided the desired *para*-dimethoxybenzene with 68% conversion after 1 hour (entries 1–5).

Regarding the appropriate choice of solvent we found that a coupling conducted in DMF provides the best conversions (entries 5–8), and the formation of the dehalogenated by-product was not significant in this solvent. In the case of this electron rich-substrate the addition of 2.5 mol% $Pd_2(dba)_3$ is necessary for the coupling (entries 5, 9, and 10).[12]

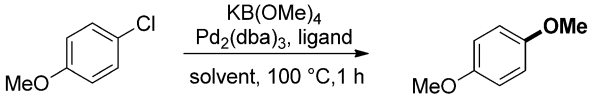
Table 1. Ligand screening study.[a]



Entry	$Pd_2(dba)_3$	Ligand	Conversion[b] [%]
1	2 mol%	4 mol%, **L1**	0
2	2 mol%	4 mol%, **L2**	0
3	2 mol%	4 mol%, **L3**	2
4	2 mol%	4 mol%, **L4**	25
5	2 mol%	4 mol%, **L5**	15
6	2 mol%	4 mol%, **L6**	49
7	2 mol%	4 mol%, **L7**	81
8	2 mol%	4 mol%, **L8**	98
9	1 mol%	2 mol%, **L8**	98
10	0.5 mol%	1 mol% **L8**	98

[a] 0.5 mmol aryl chloride, 0.5 mmol $NaB(OMe)_4$, 500 μL dioxane.
[b] Followed by GC-FID using mesitylene as a standard.

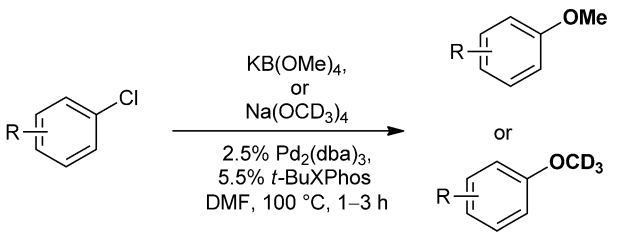
Table 2. Study of solvent effects.[a]

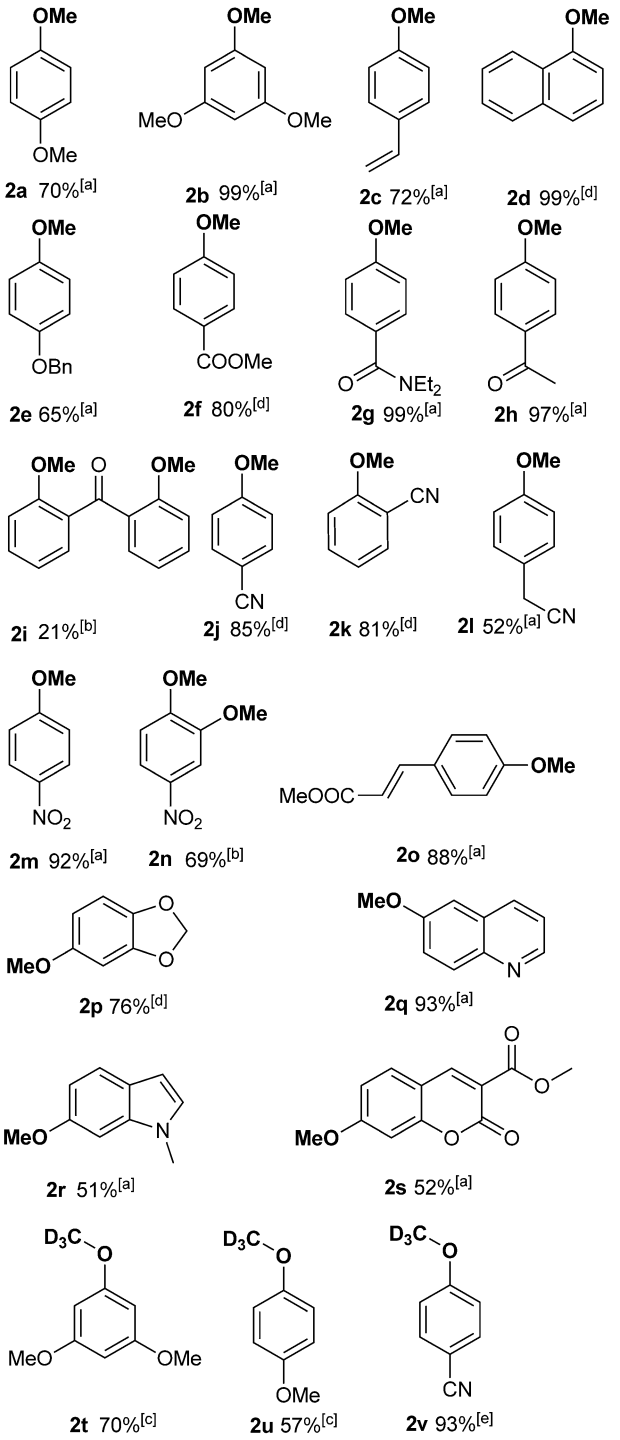


Entry	$Pd_2(dba)_3$ [mol%]	Ligand	Solvent	Conversion[b] [%]
1	5	10% XPhos	DMF	7
2	5	10% DPPE	DMF	0
3	5	10% DPPF	DMF	0
4	5	10% BINAP	DMF	0
5	5	10% *t*-BuXPhos	DMF	68
6	5	10% *t*-BuXPhos	dioxane	36
7	5	10% *t*-BuXPhos	CPME	26
8	5	10% *t*-BuXPhos	diglyme	59
9	1	10% *t*-BuXPhos	DMF	33
10	2.5	5.5% *t*-BuXPhos	DMF	67

[a] 0.5 mmol 4-chloroanisole, 0.5 mmol $KB(OMe)_4$, 500 μL solvent.
[b] followed by GC-FID using mesitylene as a standard.

Table 3. Substrate scope for the palladium-catalyzed methoxylation reaction.



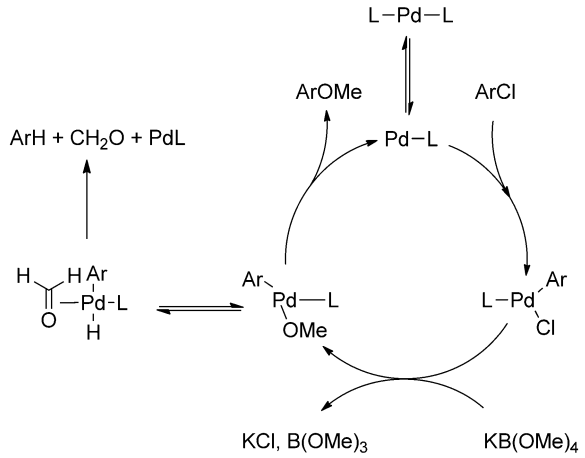


[a] 1 mmol substrate, 1.5 equiv. $KB(OMe)_4$, 2.5% $Pd_2(dba)_3$, 5.5% *t*-BuXPhos, 500 μL DMF.
[b] 1 mmol substrate, 3 equiv. $KB(OMe)_4$, 2.5% $Pd_2(dba)_3$, 5.5% *t*-BuXPhos, 1000 μL DMF.
[c] 1 mmol substrate, 1.5 equiv. $NaB(OCD_3)_4$, 2.5% $Pd_2(dba)_3$, 5.5% *t*-BuXPhos, 500 μL DMF.
[d] 5 mmol substrate, 1.5 equiv. $KB(OMe)_4$, 2.5% $Pd_2(dba)_3$, 5.5% *t*-BuXPhos, 2.5 mL DMF.
[e] 5 mmol substrate, 1.5 equiv. $NaB(OCD_3)_4$, 2.5% $Pd_2(dba)_3$, 5.5% *t*-BuXPhos, 2.5 mL DMF.

With these results in hand we turned our attention to the substrate scope of the reaction (Table 3.). The scope was examined on a 1–5 mmol scale and the reactions provided the products with good to excellent yields in the presence of electron-donating functional groups on the aromatic chlorides (Scheme 1, **2a–d**). Methoxylation of benzyl-protected 4-chlorophenol was also successful and the appropriate anisole derivative (**2e**) was obtained in 65% yield. The presence of carbonyl functionalities was also well tolerated providing products (**2f–h**) with excellent yields. Utilizing the developed conditions, the sterically demanding double methoxylation of dichlorbenzophenone was also successful, however, the yield of compound **2i** was surprisingly low (21%) compared to other substrates. By comparison, 2-and 4-chlorobenzonitriles showed that smaller electron-withdrawing groups have no steric impact on the reaction result, and both 4-methoxy- (**2j**) and 2-methoxybenzonitrile (**2k**) were isolated with good yields (85% and 81%, respectively). When a methylene group was present in the substrate between the nitrile and the aromatic core the methoxyphenylacetonitrile (**2l**) was obtained with lower (52%) yield.

Electron-deficient 4-chloronitrobenzene was methoxylated smoothly under the standard conditions and compound **2m** was isolated in 92% yield. Double methoxylation of dichloronitrobenzene provided the expected dimethoxynitrobenzene product (**2n**) in 69% yield. The methoxylation of a cinnamic acid derivative provided product **2o** in excellent yield (88%), and electron-rich 5-chlorobenzo[*d*][1,3]dioxole was also converted to the corresponding sesamol derivative (**2p**).

Heterocyclic compounds are very important structures from medicinal and biochemical aspects, therefore we examined the reactivity of several heterocyclic chlorides in the palladium-catalyzed alkoxylation. The reaction of 6-chloroquinoline provided 6-methoxyquinoline (**2q**) with an excellent 93% yield, while 6-chloroindole was also successfully methoxylated and provided the desired 6-methoxy product **2r** in 51% yield, which is an expensive starting material for total syntheses. The non-fluorescent chlorocoumarin derivative was also successfully converted to the appropriate highly fluorescent methoxycoumarin (52%).



Scheme 2. The proposed catalytic cycle.

The isotopic labelling of different groups is an important task in SAR or metabolism studies in medicinal chemistry.[13] The introduction of a trideuteromethoxy group *via* palladium-catalyzed cross coupling is also possible in CD_3OD as solvent.[6e,13c]

With our method, due to the small excess of trideuteromethoxides and the low price of starting materials, a practical method could be achieved. Due to the more efficient preparation of $Na[B(OCD_3)_4]$ we used this salt instead of the potassium derivative. The sodium salt proved to be a stable and effective methoxylating agent for aromatic chlorides. Utilizing the deuterated salt in the cross-coupling under the developed conditions we prepared deuteromethoxylated compounds bearing electron-donating and electron-withdrawing groups (**2t–v**).

Our working model for the reaction is depicted on Scheme 2. The reaction likely begins with an oxidative addition of the aromatic chloride to the palladium center, which is promoted by the bulky phosphane ligand. Then transmetallation occurs from the borate salt, providing the arylpalladium alkoxide species. The transmetallated palladium complex may be stabilized by the boron, to prevent β-hydride elimination. Following reductive elimination, the desired carbon-oxygen bond forms along with regeneration of the Pd(0) catalyst.

In conclusion, we have developed a new, simple and efficient synthetic tool for the palladium-catalyzed methoxylation of various electron-rich and electron-deficient aromatic and heteroaromatic chlorides utilizing stable, easy-to-prepare tetramethoxyborate salts as methoxylating agents. This methodology can be used to introduce methoxy or trideuteromethoxy groups into the aromatic core. The transformation has good functional group tolerance and the desired products can be prepared in good to excellent yields in short reaction time. Taking advantage of the efficient anion transfer from borate salts in palladium-catalyzed cross-coupling reactions, further applications beyond methoxylation can be envisioned for the construction of carbon-heteroatom bonds. Studies on the expansion of borate chemistry in the field of cross-coupling reactions are currently underway in our laboratory.

Experimental Section

General Procedure

The $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 2.5%), the 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (*t*BuXphos, 22.8 mg, 0.055 mmol, 5.5%) and the $KB(OMe)_4$ (260 mg, 1.50 mmol, 1.5 equiv.) or $NaB(OCD_3)_4$ (235 mg, 1.50 mmol, 1.50 equiv.) and the substrate if a solid (1 mmol) were charged into a 4-mL screw-cap vial, equipped with a stirrer bar. The atmosphere was changed 3 times to argon, and dry DMF (500 μL) was filled in. The substrate was then added if a liquid (1 mmol) and stirred at 100 °C for 60–180 min until the reaction was completed. The mixture was allowed to cool down to room temperature, diluted with EtOAc (20 mL), washed with water (20 mL), and brine (20 mL), dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography (SiO_2, hexanes/EtOAc).

Acknowledgements

This project was supported by the "Lendület" Research Scholarship of the Hungarian Academy of Sciences, and by TéT 10-1-2011-0245. The help of Dr. Zs. Eke for providing the necessary analytical background is gratefully acknowledged. The authors thank Dr. Tamás Gáti for the NMR measurements of the borate salts. The authors also thank Prof. Tim Peelen for the proof-reading of this manuscript.

References

[1] a) W. R. Gutekunst, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 19076–19079; b) E. Fuhrmann, J. Talbiersky, *Org. Process Res. Dev.* **2005**, *9*, 206–211; c) T. Offermans, P. A. van Hal, S. C. J. Meskers, M. M. Koetse, R. A. J. Janssen, *Phys. Rev. B* **2005**, *72*, 045213; d) A. Minassi, G. Sánchez-Duffhues, J. A. Collado, E. Muñoz, G. Appendino, *J. Nat. Prod.* **2013**, *76*, 1105–1112; e) R. S. Sood, B. N. Ganguli, G. C. S. Reddy, H. Dornauer, P. V. Divekar, H. W. Fehlhaber, *J. Nat. Prod.* **1982**, *45*, 74–77; f) J. Gao, M. M. Radwan, F. León, O. R. Dale, A. S. Husni, Y. Wu, S. Lupien, X. Wang, S. P. Manly, R. A. Hill, F. M. Dugan, H. G. Cutler, S. J. Cutler, *J. Nat. Prod.* **2013**, *76*, 824–828; g) R. B. Grubbs, S. R. Marder, J. W. Perry, W. P. Schaefer, *Chem. Mater.* **1991**, *3*, 3–4; h) G. Sonmez, H. Meng, F. Wudl, *Chem. Mater.* **2004**, *16*, 574–580; i) H. Mizuno, U. Haku, Y. Marutani, A. Ishizumi, H. Yanagi, F. Sasaki, S. Hotta, *Adv. Mater.* **2012**, *24*, 5744–5749; j) P. Belik, A. Gügel,

A. Kraus, J. Spickermann, V. Enkelmann, G. Frank, K. Müllen, *Adv. Mater.* **1993**, *5*, 854–856.
[2] F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853–857.
[3] a) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154–2177; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50; b) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544; c) A. Komáromi, Z. Novák, *Adv. Synth. Catal.* **2010**, *352*, 1523–1532.
[4] a) M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334; b) K. E. Torraca, S.-I. Kuwabe, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12907–12908; c) S. Harkal, K. Kumar, D. Michalik, A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, M. Beller, *Tetrahedron Lett.* **2005**, *46*, 3237–3240; d) C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 4427–4432; *Angew. Chem. Int. Ed.* **2006**, *45*, 4321–4326; e) R. Paul, M. A. Ali, T. Punniyamurthy, *Synthesis* **2010**, 4268–4272.
[5] K. E. Torraca, X. Huang, C. A. Parrish, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771.
[6] a) S. Ueda, S. Ali, B. P. Fors, S. L. Buchwald, *J. Org. Chem.* **2012**, *77*, 2543–2547; b) A. V. Vorogushin, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 8146–8149; c) Q. Shelby, N. Kataoka, G. Mann, J. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719; d) X. Wu, B. P. Fors, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 10117–10121; *Angew. Chem. Int. Ed.* **2011**, *50*, 9943–9947; e) S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 11592–11598; f) C. W. Cheung, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 3998–4001.
[7] S. Gowrisankar, H. Neumann, M. Beller, *Chem. Eur. J.* **2012**, *18*, 2498–2502.
[8] S. Bhadra, W. I. Dzik, L. J. Gooßen, *J. Am. Chem. Soc.* **2012**, *134*, 9938–9941.
[9] a) W. A. Herrmann, in: *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley-VCH, Weinheim, **2008**, pp 591–598; b) N. E. Leadbeater, *Chem. Commun.* **2005**, *41*, 2881–2902; c) G. A. Molander, B. Canturk, *Angew. Chem.* **2009**, *121*, 9404–9425; *Angew. Chem. Int. Ed.* **2009**, *48*, 9240–9261; d) A. Fihri, M. Bouhrara, B. Nekoueishahraki, J.-M. Basset, V. Polshettiwar, *Chem. Soc. Rev.* **2011**, *40*, 5181–5203.
[10] T. Knauber, F. Arikan, G.-V. Röschenthaler, L. J. Gooßen, *Chem. Eur. J.* **2011**, *17*, 2689–2697.
[11] Prepared by a modification of the following literature procedure: A. G. Campaña, N. Fuentes, E. Gómez-Bengoa, C. Mateo, J. E. Oltra, A. M. Echavarren, J. M. Cuerva, *J. Org. Chem.* **2007**, *72*, 8127–8130.
[12] For further results see the Supporting Information.
[13] a) K. Sanderson, *Nature* **2009**, *458*, 269; J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *Angew. Chem.* **2007**, *119*, 7890–7911; *Angew. Chem. Int. Ed.* **2007**, *46*, 7744–7765; b) T. Junk, W. J. Catallo, *Chem. Soc. Rev.* **1997**, *26*, 401–406; c) P. Dash, M. Janni, S. Peruncheralathan, *Eur. J. Org. Chem.* **2012**, *77*, 4914–4917.

