CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201103347

A Convenient and Practical Synthesis of Anisoles and Deuterated Anisoles by Palladium-Catalyzed Coupling Reactions of Aryl Bromides and Chlorides

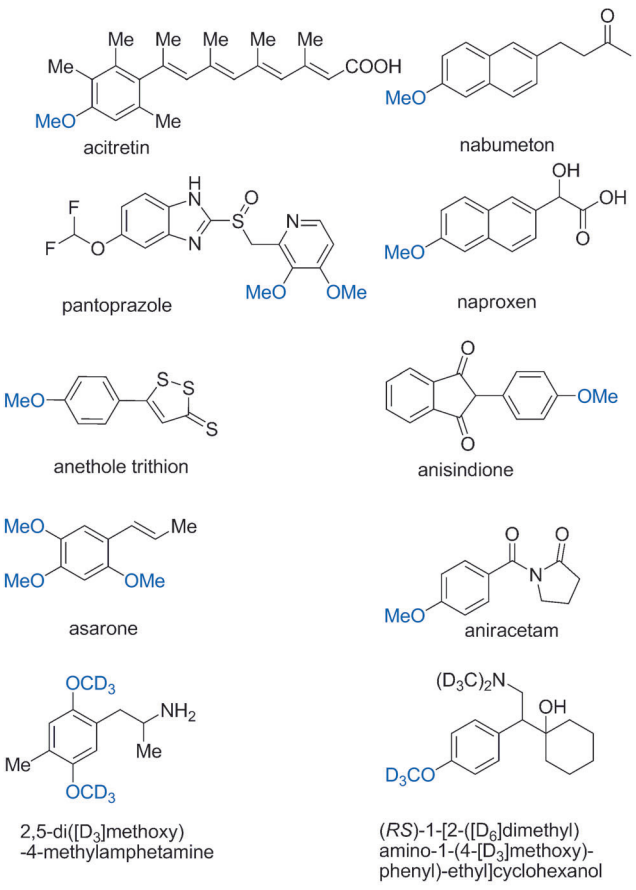
Saravanan Gowrisankar, Helfried Neumann, and Matthias Beller*[a]

Dedicated to Professor Hiriyakkanavar Ila on the occasion of his 68th birthday

In recent years, palladium- and copper-catalyzed cross-coupling reactions have become useful tools for the synthesis of (hetero)aryl ethers.[1–3] Due to the presence of aromatic ether bonds in numerous natural products, pharmaceuticals, fragrances, cosmetics, and polymers,[4] further developments of efficient C–O bond-forming reactions are of continuing interest for organic chemistry. In particular, methyl (hetero)aryl ethers (anisoles) represent an important structural motif present in numerous biologically active compounds, such as acitretin, anisindione, pantoprazole, 2,5-di([D_3]methoxy)-4-methylamphetamine, aniracetam, asarone, anethole trithion, nabumeton, and naproxen (Scheme 1).

Unfortunately, the straightforward substitution of aryl halides by methanol proceeds only with strongly electron-poor aryl halides (chlorides and fluorides) under strong basic conditions through a nucleophilic S_NAr mechanism. Thus, in general, the classical Williamson ether synthesis is still the method of choice for the preparation of methyl (hetero)aryl ethers.[5] However, this method is limited because of the drastic conditions (high temperature), the low functional group tolerance, and the necessity to use toxic methylation agents, such as methyl iodide. More benign alkylations with methanol have been reported only at high temperature, which also leads to C-alkylations as side reactions.[6]

Although palladium-catalyzed coupling reactions of aryl halides with phenols and tertiary alcohols are well developed, the apparently simple coupling reaction with methanol has been scarcely explored, because of the competing β-hydride elimination. So far, only two palladium catalyst systems have been reported for this transformation; however, they have not been shown to function in a general manner (Scheme 2). More specifically, Buchwald demonstrated solely the synthesis of 3-nitroanisole by using ligand **L1**.[7] Clarke and co-workers used a palladium catalyst and ligand **L2** for the methoxylation of aryl halides with vinyl trimethoxysilane and sodium hydroxide as activator to give anisoles in moderate yields.[8] However, this reaction was limited to substrates with electron-withdrawing substituents in the *para*-position. In this context, a related approach from Kwong and co-workers should also be noted. They elegantly described the synthesis of substituted anisoles from aryl halides by palladium-catalyzed hydroxylation followed by the addition of methyl iodide in a one-pot reaction.[9] In summary, no general methodology is available for the simple cross-coupling reaction of aryl halides with methanol to date.

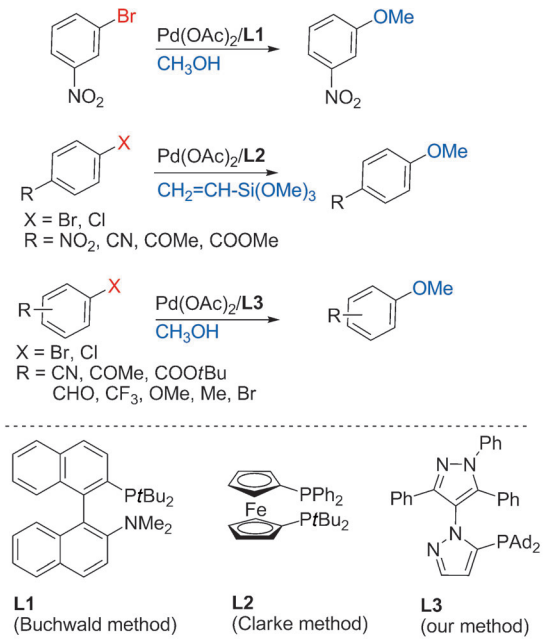


Scheme 1. Selected examples of biologically active anisole derivatives.

Based on our work on the development of novel palladium catalysts and ligands for cross-coupling reactions,[10] we

[a] Dr. S. Gowrisankar, 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

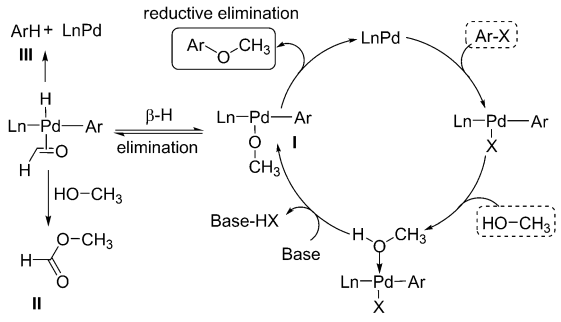
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103347.



Scheme 2. Palladium-catalyzed synthesis of anisoles from aryl halides.

recently became interested in more challenging C–O bond formations by using hydroxide[11] or primary aliphatic alcohols.[12] During these studies, we observed that the combination of palladium acetate and the adamantyl (Ad)-substituted Bipyphos derivative[13] **L3** catalyzes the coupling of a wide range of alcohols with aryl halides and heteroaryl halides. Although reactions of 1-butanol, 1-hexanol, 1-octanol, 1-hexadecanol, and benzyl alcohol occurred with a variety of aryl halides, the related cross coupling of methanol with aryl halides was still problematic under the described conditions due to β-hydride elimination of the intermediate Ar–Pd–OCH_3 complex **I**.

As shown in Scheme 3, the chemoselectivity of the overall process depends strongly on the relative rates of C–O bond-forming reductive elimination and unwanted β-hydride elimination. In most palladium(II)alkoxy complexes, β-hydride elimination proceeds faster than reductive elimination.[14] Hence, methoxides are known to be efficient hydride

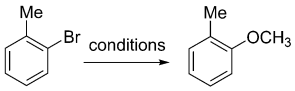


Scheme 3. Coupling reaction of methanol with aryl halides: product formation and side reactions.

donors for the reduction of aryl halides. To overcome this problem, bulky phosphine ligands[15] could be used to facilitate C–O coupling reactions by promoting reductive elimination.

Here, we describe the first general procedure for the palladium-catalyzed arylation of methanol. The key to success is the use of our di-Ad-substituted Bipyphos ligand **L3** under carefully optimized conditions. At the start of our work, we investigated the reaction of 2-bromotoluene with MeONa as a model reaction. All catalytic test reactions were carried out with 1 mol% $Pd(OAc)_2$ and 2 mol% Bipyphos-Ad. Unfortunately, under the previously described conditions,[12] no desired product was formed. Instead, we observed reductive dehalogenation, which gave toluene **III**. In addition, the formation of methyl formate **IV** is somewhat surprising, but can be explained by dehydrogenation of the intermediate 1-methoxymethan-1-ol (Scheme 3). Notably, in this case the aryl halide acts as a stoichiometric oxidant. Next, we studied the effect of different methoxylation reagents, such as MeOH, $(MeO)_2CO$, $(MeO)_4Si$, $(MeO)_3SiH$, and $(MeO)_3Si–CH=CH_2$ (Table 1). To our delight, the coupling process proceeded efficiently in 82% yield within 5 h at 80°C in the presence of methanol and cesium carbonate (Table 1, entry 1).

Table 1. Pd-catalyzed coupling reactions of 2-bromotoluene with different methoxy sources.



Entry	Methoxylation Reagent[a]	Base	Conversion [%]	Yield [%]
1	MeONa (2 equiv)	–	45	<1
2	MeOH/toluene (1:1)	Cs_2CO_3	100	82
3	$(MeO)_4Si$ (2 equiv)	Cs_2CO_3	61	43
4	$(MeO)_3SiH$ (2 equiv)	Cs_2CO_3	62	<1
5	$(MeO)_3Si–CH=CH_2$ (2 equiv)	NaOH[b]	21	<1

Reaction conditions: [a] $Pd(OAc)_2$ (1 mol%), **L3** (2 mol%), aryl halide (1.0 mmol), Cs_2CO_3 (1.5 equiv), toluene (2 mL), 80°C, 12 h. [b] 2.0 equiv.

Next, we investigated the influence of critical reaction parameters (palladium source and base) on the palladium-catalyzed coupling of 2-bromotoluene with methanol in the presence of **L3**. Notably, the chosen palladium precatalyst has a major impact on the performance of the model reaction. Apart from palladium(II) acetate, $[Pd_2(dba)_3]$ and $[Pd(PhCN)_2Cl_2]$ can be used most effectively (dba = dibenzylideneacetone). Variation of the solvent (arenes, amines, neat alcohol) confirmed that toluene was optimal for this reaction. In comparison with K_2CO_3, K_3PO_4, $NaHCO_3$, and NaOAc, Cs_2CO_3 worked best for this methoxylation. Although the reaction proceeded sluggishly at 65°C, it was completed within 6 h at 80°C in toluene (Table 2).

With the optimized conditions in hand, we examined the reaction of activated, nonactivated, and hindered aryl halides with methanol. Substituents on the (hetero)aryl bro-

Table 2. Pd-catalyzed coupling reaction of 2-bromotoluene with methanol.[a]

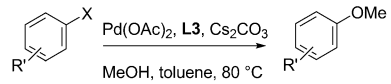
Entry	Palladium/Base	Conversion [%]	Yield [%]
1	$Pd(OAc)_2/Cs_2CO_3$	100	82
2	$[Pd(CF_3COO)_2]/Cs_2CO_3$	100	48
3	$[Pd(PhCN)_2Cl_2]/Cs_2CO_3$	100	54
4	$[Pd(PPh_3)_2Cl_2]/Cs_2CO_3$	100	46
5	$[Pd_2(dba)_3]/Cs_2CO_3$	100	73
6	$Pd(OAc)_2/K_2CO_3$	100	10
7	$Pd(OAc)_2$/NaOAc	28	<1
8	$Pd(OAc)_2/K_3PO_4$	99	24
9	$Pd(OAc)_2/NaHCO_3$	31	<1

[a] Reaction conditions: palladium (1 mol%), **L3** (2 mol%), 2-bromotoluene (1.0 mmol), base (1.5 equiv), toluene (2 mL), 80 °C, 12 h.

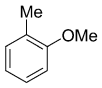
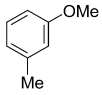
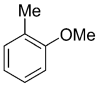
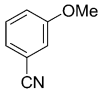
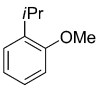
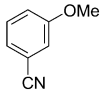
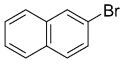
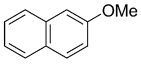
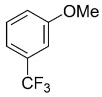
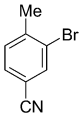
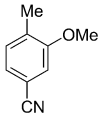
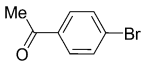
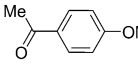
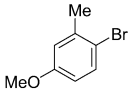
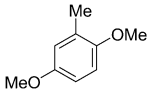
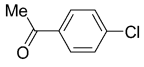
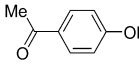
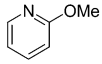
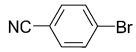
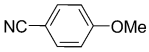
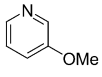
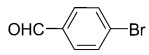
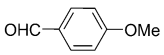
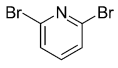
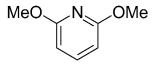
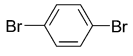
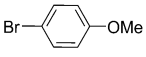
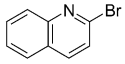
mides (chlorides) included electron-withdrawing and electron-donating groups. As shown in Table 3, methanol reacted smoothly with different alkyl-substituted bromo- and chloroarenes to give the corresponding anisoles in good yields (Table 3, entries 1–5, 11 and 12). Compared with the reaction of 2-bromotoluene, the yield in the case of the corresponding chloroarene was only slightly lower demonstrating that oxidative addition of palladium(0) to C–X is not crucial. In addition, our conditions worked well for aryl bromides and chlorides with electron-withdrawing substituents in the *para*-position (Table 3, entries 6–11). The coupling of *meta*-substituted aryl halides, the reactions of which are not facilitated by the increased rate of reductive elimination, took place in 54–85% yields (Table 3, entries 12–16). A somewhat lower yield of the desired product was obtained for 4-methoxy-2-bromotoluene with an electron-donating group at the *para*-position (Table 3, entry 17).

Finally, we were interested in the performance of our catalytic system with heteroaryl halides. Here, we were pleased to find that 2- and 3-bromopyridine, 2-chloropyridine, 2-

Table 3. Pd-catalyzed coupling reactions of (hetero)aryl halides with methanol.[a,c]



(X = Br, Cl)

Entry	Substrate	Product	Yield [%]	Entry	Substrate	Product	Yield [%]
1			82[d]	12			65[d]
2			73[d]	13			60
3			65	14			54
4			67	15			85
5			79	16			78
6			88	17			58
7			80	18			82
8			81	19			78
9			63	20			77[b]
10			51	21			89
11			68[d]	22			62

[a] Reaction conditions: $Pd(OAc)_2$ (1 mol%), **L3** (2 mol%), aryl halide (1.0 mmol), Cs_2CO_3 (1.5 equiv), methanol/toluene (1:1), 80 °C, overnight. [b] $Pd(OAc)_2$ (2 mol%), **L3** (4 mol%). [c] Isolated yield. [d] GC yield.

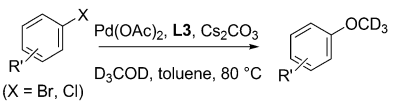
and 3-bromoquinoline are readily converted with methanol into the corresponding ether products in moderate to good yields (Table 3, entries 18–22).

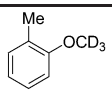
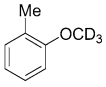
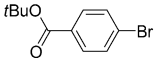
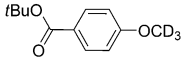
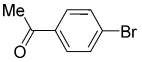
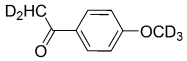
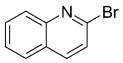
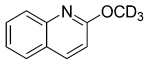
For the development of new pharmaceuticals, the use of deuterated compounds becomes increasingly interesting.[16] For example, deuterated derivatives are necessary for metabolite studies and novel bioactive compounds can be synthesized by the exchange of C–H for C–D bonds. This latter strategy aims to take advantage of the increased stability of C–D bonds. If a particular C–H bond in a drug molecule is known to be readily broken during metabolism, exchanging that hydrogen for a heavier deuterium atom can in some instances slow down the unwanted metabolic process. Obviously, our palladium-catalyzed methoxylation reaction is ideally suited to prepare deuterated analogues of anisoles simply by using inexpensive CD_3OD. To the best of our knowledge, such reactions have not been performed before.

As expected, the catalytic methoxylation with CD_3OD proceeded smoothly. Thus, coupling reactions with *tert*-butyl 4-bromobenzoate, 1-(4-bromophenyl)ethanone, 2-chlorotoluene, and 2-bromoquinoline readily produce the corresponding deuterated products in moderate to good yields (Table 4, entries 1–5). Notably, in the case of 4-bromoacetophone, deuteration was also observed at the α position of the carbonyl group. This observation is in agreement with reported results by Hashimoto and co-workers (Table 4, entry 4).[17]

In conclusion, we have described the first general protocol for palladium-catalyzed coupling reactions of aryl halides with methanol. A variety of substituted anisoles have been prepared in moderate to good yields from activated and nonactivated (hetero)aryl substrates. Key to the success is the use of methanol in the presence of cesium carbonate and the air-stable bispyrazolylphosphine ligand **L3**. Furthermore, we have demonstrated for the first time the use of inexpensive CD_3OD for the preparation of labeled (hetero)aryl alkyl ethers.

Table 4. Pd-catalyzed coupling reactions of aryl halides with deuterated methanol.[a,b]



Entry	Substrate	Product	Yield [%]
1			74
2			60
3			76
4			80
5			87

[a] Reaction conditions: $Pd(OAc)_2$ (1 mol%), **L3** (2 mol%), aryl halide (1.0 mmol), Cs_2CO_3 (1.5 equiv), [D_4]MeOH/toluene (1:1), 80 °C, overnight. [b] Isolated yield.

Experimental Section

General procedure for intermolecular coupling: An oven-dried pressure tube (10 mL) was charged with $Pd(OAc)_2$ (5 mg, 0.023 mmol, 1 mol%), ligand **L3** (31 mg, 0.047 mmol, 2 mol%), and Cs_2CO_3 (1143 mg, 3.50 mmol, 1.5 equiv). Toluene (2 mL), aryl halide (2.34 mmol), and methanol (2 mL) were added. The reaction mixture was stirred at 80 °C overnight, then cooled to RT, diluted with EtOAc (5 mL), filtered through a pad of Celite, and concentrated. The crude product was purified by flash chromatography.

Acknowledgements

This work has been funded by the State of Mecklenburg-Western Pomerania, the BMBF, and the DFG (Leibniz Prize). We thank Drs. W. Baumann, C. Fischer, and Mrs. S. Buchholz (all LIKAT) for their support. We thank Mr. Stephan Neumann for excellent technical assistance.

Keywords: anisole · cross-coupling · deuterium · palladium · synthetic methods

[1] For selected reviews on C–O bond formation, see: a) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805–818; b) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154–2177; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; c) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125–146; d) D. Prim, J.-M. Campagne, D. Joseph, B. Andrioletti, *Tetrahedron* **2002**, *58*, 2041–2075; e) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; f) R. B. Bedford, C. S. J. Cazin, D. Holder, *Coord. Chem. Rev.* **2004**, *248*, 2283–2321; g) A. R. Muci, S. L. Buchwald in *Cross-Coupling Reactions: A Practical Guide (Topics in Current Chemistry), Vol. 219: Practical Palladium Catalysts for C–N and C–O Bond Formation* (Ed.: N. Miyaura), Springer, Berlin, **2001**, pp. 131–209; h) J. F. Hartwig in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Eds.: E.-i. Negishi, A. de Meijere), Wiley-Interscience, New York, **2002**, pp. 1051; i) A. W. Czarnik, *Acc. Chem. Res.* **1996**, *29*, 112–113; j) F. Theil, *Angew. Chem.* **1999**, *111*, 2493–2495; *Angew. Chem. Int. Ed.* **1999**, *38*, 2345–2347; k) J. Scott Sawyer, *Tetrahedron* **2000**, *56*, 5045–5065; l) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558–5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; m) P. Cristau, J.-P. Vors, J. Zhu, *Tetrahedron* **2003**, *59*, 7859–7870; n) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131–209; o) S. Enthaler, A. Company, *Chem. Soc. Rev.* **2011**, *40*, 4912–4924.

[2] For selected palladium-catalyzed C–O bond formation, see: a) M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334; b) G. Mann, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110; c) M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 3395–3396; d) M. Watanabe, M. Nishiyama, Y. Koie, *Tetrahedron Lett.* **1999**, *40*, 8837–8840; e) Q. Shelby, N. Kataoka, G. Mann, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719; f) K. E. Torraca, S. Kuwabe, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12907–12908; g) C. A. Parrish, S. L. Buchwald, *J. Org. Chem.* **2001**, *66*, 2498–2500; h) N. Kataoka, Q. Shelby, J. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553–5566; i) A. R. Mucci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 133–209; j) S. Harkal, K. Kumar, D. Michalik, A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, M. Beller, *Tetrahedron Lett.* **2005**, *46*, 3237–3240; k) C. H. Burgos, T. E. Barder, X. Haung, S. L. Buch-

wald, *Angew. Chem.* **2006**, *118*, 4427–4432; *Angew. Chem. Int. Ed.* **2006**, *45*, 4321–4326; l) X. Wu, B. P. Fors, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 10117–10121; *Angew. Chem. Int. Ed.* **2011**, *50*, 9943–9947.

[3] For selected Cu-catalyzed C–O bond formation, see: a) J. F. Marcoux, S. Doye, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540; b) D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937–2940; c) P. J. Fagan, E. Hauptman, R. Shapiro, A. Casalnuovo, *J. Am. Chem. Soc.* **2000**, *122*, 5043–5051; d) R. K. Gujadhur, C. G. Bates, D. Venkataraman, *Org. Lett.* **2001**, *3*, 4315–4317; e) R. K. Gujadhur, D. Venkataraman, *Synth. Commun.* **2001**, *31*, 2865–2879; f) M. Wolter, G. Nordmann, G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 973–976; g) E. Buck, Z. J. Song, D. Tschaen, P. G. Dormer, R. P. Volante, P. J. Reider, *Org. Lett.* **2002**, *4*, 1623–1626; h) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428–2439; i) D. Ma, Q. Cai, *Org. Lett.* **2003**, *5*, 3799–3802; j) A. B. Naidu, E. A. Jaseer, G. Sekar, *J. Org. Chem.* **2009**, *74*, 3675–3679; k) H. J. A. Cristau, P. C. Pascal, S. Hamada, J. S. Francis, M. Taillefer, *Org. Lett.* **2004**, *6*, 913–916; l) R. Hosseinzadeh, M. Tajbakhsh, M. Mohadjerani, M. Alikarami, *Synlett* **2005**, 1101–1104; m) R. Frlan, D. Kikelj, *Synthesis* **2006**, *14*, 2271–2285; n) Y. J. Chen, H. H. Chen, *Org. Lett.* **2006**, *8*, 5609–5612; o) H. Zhang, D. Ma, W. Cao, *Synlett* **2007**, 0243–0246; p) Y. Zhao, Y. Wang, H. Sun, L. Li, H. Zhang, *Chem. Commun.* **2007**, 3186–3188; q) T. Miao, L. Wang, *Tetrahedron Lett.* **2007**, *48*, 95–99; r) X. Lv, W. Bao, *J. Org. Chem.* **2007**, *72*, 3863–3867; s) J. Niu, H. Zhou, Z. Li, J. Xu, S. Hu, *J. Org. Chem.* **2008**, *73*, 7814–7817; t) R. A. Altman, A. Shafir, A. Choi, P. A. Lichtor, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 284–286; u) A. B. Naidu, G. A. Sekar, *Tetrahedron Lett.* **2008**, *49*, 3147–3151; v) S. Jammi, S. Sakthivel, L. Rout, T. Mukherjee, S. Mandal, R. Mitra, P. Saha, T. Punniyamurty, *J. Org. Chem.* **2009**, *74*, 1971–1976; w) J. Niu, P. Guo, J. Kang, Z. Li, J. Xu, S. Hu, *J. Org. Chem.* **2009**, *74*, 5075–5078.

[4] For selected examples, see: a) E. J. Corey, G. A. Reichard, *Tetrahedron Lett.* **1989**, *30*, 5207–5210; b) J. Deeter, J. Frazier, G. Staten, M. Staszak, L. Weigel, *Tetrahedron Lett.* **1990**, *31*, 7101–7104; c) C. K.-F. Chiuy in *Comprehensive Organic Functional Group Transformations, Vol. 2* (Eds.: A. R. Katrizky, O. Meth-Cohn, C. W. Rees), Pergamon Press, New York, **1995**; d) J. Zhu, *Synlett* **1997**, 133–144; e) D. Barton, *Comprehensive Natural Products Chemistry, Vol. 1, 3, and 8* (Eds.: O. Meth-Cohn, D. Barton), Elsevier Science Oxford, **1999**; f) T.-X. Métro, D. G. Pardo, J. Cossy, *J. Org. Chem.* **2008**, *73*, 707–710.

[5] a) Ullmann, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853–857; b) J. Lindley, *Tetrahedron* **1984**, *40*, 1433–1456F; c) G. Chauvière, C. Viodé, J. Périé, *J. Heterocycl. Chem.* **2000**, *37*, 119–126; d) J. Zilberman, *Org. Process Res. Dev.* **2003**, *7*, 303–305; e) E. Fuhrmann, J. Talbiersky, *Org. Process Res. Dev.* **2005**, *9*, 206–211.

[6] a) S. Lee, S. W. Lee, K. S. Kim, J. J. Lee, D. Hyun, J. C. Kim, *Catal. Today* **1998**, *44*, 253–258; b) G. N. Kirichenko, V. I. Glazunova, A. V. Balaev, U. M. Dzhemilev, *Pet. Chem.* **2008**, *48*, 389–392.

[7] K. E. Torraca, X. Huang, C. A. Parrish, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771.

[8] E. J. Milton, J. A. Fuentes, M. L. Clarke, *Org. Biomol. Chem.* **2009**, *7*, 2645–2648.

[9] G. Chen, A. S. C. Chan, F. Y. Kwong, *Tetrahedron Lett.* **2007**, *48*, 473–476.

[10] a) F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen, M. Beller, *Chem. Eur. J.* **2004**, *10*, 2983–2990; b) A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431–440; c) S. Harkal, F. Rataboul, A. Zapf, C. Fuhrmann, T. Riermeier, A. Monsees, M. Beller, *Adv. Synth. Catal.* **2004**, *346*, 1742–1748; d) N. Schwarz, A. Tillack, K. Alex, I. A. Sayyed, R. Jackstell, M. Beller, *Tetrahedron Lett.* **2007**, *48*, 2897–2900; e) C. Torborg, A. Zapf, M. Beller, *ChemSusChem* **2008**, *1*, 91–96; f) A. Zapf, A. Ehrentraut, M. Beller, *Angew. Chem.* **2000**, *112*, 4315–4317; *Angew. Chem. Int. Ed.* **2000**, *39*, 4153–4155; g) S. Klaus, H. Neumann, A. Zapf, D. Strübing, S. Hübner, J. Almena, T. Riermeier, P. Groß, M. Sarich, W.-R. Krahnert, K. Rossen, M. Beller, *Angew. Chem.* **2006**, *118*, 161–165; *Angew. Chem. Int. Ed.* **2006**, *45*, 154–156; h) A. Ehrentraut, A. Zapf, M. Beller, *J. Mol. Catal.* **2002**, *182–183*, 515–523; i) A. Ehrentraut, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 209–217; j) A. Tewari, M. Hein, A. Zapf, M. Beller, *Synthesis* **2004**, *6*, 935–941; k) H. Neumann, A. Brennführer, P. Groß, T. Riermeier, J. Almena, M. Beller, *Adv. Synth. Catal.* **2006**, *348*, 1255–1261; l) A. Brennführer, H. Neumann, S. Klaus, P. Groß, T. Riermeier, J. Almena, M. Beller, *Tetrahedron* **2007**, *63*, 6252–6258; m) A. Brennführer, H. Neumann, M. Beller, *Synlett* **2007**, 2537–2540; n) T. Schareina, A. Zapf, W. Mägerlein, N. Müller, M. Beller, *Tetrahedron Lett.* **2007**, *48*, 1087–1090; o) H. Neumann, A. Brennführer, M. Beller, *Chem. Eur. J.* **2008**, *14*, 3645–3652; p) H. Neumann, A. Brennführer, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2437–2442; q) H. Neumann, A. Sergeev, M. Beller, *Angew. Chem.* **2008**, *120*, 4965–4969; *Angew. Chem. Int. Ed.* **2008**, *47*, 4887–4891.

[11] a) 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; b) T. Schulz, C. Torborg, B. Schäffner, J. Huang, A. Zapf, R. Kadyrov, A. Börner, M. Beller, *Angew. Chem.* **2009**, *121*, 936–939; *Angew. Chem. Int. Ed.* **2009**, *48*, 918–921; c) A. Dumrath, X.-F. Wu, H. Neumann, A. Spannenberg, R. Jackstell, M. Beller, *Angew. Chem.* **2010**, *122*, 9172–9176; *Angew. Chem. Int. Ed.* **2010**, *49*, 8988–8992.

[12] a) S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 11592–11598; b) S. Gowrisankar, H. Neumann, M. Beller, *ChemCatChem* **2011**, *3*, 1439–1441.

[13] The so-called Bipyphos ligand [(5-(di-*tert*-butylphosphino)-1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1H-pyrazole)] was developed by Singer and co-workers for palladium-catalyzed C–O bond formation. It was also used successfully for methoxylation of 2- and 3-bromopyridine, 2,6-dibromopyridine, and 2-bromotoluene. However, no isolated anisole products were reported. For the ligand synthesis and application, see: G. J. Withbroe, R. A. Singer, J. E. Sieser, *Org. Process Res. Dev.* **2008**, *12*, 480–489.

[14] For mechanistic studies on C–O bond-forming reactions, see: a) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852–860; b) J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575–5580; c) G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225; d) J. P. Stambuli, R. Kuwano, J. F. Hartwig, *Angew. Chem.* **2002**, *114*, 4940–4942; *Angew. Chem. Int. Ed.* **2002**, *41*, 4746–4748; e) G. Mann, Q. Shelby, A. H. Roy, J. F. Hartwig, *Organometallics* **2003**, *22*, 2775–2789; f) J. M. Brunel, *Mini-Rev. Org. Chem.* **2004**, *1*, 249–277; g) J. P. Stambuli, Z. Weng, C. D. Incarvito, J. F. Hartwig, *Angew. Chem.* **2007**, *119*, 7818–7821; *Angew. Chem. Int. Ed.* **2007**, *46*, 7674–7677; h) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438–6461; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361; i) F. Barrios-Landeros, B. P. Carrow, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 8141–8154; j) L. M. Huffman, A. Casitas, M. Font, M. Canta, M. Costas, X. Ribas, S. S. Stahl, *Chem. Eur. J.* **2011**, *17*, 10643–10650.

[15] For reviews with bulky phosphine ligands, see: a) A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350–4386; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211; b) B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599–1626; c) G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555–1564; d) C. M. So, F. Y. Kwong, *Chem. Soc. Rev.* **2011**, *40*, 4963–4972; e) R. J. Lundgren, K. D. Hesp, M. Stradiotto, *Synlett* **2011**, 2443–2458.

[16] For comprehensive reviews, see: a) T. Junk, W. J. Catallo, *Chem. Soc. Rev.* **1997**, *26*, 401–406; b) J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *Angew. Chem.* **2007**, *119*, 7890–7911; *Angew. Chem. Int. Ed.* **2007**, *46*, 7744–7765.

[17] Y. Murai, M. Takahashi, Y. Muto, Y. Hatanaka, M. Hashimoto, *Heterocycles* **2010**, *82*, 909–915.

Received: October 24, 2011
Published online: February 1, 2012

