DOI: 10.1002/chem.201103797

A General and Efficient Palladium-Catalyzed Alkoxycarbonylation of Phenols To Form Esters through In Situ Formed Aryl Nonaflates

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Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday

The synthesis of carboxylic acid esters has attracted the interest of organic chemists for more than 100 years. The most common strategy for their preparation involves the stoichiometric activation of the parent acid to form a more reactive acyl halide, anhydride, or activated ester that is amenable to subsequent nucleophilic substitution.[1] An interesting and complementary transformation is the palladium-catalyzed carbonylation of aryl halides, which makes use of CO as an inexpensive and easily available C1 source.[2,3] Originally, these carbonylation reactions were established in the mid 1970s by the pioneering work of Heck and co-workers.[4] Since that time, palladium-catalyzed carbonylations of haloarenes have found numerous applications in organic synthesis, and even in related industrial processes that have been realized on a >1000 ton scale, such as the alkoxycarbonylation of a benzylic alcohol in the synthesis of ibuprofen.[5]

For more than a decade, our group has been interested in the advancement of the palladium-catalyzed carbonylation of aryl halides.[6] Recent examples include the development of carbonylative activation of C–H bonds in heteroarenes to form ketones,[6c] the aminocarbonylation with ammonia to give primary amides,[6j,k] and the carbonylative vinylation to to give alkenones.[6b,h] Based on this work, we became interested in the carbonylation of activated phenols. In addition to aryl halides, phenols are frequently found in pharmaceuticals, agrochemicals, polymers, and natural products.[7] Gratifyingly, phenols can be easily transformed into aryl sulfonates, which offer a highly reactive leaving group.[8] Consequently, they have been used as versatile intermediates in modern organic synthesis, particularly in the preparation of biologically active compounds.

Among the different classes of aryl sulfonate, aryl nonaflates offer interesting properties. On the one hand, they are more stable than the corresponding triflates; on the other, they are more reactive than the corresponding mesylates or toyslates.[9,10] Moreover, $C_4F_9SO_2F$, which is used as the main reagent for aryl nonaflate synthesis, is relatively inexpensive, stable in air, not sensitive to moisture, and can be stored at room temperature.[11] As a consequence of these interesting properties of aryl nonaflates, we report here a general protocol for the palladium-catalyzed alkoxycarbonylation of in situ formed aryl nonaflates with phenols and aliphatic alcohols. Additionally, this approach is also applied for homoesterification, yielding esters with identical residues.

At the start of our investigation, the carbonylation of phenol was studied as a model system in the presence of $[\{Pd(cinnamyl)Cl\}_2]$ and different ligands at 100 °C and under an atmosphere of CO (5 bar). Activation of the substrate occurred by adding 0.5 equivalents of $C_4F_9SO_2F$ (with respect to phenol) in toluene.

As shown in Table 1, the use of monodentate ligands, such as PPh_3, PCy_3, and P(*o*-tolyl)$_3$, gave only low yields, or none at all, of the desired phenyl benzoate (Table 1, entries 1–3). To our delight, the application of bidentate phosphine ligands provided moderate to good yields of the desired product (Table 1, entries 4–12). Interestingly, bidentate ligands with larger bite angles gave improved product yields, whereas the more electron-donating ligands resulted in lower yields of the ester (Table 1, entries 9 and 10). Decreasing the catalyst loading to 0.5 mol% of the palladium complex still led to a 73% yield of phenyl benzoate (Table 1, entry 13). However, a further decrease of the catalyst concentration to 0.25 mol% Pd provided only 51% of the desired product. Notably, a good yield of phenyl benzoate was achieved even at either 1 bar CO or 80 °C (Table 1, entries 15 and 16).

Based on our experimental data and former mechanistic studies of palladium-catalyzed carbonylations of aryl halides,[12] the reaction mechanism for this homoesterification is proposed in Scheme 1. After in situ generation of the phenyl nonaflate, oxidative addition to the $[Pd^0L_n]$ species occurred. After coordination and insertion of CO, the terminal ester is formed by nucleophilic attack of phenol (R = Ph). Under the assistance of base, the active Pd^0 catalyst is regenerated and the catalytic cycle may start again. Nevertheless, the reaction of a cationic benzoylpalladium(II) species with phenol and NEt_3 to form benzoylpalladium(II)

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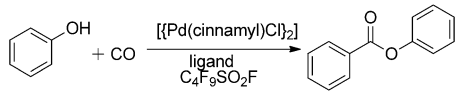
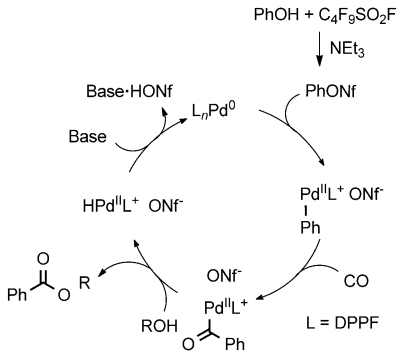
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103797.

Table 1. Palladium-catalyzed alkoxycarbonylation of in situ formed phenyl nonaflate.[a]



Entry	Ligand ([mol%])	CO [bar]	T [°C]	Yield [%][b]
1	PPh_3 (4)	5	100	18
2	PCy_3 (4)	5	100	0
3	P(*o*-tolyl)$_3$ (4)	5	100	0
4	DPPE (2)	5	100	62
5	DPPP (2)	5	100	78
6	DPPB (2)	5	100	80
7	DPEphos (2)	5	100	78
8	Xantphos (2)	5	100	81
9	DPPF (2)	5	100	83
10	D*t*BPF (2)	5	100	63
11	DIOP (2)	5	100	60
12	BINAP (2)	5	100	83
13	DPPF (1)	5	100	73[c]
14	DPPF (0.5)	5	100	51[d]
15	DPPF (2)	1	100	80
16	DPPF (2)	5	80	79

[a] [{Pd(cinnamyl)Cl}$_2$] (1 mol%, 0.01 mmol), ligand, toluene (2 mL), phenol (2 mmol), $C_4F_9SO_2F$ (1 mmol), NEt_3 (2 mmol), CO, 16 h; Cy = cyclohexyl, DPPE = 1,2-bis(diphenylphosphino)ethane, DPPP = 1,3-bis(diphenylphosphino)propane, DPPB = 1,4-bis(diphenylphosphino)butane, DPEphos = bis(2-diphenylphosphinophenyl)ether, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, DPPF = 1,1′-bis(diphenylphosphino)ferrocene, D*t*BPF = 1,1′-bis(di-*tert*-butylphosphino)ferrocene, DIOP = (+)-2,3-*ortho*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, BINAP = (*R*)-(+)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine). [b] Yields were determined by GC using hexadecane as the internal standard and based on 1 mmol of phenol. [c] [{Pd(cinnamyl)Cl}$_2$] (0.5 mol%, 0.005 mmol). [d] [{Pd(cinnamyl)Cl}$_2$] (0.25 mol%, 0.0025 mmol).

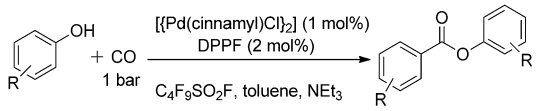


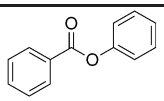
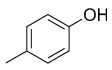
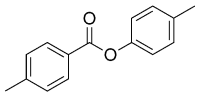
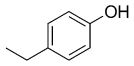
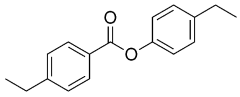
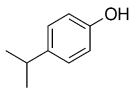
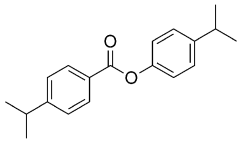
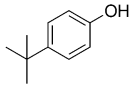
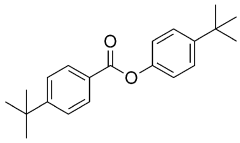
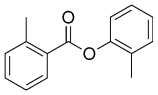
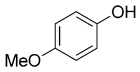
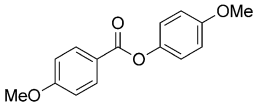
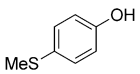
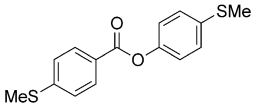
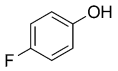
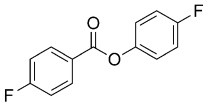
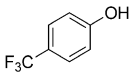
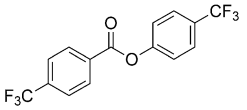
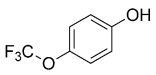
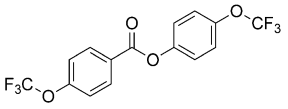
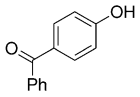
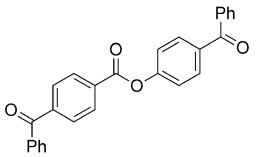
Scheme 1. Proposed reaction mechanism.

phenoxide as a stable intermediate (and $Et_3NH^+NfO^-$) cannot be ruled out. In the latter case, final reductive elimination would give the ester and regenerate the active Pd^0 species.

Having suitable reaction conditions in hand, we decided to test the generality of our protocol by using 1 mol% of the palladium complex under 1 bar of CO at 100 °C. The homoesterification of various phenols is shown in Table 2. The corresponding esters were isolated in good to excellent yields for reactions of electron-rich phenols (Table 2, entries 2–8). Methoxy- and methylthio-substituents were toler-

Table 2. Palladium-catalyzed alkoxycarbonylation of in situ formed aryl nonaflates: Homoesterification reactions.[a]



Entry	Phenol	Ester	Yield [%][b]
1			80
2			92
3			88
4			90
5			93
6			76
7			89
8			80
9			63
10			60
11			72
12			85

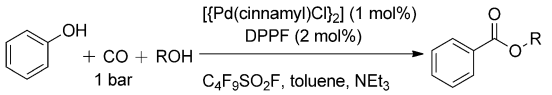
[a] [{Pd(cinnamyl)Cl}$_2$] (1 mol%, 0.01 mmol), DPPF (2 mol%, 0.02 mmol), toluene (2 mL), phenol (2 mmol), $C_4F_9SO_2F$ (1 mmol), NEt_3 (2 mmol), CO (1 bar), 100 °C, 16 h. [b] Isolated yields.

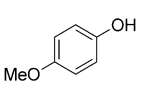
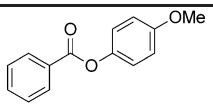
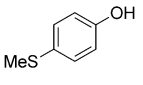
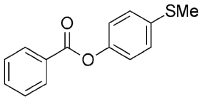
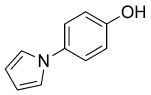
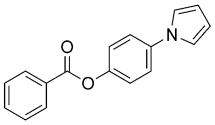
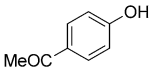
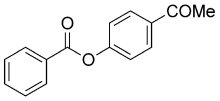
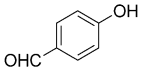
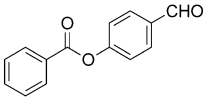
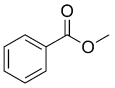
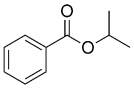
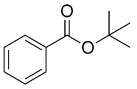
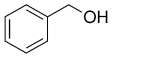
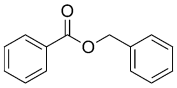
ated under our conditions and gave good yields of the respective esters. As well as electron-rich phenols, phenols with electron-withdrawing substituents can be applied in this reaction. Hence, fluoro-, trifluoromethyl-, and trifluoromethoxy-substituted phenols were transformed into the desired esters in moderate to good yields (60–72%) by applying this one-pot methodology (Table 2, entries 9–11). Furthermore, a benzoyl-functionalized phenol resulted in an 85% yield of the corresponding ester (Table 2, entry 12). A possible reason for the decreased yields for the homoesterification of electron-poor phenols could be the lower stability of the corresponding aryl nonaflates, which are more prone to non-selective decomposition reactions. It is worth mentioning that we also tested 4-hydroxypyridine as a substrate, but unfortunately no ester product was detected.

Clearly, the cross-coupling of two different phenols or a phenol and an aliphatic alcohol is a more interesting reaction for organic synthesis than these homoesterification reactions. Key to the success of this type of cross-esterification process is the addition of the second alcohol after the initial formation of the aryl nonaflate. In general, adding the second alcohol one hour after mixing the other reagents was sufficient and allowed for the selective activation and coupling reaction (Table 3). Notably, both electron-donating and electron-withdrawing groups were tolerated under our conditions and good yields of the biaryl esters were obtained (Table 3, entries 1–5). As well as different phenols, methanol, 2-propanol, *tert*-butyl alcohol, and benzyl alcohol were coupled successfully under the same conditions and the corresponding benzoates were isolated in 40–82% yields (Table 3, entries 6–9).

In conclusion, a novel methodology for the palladium-catalyzed alkoxycarbonylation of phenols has been developed. Activation of the phenols occurs through the convenient in situ generation of aryl nonaflates. Both electron-donating and electron-withdrawing substituents on the aryl and ester component are tolerated and 21 different esters were isolated in good yields. Notably, not only homoesterification, but also the cross-coupling of two different phenols or cross-coupling of phenol with aliphatic alcohols are possible under these reaction conditions.

Table 3. Palladium-catalyzed alkoxycarbonylation of in situ formed phenyl nonaflate with different alcohols.[a]



Entry	Alcohol	Ester	Yield [%][b]
1			87
2			89
3			75
4			85
5			82
6	methanol		68
7	2-propanol		60
8	*tert*-butyl alcohol		40
9			82

[a] [{Pd(cinnamyl)Cl}$_2$] (1 mol%, 0.01 mmol), DPPF (2 mol%, 0.02 mmol), toluene (2 mL), phenol (1 mmol), $C_4F_9SO_2F$ (1 mmol), NEt_3 (2 mmol), RT, 1 h; then, alcohol (1 mmol), CO (1 bar), 100 °C 16 h. [b] Isolated yields.

Experimental Section

Typical reaction procedure for the carbonylation reaction of in situ formed phenyl nonaflate with phenol: [{Pd(cinnamyl)Cl}$_2$] (1 mol%, 0.01 mmol), DPPF (2 mol%), and phenol (2 mmol) were transferred into a vial (4 mL reaction volume) equipped with a septum, a small cannula, and a stirring bar. After the vial was purged with argon, toluene (distilled from sodium ketyl, 2 mL), $C_4F_9SO_2F$ (1 mmol), and NEt_3 (2 mmol) were injected into the vial by syringe. The vial was then placed in an alloy plate, which was transferred into a 300 mL autoclave (4560 series from Parr Instruments), under an argon atmosphere. After flushing the autoclave three times with CO, the pressure was adjusted to 1 bar and the reaction was performed for 16 h at 100 °C. After the reaction, the autoclave was cooled to room temperature and the pressure was carefully released. Water (6 mL) was added to the reaction mixture and the solution was extracted 3–5 times with ethyl acetate (2–3 mL). The combined extracts were evaporated with adsorption on silica gel and the crude product was purified by column chromatography using *n*-heptane and *n*-heptane/AcOEt (18:1) as the eluent.

Typical reaction procedure for the alkoxycarbonylation of in situ formed phenyl nonaflate with other alcohols: [{Pd(cinnamyl)Cl}$_2$] (1 mol%, 0.01 mmol), DPPF (2 mol%), and phenol (1 mmol) were transferred into a vial (4 mL reaction volume) equipped with a septum, a small cannula, and a stirring bar. After the vial was purged with argon, toluene (distilled from sodium ketyl, 2 mL), $C_4F_9SO_2F$ (1 mmol), and NEt_3 (2 mmol) were injected into the vial by syringe. After stirring at room temperature for 1 h, the respective alcohol (1 mmol) was added by syringe. The vial was then placed in an alloy plate, which was transferred into a 300 mL autoclave (4560 series from Parr Instruments), under an argon atmosphere. After flushing the autoclave three times with CO, the pressure was adjusted to 1 bar and the reaction was performed for 16 h at 100 °C. After the reaction, the autoclave was cooled to room temperature and the pressure was carefully released. Water (6 mL) was added to the reaction mixture and the solution was extracted 3–5 times with ethyl acetate (2–3 mL). The combined extracts were evaporated with adsorption on silica gel and the crude product was purified by column chromatography using *n*-heptane and *n*-heptane/AcOEt (18:1) as the eluent.

Acknowledgements

The authors thank the state of Mecklenburg–Vorpommern and the Bundesministerium für Bildung und Forschung (BMBF) for financial support. We also thank Dr. W. Baumann and Dr. C. Fischer (all LIKAT) for analytical support.

Keywords: aryl nonaflate · carbonylation · esters · palladium · phenols

[1] For a list of methods, see: R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, VCH, Weinheim, **1989**, pp. 840–841, and references therein.

[2] For reviews of 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 in *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed. (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **2002**, pp. 145–156; d) R. Skoda-Foldes, L. Kollár, *Curr. Org. Chem.* **2002**, *6*, 1097–1119; e) M. Beller, B. Cornils, C. D. Frohning, C. W. Kohlpaintner, *J. Mol. Catal. A: Chem.* **1995**, *104*, 17–85; f) R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515–5548; g) X. F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986–5009.

[3] For recent examples of palladium-catalyzed alkoxycarbonylations, see: a) T. Schareina, A. Zapf, A. Cotte, M. Gotta, M. Beller, *Adv. Synth. Catal.* **2010**, *352*, 1205–1209; b) G. E. Akpinar, M. Kus, M. U. Cuncu, E. Karakus, L. Artok, *Org. Lett.* **2011**, *13*, 748–751; c) M. A. Mercadante, N. E. Leadbeater, *Org. Biomol. Chem.* **2011**, *9*, 6575–6578; d) D. C. Reeves, S. Rodriquez, H. Lee, N. Haddad, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.* **2011**, *13*, 2495–2497; e) C. B. Kelly, C. Lee, M. A. Mercadante, N. E. Leadbeater, *Org. Process Res. Dev.* **2011**, *15*, 717–720.

[4] a) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3318–3326; b) A. Schoenberg, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3327–3331; c) A. Schoenberg, R. F. Heck, *J. Am. Chem. Soc.* **1974**, *96*, 7761–7764.

[5] a) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027–3043; b) A. Zapf, M. Beller, *Top. Catal.* **2002**, *19*, 101–109.

[6] a) X.-F. Wu, H. Neumann, M. Beller, *Adv. Synth. Catal.* **2011**, *353*, 788–792; b) X.-F. Wu, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 5412–5416; *Angew. Chem. Int. Ed.* **2010**, *49*, 5284–5288; c) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 7474–7477; *Angew. Chem. Int. Ed.* **2010**, *49*, 7316–7319; d) X.-F. Wu, H. Neumann, M. Beller, *ChemCatChem* **2010**, *2*, 509–513; e) X.-F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 12104–12107; f) X.-F. Wu, B. Sundararaju, H. Neumann, P. H. Dixneuf, M. Beller, *Chem. Eur. J.* **2011**, *17*, 106–110; g) X.-F. Wu, H. Neumann, M. Beller, *Tetrahedron Lett.* **2010**, *51*, 6146–6149; h) X.-F. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 14596–14602; i) X.-F. Wu, H. Jiao, H. Neumann, M. Beller, *ChemCatChem* **2011**, *3*, 726–733; j) X. F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 9750–9753; k) X. F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2010**, *5*, 2168–2172; l) X.-F. Wu, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 11142–11146; m) X.-F. Wu, H. Neumann, M. Beller, *Org. Biomol. Chem.* **2011**, *9*, 8003–8005; n) X. F. Wu, J. Schranck, H. Neumann, M. Beller, *Chem. Eur. J.* **2011**, *17*, 12246–12249; o) X. F. Wu, J. Schranck, H. Neumann, M. Beller, *Tetrahedron Lett.* **2011**, *52*, 3702–3704.

[7] a) J. H. P. Tyman, *Synthetic and Natural Phenols*, Elsevier, New York, **1996**; b) *The Chemistry of Phenols* (Ed.: Z. Rappoport), Wiley, New York, **2003**; c) J. F. Hartwig in *Handbook of Organopalladium Chemistry for Organic Synthesis, Vol. 1* (Eds.: E.-I. Negishi), Wiley, New York, **2002**, p. 1097.

[8] For selected recent palladium-catalyzed coupling reactions of aryl sulfonates, see: a) P. Y. Choy, W. K. Chow, C. M. So, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2010**, *16*, 9982–9985; b) C. M. So, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2011**, *17*, 761–765; c) C. M. So, C. P. Lau, A. S. Chan, F. Y. Kwong, *J. Org. Chem.* **2008**, *73*, 7731–7734; d) M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *70*, 9364–9370; e) W. K. Chow, C. M. So, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2011**, *17*, 6913–6917; f) P. Y. Yeung, C. M. So, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2010**, *122*, 9102–9106; *Angew. Chem. Int. Ed.* **2010**, *49*, 8918–8922; for a recent review on the use of mesylates, see: g) C. M. So, F. Y. Kwong, *Chem. Soc. Rev.* **2011**, *40*, 4963–4972.

[9] For an excellent review on the application of nonaflate, see: J. Högermeier, H. U. Reissig, *Adv. Synth. Catal.* **2009**, *351*, 2747–2763.

[10] For recent examples of the use of aryl nonaflates in organic synthesis, see: a) C. Eidamshaus, H. U. Reissig, *Eur. J. Org. Chem.* **2011**, 6056–6069; b) S. Shekhar, T. B. Dunn, B. J. Kotecki, D. K. Montavon, S. C. Cullen, *J. Org. Chem.* **2011**, *76*, 4552–4563; c) E. V. Boltukhina, A. E. Sheshenev, I. M. Lyapkalo, *Tetrahedron* **2011**, *67*, 5382–5388; d) A. Y. Peng, B. T. Chen, Z. Wang, B. Wang, X. B. Mo, Y. Y. Wang, P. J. Chen, *J. Fluorine Chem.* **2011**, *132*, 982–986; e) M. K. Bera, P. Hommes, H. U. Reissig, *Chem. Eur. J.* **2011**, *17*, 11838–11843.

[11] The price of perfluoro-1-butanesulfonyl fluoride was quoted as €78.20 for 25 g (CAS: 375–72–4) in the 2011 Aldrich catalogue.

[12] a) M. A. Carvajal, G. P. Miscione, J. J. Novoa, A. Bottoni, *Organometallics* **2005**, *24*, 2086–2093; b) S. A. Macgregor, G. W. Neave, *Organometallics* **2003**, *22*, 4547–4556; c) A. Bottoni, G. P. Miscione, M. A. Carvajal, J. J. Novoa, *J. Organomet. Chem.* **2006**, *691*, 4498–4507; d) R. J. van Haaren, H. Overing, P. C. J. Kamer, K. Goubitz, J. Fraanje, P. W. N. M. van Leeuwen, G. P. F. van Strijdonck, *J. Organomet. Chem.* **2004**, *689*, 3800–3805.

Received: December 2, 2011
Revised: January 11, 2012
Published online: February 29, 2012

