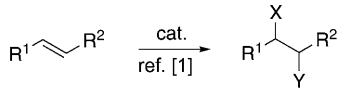
Oxyarylation

DOI: 10.1002/anie.201002214

1,2,3-Trisubstituted Indanes by Highly Diastereoselective Palladium-Catalyzed Oxyarylation of Indenes with Arylboronic Acids and Nitroxides**

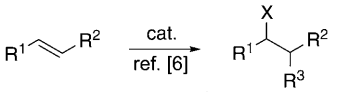
*Sylvia Kirchberg, Roland Fröhlich, and Armido Studer**

Palladium-catalyzed oxidative difunctionalization of olefins is a heavily investigated field of research [Eq. (1)].[1] Dioxygenations,[2] diamidations,[3] and oxyamidations[4] have been realized. However, compared to difunctionalization, in which two heteroatom-containing groups are added to the olefin, and even when considering metals other than palladium, there are only very few reports on intermolecular metal-mediated oxidative carbofunctionalization of olefins [Eq. (2)].[5–7] Herein we present highly stereoselective intermolecular palladium-catalyzed oxyarylation of indenes with various aryl boronic acids and the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical[8] (TEMPO) as an oxidant and trapping reagent to provide 1,2,3-trisubstituted indanes [Eq. (3)]. Indenes[9] and indanes[10] have found widespread application as biologically important substructures in medicinal chemistry. Therefore, development of novel methods for their preparation is highly important.



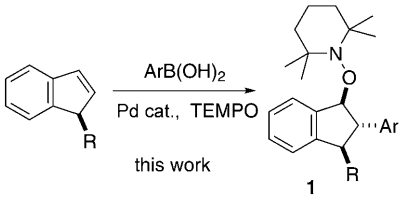
(1)

X, Y = heteroatom group → many examples



(2)

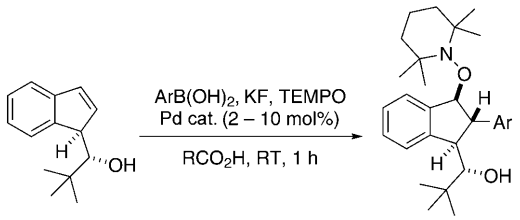
X = heteroatom group and R^3 = alkyl, aryl, vinyl → seldom



(3)

Recently we reported the successful use of TEMPO as an environmentally benign organic oxidant in rhodium- and palladium-catalyzed C–C bond forming reactions.[8b,11] Moreover, we have shown that indoles undergo highly diastereoselective palladium-catalyzed TEMPO-mediated carboaminoxylations.[12] During our ongoing studies in that area we found that the double bond of indene can be highly regioselectively carbofunctionalized under oxidative palladium catalysis using aryl boronic acids with excellent stereocontrol. Treatment of indene with $Pd(OAc)_2$ in the presence of TEMPO, $PhB(OH)_2$, and KF (4 equiv each) in propionic acid at room temperature provided carboaminoxylation product **1** (R = H, Ar = Ph) as a single diastereoisomer in 79% yield [Eq. (3)].[13] Based on this highly promising initial result, we decided to further investigate that reaction and to extend the studies to 3-substituted indenes for the synthesis of 1,2,3-trisubstituted indanes. Along with the simple diastereocontrol of the carboaminoxylation reaction, the induced stereoselectivity exerted by the indene substituent posed an additional challenge. Moreover, also the regioselectivity needed to be controlled.

As a test substrate, we chose racemic indene **2**, which was readily obtained as a single diastereoisomer by lithiation of indene (Et_2O, *n*BuLi, tetramethylethylenediamine) and subsequent trapping with pivaldehyde.[14] Indene **2** was then reacted under different conditions with various commercially available aryl boronic acids under oxidative palladium catalysis (Scheme 1, Table 1).



Scheme 1. Carboaminoxylation of indene **2**.

We were very pleased to observe that with $Pd(OAc)_2$ (10 mol%) as a catalyst in $EtCO_2H$ at RT for 1 h by using 4 equiv of $PhB(OH)_2$, KF, and TEMPO the highly substituted indane **3a** bearing four contiguous stereogenic centers was formed as a single isomer in 73% yield (Table 1, entry 1). The assignment of the relative configuration was based on the X-ray structure of **3a** (Figure 1).[15] This structure furthermore

[*] S. Kirchberg, Dr. R. Fröhlich, Prof. Dr. A. Studer
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 281-833-6523
E-mail: studer@uni-muenster.de

[**] We thank the International Research Training Group Münster/Nagoya for funding. A.S. thanks Novartis Pharma AG for financial support (Novartis Young Investigator Award).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201002214.

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1: Arylcarboaminoxylation of **2** with various arylboronic acids (4 equiv each of $ArB(OH)_2$, TEMPO, and KF).

Entry	Solvent	Catalyst (10 mol%)	Ar	Product	Yield [%] [a]
1	$EtCO_2H$	$Pd(OAc)_2$	C_6H_5	**3a**	73
2	$MeCO_2H$	$Pd(OAc)_2$	C_6H_5	**3a**	30
3	$nPrCO_2H$	$Pd(OAc)_2$	C_6H_5	**3a**	54
4	$EtCO_2H$	$Pd(O_2CCF_3)_2$	C_6H_5	**3a**	72
5	$EtCO_2H$	$[Pd(acac)_2]$	C_6H_5	**3a**	53
6[b]	$EtCO_2H$	$Pd(OAc)_2$	C_6H_5	**3a**	45
7[c]	$EtCO_2H$	$Pd(OAc)_2$	C_6H_5	**3a**	25
8	$EtCO_2H$	$Pd(OAc)_2$	$4\text{-}CH_3C_6H_4$	**3b**	66
9	$EtCO_2H$	$Pd(OAc)_2$	$4\text{-}FC_6H_4$	**3c**	69
10	$EtCO_2H$	$Pd(OAc)_2$	$4\text{-}BrC_6H_4$	**3d**	43
11	$EtCO_2H$	$Pd(OAc)_2$	$4\text{-}CH_3OC_6H_4$	**3e**	45
12	$EtCO_2H$	$Pd(OAc)_2$	$3\text{-}CH_3C_6H_4$	**3f**	73
13	$EtCO_2H$	$Pd(OAc)_2$	$3\text{-}ClC_6H_4$	**3g**	57
14	$EtCO_2H$	$Pd(OAc)_2$	$2\text{-}CH_3C_6H_4$	**3h**	20

[a] Yield of isolated product. [b] With 5 mol% $Pd(OAc)_2$. [c] With 2 mol% $Pd(OAc)_2$.

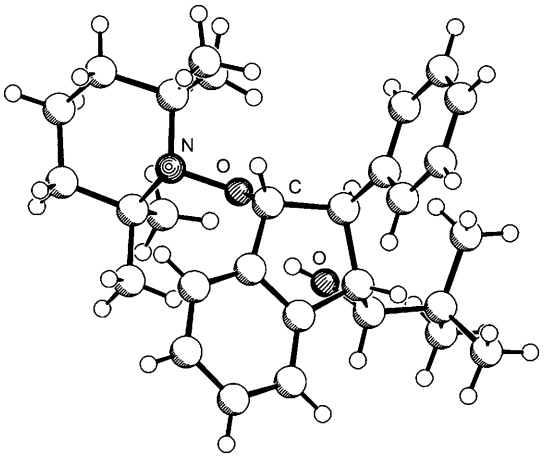
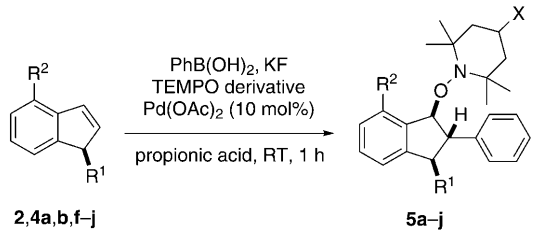


Figure 1. Structure of **3a** in the solid state.

allowed us to unambiguously assign the relative stereochemistry obtained for the initial hydroxyalkylation of indene **2** and also for the subsequent carboaminoxylation. All further compounds prepared were assigned in analogy. Reactions in acetic or butyric acid were lower-yielding (entries 2 and 3). Replacing $Pd(OAc)_2$ by $Pd(O_2CCF_3)_2$ did not influence reaction outcome, whereas with $[Pd(acac)_2]$ a significantly lower yield was obtained under otherwise identical conditions (entries 4 and 5). Reducing catalyst loading to 5 and 2 mol%, respectively, led to a decrease of the yield (entries 6 and 7).

Under the optimized conditions, other arylboronic acids were tested. No trends on electronic effects exerted by the 4-substituent of the arylboronic acids could be extracted from the experimental results. Good yields were achieved with 4-methyl and 4-F-substituted phenylboronic acids, whereas the methoxy and bromo congeners delivered slightly lower yields (entries 8–11). Substituents at the *meta* position were tolerated (entries 12 and 13); however, with *ortho*-methylphenylboronic acid a poor yield resulted, probably for steric reasons (entry 14).

We then varied the substituent R at the indene moiety. (Experimental details on the synthesis of indenes **4a**,**b**,**f–i** can be found in the Supporting Information.) Palladium-catalyzed carboaminoxylations to provide **5a–i** were performed under the optimized conditions by using phenylboronic acid (Scheme 2).



Scheme 2. Carboaminoxylation of various indenes **2** and **4a**,**b**,**f–j**.

Reaction of indene **4a** with TEMPO as an oxidant/trapping reagent gave **5a** in 65% yield of isolated product as a single isomer (Table 2, entry 1). A slightly lower yield (58%) was noted in the reaction with the acetone adduct of indene (**4b**), where we observed the formation of the 2,3-bispheny-

Table 2: Phenylcarboaminoxylation of the 3-substituted indenes **2** and **4a**,**b**,**f–j** (4 equiv each of $PhB(OH)_2$, X-TEMPO, and KF).

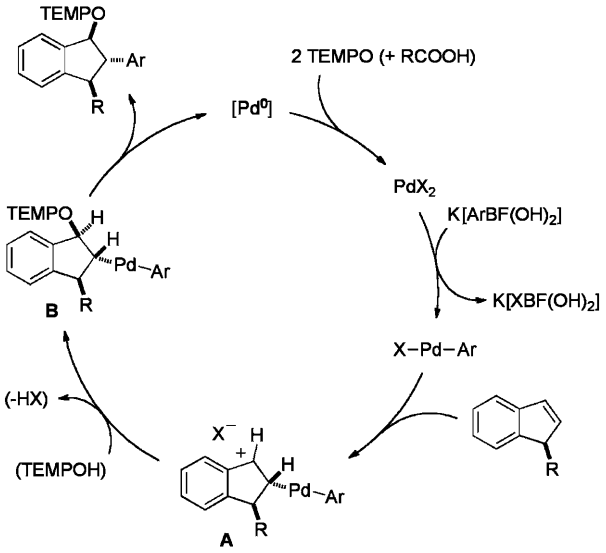
Entry	R^1	R^2	X	Product	Yield [%]
1	$CH(OH)Ph$	H	H	**5a**	65
2[a]	$COH(CH_3)_2$	H	H	**5b**	58
3	$CH(OH)C(CH_3)_3$	H	OH	**5c**	50
4	$CH(OH)C(CH_3)_3$	H	NHAc	**5d**	54
5	$CH(OH)C(CH_3)_3$	H	NH-Ala-Boc	**5e**	80
6	Me	H	NHAc	**5f**	76
7	*i*Pr	H	NHAc	**5g**	65
8	cyclohexyl	H	NHAc	**5h**	70
9	benzyl	H	NHAc	**5i**	68
10	$CH(OH)C(CH_3)_3$	Br	H	**5j**	34

[a] The 2,3-bisphenylated indene was formed as a side product (see the Supporting Information).

lated indene as a side product (entry 2). TEMPO could be replaced by the cheaper HO-TEMPO (**5c**, entry 3) or AcNH-TEMPO (**5d**, entry 4). Importantly, the oxidation/trapping reagent can also be successfully used for the installation of interesting functionalities at the 1-position of the indane core. This is documented by the reaction of **2** with the amino acid conjugated nitroxide (Boc-Ala-NH-TEMPO) to afford the carboaminoxylation product **5e** in a very good yield with perfect diastereocontrol (entry 5). Moreover, with smaller unbranched R^1-substituents, such as methyl and benzyl groups, diastereoselectivity remained excellent (entries 6 and 9). A similar result was achieved for reaction of indenes **4g** and **4h** bearing secondary alkyl substitutents as stereodirecting groups (entries 7,8). Decreasing electron density in the arene moiety (see **4j**) led to a significantly reduced reactivity of the indene substrate (entry 10).

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

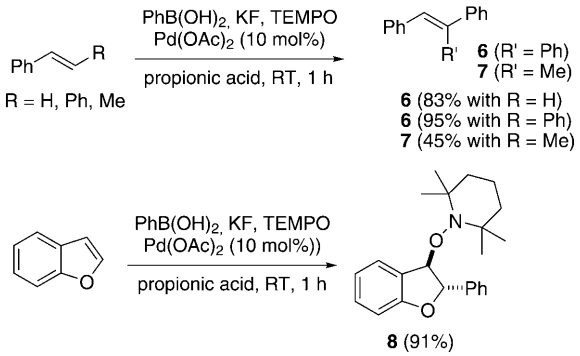
We propose the mechanism depicted in Scheme 3 for our highly diastereoselective carboaminoxylation. Reaction of PdX_2 with $K[ArBF(OH)_2]$ by transmetalation from boron to palladium affords X-Pd-Ar which undergoes electrophilic



Scheme 3. Proposed mechanism.

addition at the 2-position of the indene *trans* to the steering R substitutent to generate the benzylic cationic intermediate **A**. The counteranion X^- can either be $EtCO_2^-$ or $TEMPO^-$. The fact that a lower yield was achieved with the brominated indene **4j** supports the suggested electrophilic process. Stereoselective *trans* trapping of **A** with TEMPOH provides **B**, which upon reductive elimination gives the 1,2,3-trisubstituted indane with an *anti*,*anti* relative configuration along with palladium(0). We believe that TEMPO or TEMPOH helps stabilize the palladium(0) species, as no palladium black was observed during the reaction. Oxidation of palladium(0) with 2 equiv of TEMPO eventually regenerates the palladium(II) salt. We currently disfavour a mechanism comprising regio and *trans*-selective (with respect to the substituent R) Heck-type addition of TEMPO-Pd-Aryl to the indene double bond followed by oxidation of the thus formed benzylic palladium species to the corresponding palladium(IV) species and subsequent reductive elimination. For that mechanism to be operative, TEMPO and the aryl group would have to be *syn*-orientated in the final product.[1c] However, the benzylic palladium(IV) species might also act as an electrophile in a S_N2-type substitution with $TEMPO^-$ to give the isolated *anti* product.[1c] This pathway can not be excluded based on the stereoselectivity observed.

We then tested whether our carboaminoxylation works also on other alkenes. *trans*-Stilbene reacted with $PhB(OH)_2$ to triphenylethene **6** (95%), and the same product was also isolated in the reaction with styrene (83%, Scheme 4; see also the Supporting Information). β-Methylstyrene provided methylstilbene **7** in 45% yield. It seems that for noncyclic

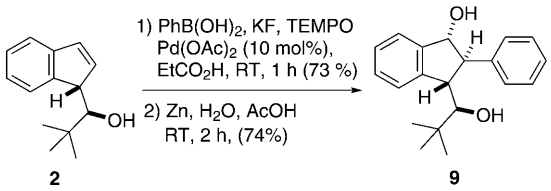


Scheme 4. Transformation of styrene, *trans*-stilbene, *trans*-β-methylstyrene, and benzofuran.

systems, deprotonation of the cationic intermediate of type **A** is faster than cation interception giving compounds of type **B**. Along this line, carboaminoxylation of benzofuran provided **8** in 91% yield.

To document the potential of our approach for the synthesis of enantiomerically pure trisubstituted indanes, we had to make sure that the stereocenter of the starting indene is configurationally stable under the applied conditions. We therefore prepared enantioenriched indene **2** (65% *ee*) by using the Hoppe approach with (−)-sparteine as an additive for indene lithiation.[14c] Palladium-mediated phenylaminoxylation afforded **3a** with 65% *ee* (see the Supporting Information).

Finally, we ran a sequence on **2** comprising a phenylaminoxylation with subsequent reductive N–O bond cleavage with zinc in $AcOH/H_2O$ (3:1) to provide benzylic alcohol **9** (Scheme 5). The TEMPO moiety can therefore be regarded



Scheme 5. Carboaminoxylation and reductive N–O bond cleavage.

as a protected hydroxy group. Recrystallization of **9** afforded crystals suitable for X-ray analysis, which confirmed the relative configuration of all four stereogenic centers and showed that N–O bond cleavage in the last step occurred stereospecifically (Figure 2).[15]

In conclusion, we introduced palladium-catalyzed highly stereoselective carboaminoxylation of readily available 3-substituted indenes with commercially available arylboronic acids and nitroxides to give biologically interesting 1,2,3-trisubstituted indanes. The reactions occur under mild conditions (room temperature) in a short time (1 h). The palladium-mediated oxyarylation occurs stereospecifically, and the alkoxyamine moiety can readily be converted into

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

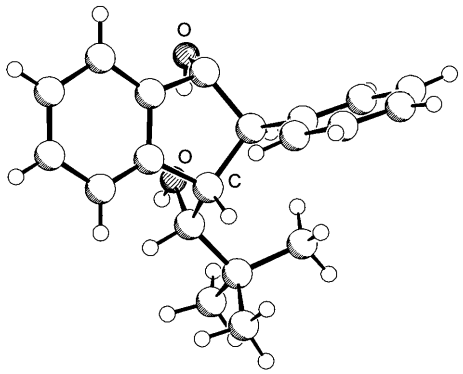


Figure 2. Structure of **9** in the solid state.

the corresponding alcohol by reductive N–O bond cleavage. We are currently working on the development of a general method for enantioselective synthesis of 3-substituted indenes.

Received: April 14, 2010
Published online: August 4, 2010

Keywords: homogeneous catalysis · nitroxides · palladium · stereoselective reactions · synthetic methods

[1] Reviews: a) K. H. Jensen, M. S. Sigman, *Org. Biomol. Chem.* **2008**, *6*, 4083; b) S. D. R. Christie, A. D. Warrington, *Synthesis* **2008**, 1325; c) K. Muñiz, *Angew. Chem.* **2009**, *121*, 9576; *Angew. Chem. Int. Ed.* **2009**, *48*, 9412.

[2] Palladium-catalyzed dioxygenation: a) Y. Li, D. Song, V. M. Dong, *J. Am. Chem. Soc.* **2008**, *130*, 2962; b) K. H. Jensen, T. P. Pathak, Y. Zhang, M. S. Sigman, *J. Am. Chem. Soc.* **2009**, *131*, 17074; c) A. Wang, H. Jiang, H. Chen, *J. Am. Chem. Soc.* **2009**, *131*, 3846; d) W. Wang, F. Wang, M. Shi, *Organometallics* **2010**, *29*, 928.

[3] Palladium-catalyzed diamidation: a) J. Streuff, C. H. Hövelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.* **2005**, *127*, 14586; b) H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 11688; c) B. Wang, H. Du, Y. Shi, *Angew. Chem.* **2008**, *120*, 8348; *Angew. Chem. Int. Ed.* **2008**, *47*, 8224.

[4] Palladium-catalyzed oxyamidation: a) L. V. Desai, M. S. Sanford, *Angew. Chem.* **2007**, *119*, 5839; *Angew. Chem. Int. Ed.* **2007**, *46*, 5737; b) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 7179; c) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.* **2005**, *127*, 7690.

[5] The intramolecular oxidative carbofunctionalization of olefins has been far more intensively investigated than the intermolecular variants. For a review, see: J. P. Wolfe, *Eur. J. Org. Chem.* **2007**, 571. Some recent publications: a) K.-T. Yip, M. Yang, K.-L. Law, N.-Y. Zhu, D. Yang, *J. Am. Chem. Soc.* **2006**, *128*, 3130; b) J. S. Nakhla, J. P. Wolfe, *Org. Lett.* **2007**, *9*, 3279; c) W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948; d) C. E. Houlden, C. D. Bailey, J. G. Ford, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2008**, *130*, 10066; e) C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 9488.

[6] Intermolecular oxidative carbofunctionalization of olefins: a) D. Kalyani, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, *130*, 2150; b) K. Cheng, L. Huang, Y. Zhang, *Org. Lett.* **2009**, *11*, 2908.

[7] Radical carboaminoxylations: a) A. Studer, *Chem. Eur. J.* **2001**, *7*, 1159; b) A. Studer, *Chem. Soc. Rev.* **2004**, *33*, 267; c) A. Studer, T. Schulte, *Chem. Rec.* **2005**, *5*, 27; d) M. R. Heinrich, *Chem. Eur. J.* **2009**, *15*, 820.

[8] For a review, see: a) T. Vogler, A. Studer, *Synthesis* **2008**, 1979; see also: b) T. Vogler, A. Studer, *Org. Lett.* **2008**, *10*, 129; c) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem.* **2008**, *120*, 8855; *Angew. Chem. Int. Ed.* **2008**, *47*, 8727; d) M. S. Maji, T. Pfeifer, A. Studer, *Angew. Chem.* **2008**, *120*, 9690; *Angew. Chem. Int. Ed.* **2008**, *47*, 9547; e) M. S. Maji, T. Pfeifer, A. Studer, *Chem. Eur. J.* **2010**, *16*, 5872.

[9] For a review, see: H. Gao, J. A. Katzenellenbogen, R. Garg, C. Hansch, *Chem. Rev.* **1999**, *99*, 723.

[10] a) H. Hu, S. P. Hollinshead, S. E. Hall, K. Kalter, L. M. Ballas, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 973; b) M. F. Gross, S. Beaudoin, G. McNaughton-Smith, G. S. Amato, N. A. Castle, C. Huang, A. Zou, W. Yu, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2849; c) S. Hudson, M. Kiankarimi, W. Eccles, Y. S. Mostofi, M. J. Genicot, W. Dwight, B. A. Fleck, K. Gogas, W. S. Wade, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4495; d) S. Ulmschneider, U. Müller-Vieira, C. D. Klein, I. Antes, T. Lengauer, R. W. Hartmann, *J. Med. Chem.* **2005**, *48*, 1563; e) P. Camps, X. Formosa, C. Galdeano, T. Gómez, D. Muñoz-Torrero, M. Scarpellini, E. Viayna, A. Badia, M. V. Clos, A. Camins, M. Pallàs, M. Bartolini, F. Mancini, V. Andrisano, J. Estelrich, M. Lizondo, A. Bidon-Chanal, F. J. Luque, *J. Med. Chem.* **2008**, *51*, 3588.

[11] a) S. Kirchberg, T. Vogler, A. Studer, *Synlett* **2008**, *18*, 2841; b) T. Vogler, A. Studer, *Adv. Synth. Catal.* **2008**, *350*, 1963.

[12] S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem.* **2009**, *121*, 4299; *Angew. Chem. Int. Ed.* **2009**, *48*, 4235.

[13] As a side product, the product of a double phenylation oxidation reaction was isolated in 9% yield (see the Supporting Information).

[14] a) L. Cedheim, L. Eberson, *Synthesis* **1973**, 159; b) N. E. Grimmer, N. J. Coville, C. B. de Koning, J. M. Smith, L. M. Cook, *J. Organomet. Chem.* **2000**, *616*, 112; c) I. Hoppe, D. Hoppe, G. Boche, M. Marsch, K. Harms, *Angew. Chem.* **1995**, *107*, 2328; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2158.

[15] CCDC 771860 (**3a**) and CCDC 771861 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim