DOI: 10.1002/ejoc.201000237

Chiral Chalcogen Peptides as Ligands for the Catalytic Enantioselective Aryl Transfer Reaction to Aldehydes

Ricardo S. Schwab,[a] Letiere C. Soares,[a] Luciano Dornelles,[a] Oscar E. D. Rodrigues,*[a] Márcio W. Paixão,[b] Marcelo Godoi,[c] and Antonio L. Braga*[c]

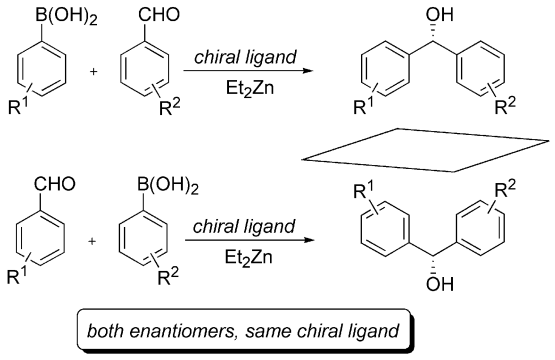
Keywords: Asymmetric synthesis / Chalcogen peptides / Arylboronic acids / Diarylmethanols / Organozinc reagents / Selenium

A new series of chiral chalcogen peptides were synthesized from inexpensive and commercially available starting materials. The synthesized compounds were tested as catalysts in the enantioselective arylation of aldehydes by using arylboronic acids as the aryl source. The desired diarylmethanols were obtained in excellent yields and with enantioselectivities up to 91 % *ee*.

Introduction

The addition of organometallic reagents to carbonyl compounds is one of the most important carbon–carbon bond-forming processes in synthetic organic chemistry.[1] The enantioselective nature of this reaction provides particularly useful access to chiral secondary alcohols, which are important building blocks and ubiquitous subunits present in many biologically active compounds as well as in medicinal applications. In this context the asymmetric arylation of aldehydes in the presence of a chiral ligand has received special attention[2] since it affords access to chiral diarylmethanols,[3] which are useful intermediates in the synthesis of bioactive compounds and natural products.[4]

The application of boronic acids as a nucleophilic aryl species source, through a boron/zinc[5] exchange, is the most commonly used protocol to afford the respective diarylmethanols. This method allows the exploitation of a broad range of substituted aryl transfer reagents, since a large number of arylboronic acids are commercially available. Another interesting feature of this reaction is that both enantiomers of a given product can be prepared by using the same chiral ligand, simply with an appropriate choice of the reaction partners: arylboronic acid and aldehyde (Scheme 1).



Scheme 1. Catalytic arylation of aldehydes with arylboronic acids.

Despite the potential usefulness of this protocol, the asymmetric version of this addition is a dynamic field. The design of catalysts for the enantioselective addition of organozinc reagents to aldehydes has been the focus of intensive research. However, only a few efficient catalysts have been developed for this purpose, and most of them are based on bidentate compounds. Successful results for the synthesis of optically active diarylmethanols have been obtained mainly by using chiral β-amino alcohols.[6] Furthermore, the efficient application of ligands bearing organochalcogen moieties are still rare. Recently, the use of chiral amino sulfides for this purpose has been described, affording the desired product with high yields and selectivities (Figure 1).[7]

However, to the best of our knowledge, the application of chiral selenium-based compounds as catalysts for the enantioselective addition of PhZnEt to carbonyl compounds is not common, and only the ligand developed by Bolm et al.[8] has been applied for this purpose (Figure 1).

In addition, peptide-based ligands offer attractive and practical options in the development of new ligands for

[a] Departamento de Química, Universidade Federal de Santa Maria,
97105-900 Santa Maria, RS, Brazil
Fax: +55-55-3220-8998
E-mail: rodriguesoed@gmail.com
[b] Departamento de Química, Universidade Federal de São Carlos,
13565-905 São Carlos, SP, Brazil
[c] Departamento de Química, Universidade Federal de Santa Catarina,
88040-970 Florianópolis, SC, Brazil
E-mail: albraga@qmc.ufsc.br

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000237.

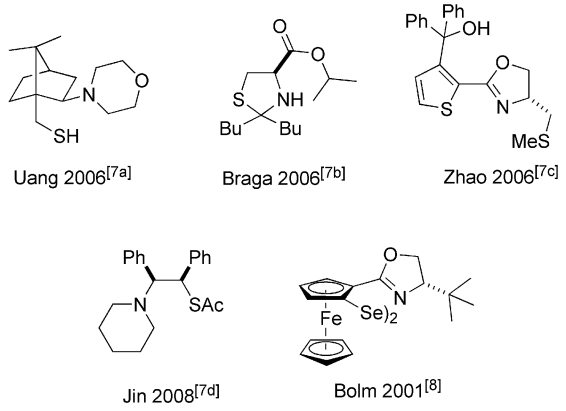


Figure 1. Chiral amino chalcogenides employed as ligands in the enantioselective arylation of aldehydes.

asymmetric transformations. Peptides are easily prepared, consist of readily available chiral building blocks and are modular. They have been extensively applied in asymmetric organocatalysis.[9] Nevertheless, their applications in the asymmetric addition of organozinc reagents to carbonyl compounds has rarely been described.[10]

As part of our growing interest in the development of new chiral organochalcogen compounds for asymmetric transformations,[11] we describe herein the application of this new class of peptides (**1**–**4**, Figure 2) as chiral ligands for the catalytic enantioselective arylation of aromatic aldehydes with boronic acids. As far as we are aware these are the first chalcogen peptides successfully employed to this aim.

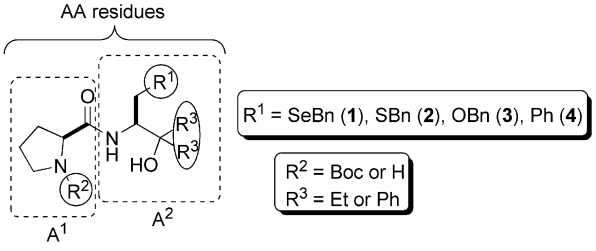


Figure 2. General design of ligands. AA = amino acid.

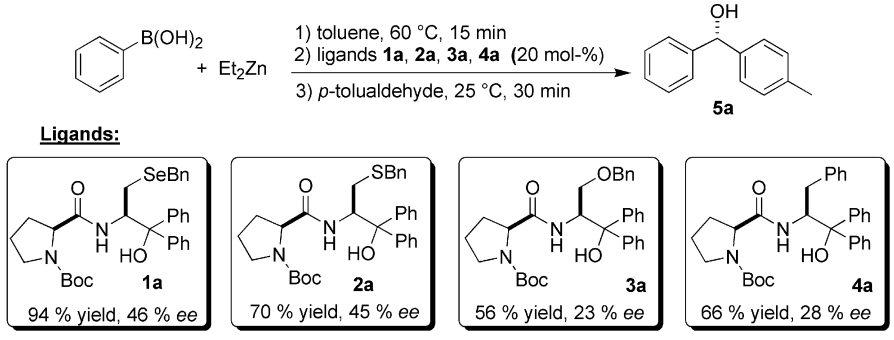
Results and Discussion

Firstly, the *N*-Boc peptides **1**–**4** were synthesized in a few steps with high yields.[9c] The modular nature of chalcogen peptide ligands was exploited in the systematic alteration of each structural unit. Initially, we decided to examine the influence of the R^1 group of chalcogeno peptides, while the R^2 and R^3 positions were held constant. The compounds were evaluated as ligands for the enantioselective addition of PhZnEt to *p*-tolualdehyde as depicted in the Scheme 2.

Variations in the R^1 group showed that it plays an import role in the enantioselectivity and yield of the reaction. On analyzing Scheme 2, it is possible to observe that the peptide derived from L-selenocysteine derivative **1a**, presented the best performance, affording the desired diarylmethanol in high yield (94%) and with reasonable enantioselectivity (46%). Interestingly, by replacing selenium (ligand **1a**) with sulfur (ligand **2a**) the optical purity remained, but the yield dramatically decreased (70%). Thus, based on these results the greater ability of selenium to act as a ligand, compared with sulfur, leads us to conclude that the selenium moiety plays an important role in this reaction.[12] In order to bring to light this chemical behaviour, we replaced the chalcogen-Bn group (R^1) by an oxygen-Bn or a phenyl group. Thus, ligands **3a** and **4a** were tested under the same general protocol, affording the desired products, however in only 56 and 66% yield and with 23 and 28% *ee*, respectively (Scheme 2). These results suggest that the chalcogen group is an important component of the catalyst for this reaction, having considerable influence on the yield and selectivity.

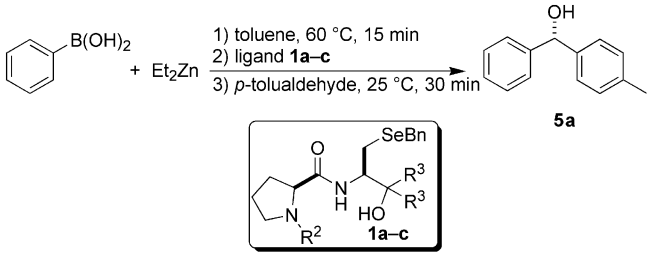
To verify the possibility for steric and electronic refinement in the structure of ligands **1**, we performed the deprotection of the Boc group (Table 1). The reaction of the chiral peptide **1a** with TFA proceeded smoothly at room temperature to give the free amino peptide **1b** in good yield. The ligand **1b** showed better performance than **1a** in terms of conversion and enantioselection (Entry 2). This result might be explained based on the fact that the amine group possesses a lone pair, and thus it coordinates with the zinc atom more efficiently than the carbamate moiety.

By extending our studies to other chiral seleno ligands with variations at the R^3 position, we could observe that the presence of a sterically hindered group was crucial for a high enantioselectivity. When the *gem*-diphenyl group was



Scheme 2. Evaluation of chiral relay ligands in the catalytic arylation of *p*-tolualdehyde with phenylboronic acid.

Table 1. Catalytic arylation of *p*-tolualdehyde with phenylboronic acid.[a]



Entry	Ligand (mol-%)	R^2	R^3	Yield[b] [%]	*ee*[c,d] [%]
1	**1a** (20)	Boc	Ph	94	46 (*S*)
2	**1b** (20)	H	Ph	97	71 (*S*)
3[e]	**1b** (20)	H	Ph	50	57 (*S*)
4[f]	**1b** (20)	H	Ph	50	63 (*S*)
5	**1b** (10)	H	Ph	80	40 (*S*)
6	**1c** (20)	H	Et	67	racemic

[a] Reactions were performed on a 0.5 mmol scale with $PhB(OH)_2$ (2.4 equiv.), Et_2Zn (7.2 equiv.) in toluene (first at 60 °C for 15 min, then at room temperature for 30 min).[14] [b] Isolated yield of the corresponding product. [c] Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H column. [d] Absolute configuration assigned by correlation to literature data.[15] [e] Reaction was carried out at 0 °C. [f] 5 mol-% of DiMPEG 1000 was added.

replaced by a *gem*-diethyl group, total racemization of the substrate took place (Entry 2 vs. 6). Therefore, steric factors appear to play a dominant role in determining the enantioselectivity in this series of ligands.

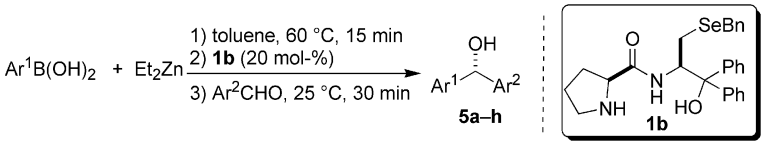
We also found that the temperature has a significant influence on the reaction, and the best result were achieved at room temperature. When the reaction was performed at 0 °C, the desired product was obtained with lower yield and enantioselectivity (Entry 2 vs. 3). In order to improve the enantioselectivity, an additive (DiMPEG)[13] was added, and again lower enantioselectivity and yield were observed (Entry 4). These findings may be due to the strong interactions between DiMPEG and PhZnEt, leading to the delivery of the phenyl group without the influence of a chiral environment.[7b] We also evaluated the ligand loading; however, on decreasing the amount of ligand to 10 mol-% the diarylmethanol was obtained with 80% yield and 40% *ee* (Entry 5).

With the optimized conditions and having established ligand **1b** as the most effective one for the asymmetric addition of arylzinc reagents to aromatic aldehydes, we extended the scope of our protocol to several aldehydes with different steric and electronic features (Table 2). In terms of steric effect, the reaction with 2-tolualdehyde underwent smooth aryl addition with 91% *ee* and nearly quantitative yield (Entry 2). It seems that due to the nearness of the carbonyl position of the bulky group in the 2-tolualdehyde to that of 4-tolualdehyde, the transfer of the aryl group occurs with a slightly higher enantiomeric control (Entry 1 vs. 2). A contrasting result was achieved when 2-methoxybenzaldehyde was used as the electrophile. In this case a potential chelating effect between the zinc atom and the methoxy substituent might be responsible for the decrease in enantioselectivity (Entry 2 vs. 4). However, the reaction was not greatly influenced by electronic effects. As shown in Table 2, electron-donating or -withdrawing groups afforded the respective products with the same level of enantioselectivity (Entries 3 and 5).

To extend the scope of our methodology and the efficiency of the aryl transfer to aldehydes, we tested different substituted arylboronic acids. The corresponding compounds were obtained with good yields and with remarkable enantioselectivities (Entries 7 and 8). For example, the aryl transfer reaction from (4-methylphenyl)boronic acid to benzaldehyde occurred with 66% *ee* (Entry 7). This is an interesting feature of the methodology employed, since both enantiomers of a given product can be easily prepared in good yield and with reasonable enantiomeric excesses by using the same chiral ligand, simply through the appropriate choice of reaction partners: arylboronic acid and aldehyde.

In order to demonstrate the utility of this method in synthesizing building blocks for biologically active compounds, their application to important target molecules is shown in Figure 3. The synthesis of a direct precursor for (*S*)-orphen-

Table 2. Catalytic arylation of aldehydes with arylboronic acids by using ligand **1b**.



Entry	Product	Ar^1	Ar^2	Yield[a] [%]	*ee*[b,c] [%]
1	**5a**	Ph	4-$CH_3C_6H_4$	96	71 (*S*)
2	**5b**	Ph	2-$CH_3C_6H_4$	98	91(*S*)
3	**5c**	Ph	4-$CH_3OC_6H_4$	85	80 (*S*)
4	**5d**	Ph	2-$CH_3OC_6H_4$	87	65 (*S*)
5	**5e**	Ph	4-ClC_6H_4	86	77 (*S*)
6	**5f**	Ph	2-ClC_6H_4	94	78 (*S*)
7	**5g**	4-$CH_3C_6H_4$	Ph	63	66 (*R*)
8	**5h**	4-ClC_6H_4	Ph	88	51 (*R*)

[a] Isolated yield of the corresponding product. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Absolute configuration assigned by correlation to literature data.[15]

adrine,[16] an anticholinergic and antihistaminic agent,[4] could be achieved by the reaction of 2-toluadehyde with high efficiency (91% *ee* and 98% yield).

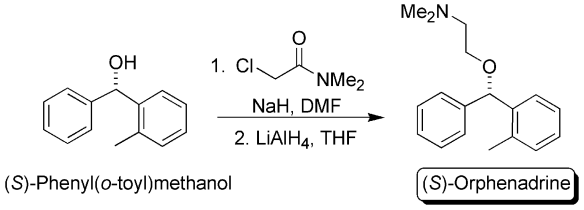


Figure 3. Biologically active (*S*)-orphenadrine.

Conclusions

We have developed a new class of chalcogen-based ligands for the enantioselective arylation of aromatic aldehydes. This is the first time that seleno peptides have been applied in the asymmetric arylation of aromatic aldehydes with good results. The modular synthesis of these ligands allowed the easy modification of three different sites. In the presence of chiral ligand **1b**, the corresponding diarylmethanols were obtained in excellent yields and with high enantioselectivities (up to 91% *ee*).

We believe that the chemistry described herein represents a new direction for the design of bifunctional, chiral chalcogen peptide ligands and their application in asymmetric catalysis. Intensive research in this area is in progress in our laboratory.

Supporting Information (see footnote on the first page of this article): General experimental methods and characterization data.

Acknowledgments

The authors gratefully acknowledge Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq – INCT Catálise e INCT NANOBIOSIMES) for financial support. R. S. S. also thanks CAPES for a PhD fellowship. M. W. P. acknowledges Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (grants 2009/07281-0 and 2009/14352-0).

[1] a) D. A. Evans, *Science* **1988**, *240*, 420–426; b) R. Noyori, M. Kitamura, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49–69; c) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117–2188; d) K. Soai, T. Shibata, in: E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*, Springer-Verlag, Berlin, **1999**, pp. 1–911.

[2] For a recent review on catalytic enantioselective arylation, see: a) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454–470; b) M. W. Paixão, A. L. Braga, D. S. Lüdtke, *J. Braz. Chem. Soc.* **2008**, *19*, 813–830.

[3] a) C. Bolm, N. Hermanns, J. P. Hildebrand, K. Muñiz, *Angew. Chem. Int. Ed.* **2001**, *40*, 3284–3308; b) V. Dimitrovi, K. Kostova, *Lett. Org. Chem.* **2006**, *3*, 176–182; c) J. G. Kim, P. J. Walsh, *Angew. Chem. Int. Ed.* **2006**, *45*, 4175–4178; d) L. Salvi, J. G. Kim, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 12483–12493.

[4] a) K. Meguro, M. Aizawa, T. Sohda, Y. Kawamatsu, A. Nagaoka, *Chem. Pharm. Bull.* **1985**, *33*, 3787–3797; b) F. Toda, K. Tanaka, K. Koshiro, *Tetrahedron: Asymmetry* **1991**, *2*, 873–874; c) S. Stanchev, R. Rakovska, N. Berova, G. Snatzke, *Tetrahedron: Asymmetry* **1995**, *6*, 183–198; d) M. Botta, V. Summa, F. Corelli, G. Di Pietro, P. Lombardi, *Tetrahedron: Asymmetry* **1996**, *7*, 1263–1266; e) K. Yamamoto, K. Tsurumi, F. Sakurai, K. Kondo, T. Aoyama, *Synthesis* **2008**, 3585–3590.

[5] For B/Zn exchange reactions, see: a) M. Srebnik, *Tetrahedron Lett.* **1991**, *32*, 2449–2452; b) W. Oppolzer, R. N. Radinov, *Helv. Chim. Acta* **1992**, *75*, 170–173; c) W. Oppolzer, R. N. Radinov, *J. Am. Chem. Soc.* **1993**, *115*, 1593–1594; d) F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, *J. Org. Chem.* **1996**, *61*, 8229–8243; e) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414–4435; f) O. Pietro, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2003**, *14*, 1955–1957; g) V. J. Forrat, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2005**, *16*, 3341–3344; h) V. J. Forrat, O. Pietro, D. Ramón, M. Yus, *Chem. Eur. J.* **2006**, *12*, 4431–4445; i) V. J. Forrat, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2006**, *17*, 2054–2058; j) V. J. Forrat, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2008**, *19*, 537–541; k) X. Huang, L. Wu, J. Xu, L. Zong, H. Hu, Y. Cheng, *Tetrahedron Lett.* **2008**, *49*, 6823–6826; l) V. J. Forrat, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2009**, *20*, 65–67.

[6] a) C. Bolm, J. Rudolph, F. Schmidt, *Synthesis* **2005**, 840–842; b) S. Özçubukçu, F. Schmidt, C. Bolm, *Org. Lett.* **2005**, *7*, 1407–1409; c) A. L. Braga, D. S. Lüdtke, F. Vargas, M. W. Paixão, *Chem. Commun.* **2005**, 2512–2514; d) A. L. Braga, D. S. Lüdtke, F. Vargas, P. H. Schneider, M. W. Paixão, A. Schneider, L. A. Wessjohann, *Tetrahedron Lett.* **2005**, *46*, 7827–7830; e) X. y. Liu, X. y. Wu, Z. Chai, Y. y. Wu, G. Zhao, S. z. Zhu, *J. Org. Chem.* **2005**, *70*, 7432–7435; f) S. Dahmen, M. Lormann, *Org. Lett.* **2005**, *7*, 4597–4600; g) J. G. Kim, P. J. Walsh, *Angew. Chem. Int. Ed.* **2006**, *45*, 4175–4178; h) G. Lu, F. Y. Kwong, J.-W. Ruan, Y.-M. Li, A. S. C. Chan, *Chem. Eur. J.* **2006**, *12*, 4115–4120; i) M. W. Paixão, M. de Godoi, C. R. B. Rhoden, B. Westermann, L. A. Wessjohann, D. S. Lüdtke, A. L. Braga, *J. Mol. Cat. A: Chem.* **2007**, *261*, 120–124; j) A. L. Braga, M. W. Paixão, B. Westermann, P. H. Schneider, L. A. Wessjohann, *J. Org. Chem.* **2008**, *73*, 2879–2882; k) J. Ruan, G. Lu, L. Xu, Y.-M. Li, A. S. C. Chan, *Adv. Synth. Catal.* **2008**, *350*, 76–84; l) M.-C. Wang, Q.-J. Zhang, W.-X. Zhao, X.-D. Wang, X. Ding, T.-T. Jing, M.-P. Song, *J. Org. Chem.* **2008**, *73*, 168–176; m) C. Liu, Z.-L. Guo, J. Weng, G. Lu, A. S. C. Chan, *Chirality* **2010**, *22*, 159–164.

[7] a) P.-Y. Wu, H.-L. Wu, B.-J. Uang, *J. Org. Chem.* **2006**, *71*, 833–835; b) A. L. Braga, P. Milani, F. Vargas, M. W. Paixão, J. A. Sehnem, *Tetrahedron: Asymmetry* **2006**, *17*, 2793–2797; c) Z. Chai, X.-Y. Liu, X.-Y. Wu, G. Zhao, *Tetrahedron: Asymmetry* **2006**, *17*, 2442–2447; d) M.-J. Jin, S. M. Sarkar, D.-H. Lee, H. Qiu, *Org. Lett.* **2008**, *10*, 1235–1237.

[8] C. Bolm, M. Kesselgruber, A. Grenz, N. Hermmanns, J. P. Hildebrand, *New J. Chem.* **2001**, *25*, 13–15.

[9] a) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481–2495; b) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759–5812; c) R. S. Schwab, F. Z. Galetto, J. B. Azeredo, A. L. Braga, D. S. Lüdtke, M. W. Paixão, *Tetrahedron Lett.* **2008**, *49*, 5094–5097.

[10] For selected examples, see: a) H.-Q. Cai, C. Chen, L. Liu, J.-M. Ni, R. Wang, *J. Mol. Cat. A: Chem.* **2006**, *253*, 86–91; b) C. L. Wieland, H. Deng, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 15453–15456; c) C. M. Sprout, M. L. Richmond, C. T. Seto, *J. Org. Chem.* **2005**, *70*, 7408–7417.

[11] For selected examples, see: a) A. L. Braga, D. S. Lüdtke, F. Vargas, R. C. Braga, *Synlett* **2006**, 1453–1466; b) A. L. Braga, D. S. Lüdtke, F. Vargas, *Curr. Org. Chem.* **2006**, *10*, 1921–1938; c) A. L. Braga, M. W. Paixão, D. S. Lüdtke, C. C. Silveira, O. E. D. Rodrigues, *Org. Lett.* **2003**, *5*, 2635–2638; d) A. L. Braga, P. Milani, M. W. Paixão, G. Zeni, O. E. D. Rodrigues, E. F. Alves, *Chem. Commun.* **2004**, 2488–2489; e) P. H. Schnei-

der, H. S. Schrekker, C. C. Silveira, L. A. Wessjohann, A. L. Braga, *Eur. J. Org. Chem.* **2004**, 2715–2722; f) A. L. Braga, D. S. Lüdtke, E. E. Alberto, J. A. Sehnem, *Tetrahedron* **2005**, *61*, 11664–11671; g) A. L. Braga, J. A. Sehnem, F. Vargas, R. C. Braga, *J. Org. Chem.* **2005**, *70*, 9021–9024.
[12] A. L. Braga, O. E. D. Rodrigues, M. W. Paixão, H. R. Appelt, C. C. Silveira, D. P. Bottega, *Synthesis* **2002**, 2338–2340.
[13] J. Rudolph, N. Hermanns, C. Bolm, *J. Org. Chem.* **2004**, *69*, 3997–4000.
[14] C. Jimeno, S. Sayalero, T. Fjermestad, G. Colet, F. Maseras, M. A. Pericàs, *Angew. Chem. Int. Ed.* **2008**, *47*, 1098–1101.
[15] a) C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; b) F. Schimdt, J. Rudolph, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 703–708.
[16] K. Yamamoto, K. Tsurumi, F. Sakurai, K. Kondo, T. Aoyama, *Synthesis* **2008**, 3585–3590.

Received: February 21, 2010
Published Online: May 27, 2010

