Communication

Mild and efficient one-pot synthesis of chiral β-chalcogen amides via 2-oxazoline ring-opening reaction mediated by indium metal

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ABSTRACT

A simple and efficient procedure for the synthesis of β-seleno and β-thio amides via the ring-opening reaction of chiral 2-oxazolines in the presence of indium metal has been developed. Features of this method include the following: (i) easily and accessible starting materials; (ii) indium metal is more stable and less expensive then its respective salts; (iii) useful to excellent yields of β-chalcogen amides derivatives.

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1. Introduction

Organoselenium and sulfur compounds have been employed as very useful reagents in organic synthesis [1]. They allow the chemo-, regio- and stereoselective introduction of new functional groups into complex organic substrates under mild experimental conditions. In addition, these compounds are gaining contemporary interest due to their applications as powerful ligands in asymmetric catalysis [2] as well as for the design, synthesis and investigation of new molecular materials, especially for conducting or superconducting materials and for liquid crystals [3].

Besides, the biological and medicinal role of selenium and organoselenium compounds has also become increasingly esteemed, mainly due to their antioxidant, anti-tumor, antimicrobial, and antiviral properties [4]. Therefore, the development of new methods for the introduction of selenium-containing groups into organic molecules [5], particularly in a stereocontrolled manner, remains a significant challenge.

It is well known that the selenium anions are generated in situ via chemical Se–Se bonds cleavage to avoid handling unstable reagents such as selenols. Reduction of Se–Se bonds, especially cleavage of diaryl diselenides were performed with reducing agents such as $NaBH_4$, Na/NH_3, Bu_3SnH and $LiAlH_4$ [6]. In recent years, some protocols with indium(I) iodide-mediating cleavage of diorganoyl diselenides have been developed to prepare vinylic selenides [7],

seleno esters [8], β-hydroxyl selenides [9], selenocysteine derivatives [10] with special attention given to unsymmetrical diorganyl selenydes [11].

In this context, we recently reported an indium(I) protocol for the preparation a wide range of useful chiral β-seleno amides and selenocysteine derivatives via 2-oxazolines ring-opening reaction promoted by in situ generated bis(organoseleno)iodoindium(III) [12]. This method provided a practical and concise synthesis of a structurally diverse organochalcogen compounds in a straightforward and flexible strategy in the absence of a Lewis acid [13]. Attempting to disclose further extension of these previous reports, we describe herein a simple experimental procedure which uses metallic indium it is easy to handle, less expensive when compared to indium(I) protocols and active enough to promote the heterocycle ring-opening reaction (Scheme 1). The study resulted in an efficient synthesis of β-chalcogen amides 2 under mild and neutral conditions.

2. Results and discussion

Aiming to determine the optimum conditions, we performed studies about effects that can influence this reaction, such as: (i) loading and structure of organoyl halide; (ii) loading of indium metal; (iii) temperature and; (iv) solvent. We first investigated the present reaction under the following conditions: oxazoline **1a**, PhSeSePh, indium powder in refluxing 1,4-dioxane on varying the halide R^3-X (Table 1). When a tert-alkyl, benzylic or allylic halide were employed under the above conditions, **2a** was obtained in

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E-mail address: albraga@quimica.ufsm.br (A.L. Braga).
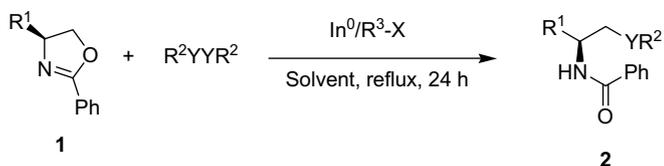
Scheme 1. General procedure for the synthesis of β-chalcogen amides mediated by indium metal.

Table 1
Ring-opening reaction of 2-oxazoline **1a** in the presence of structurally diverse R^3-X
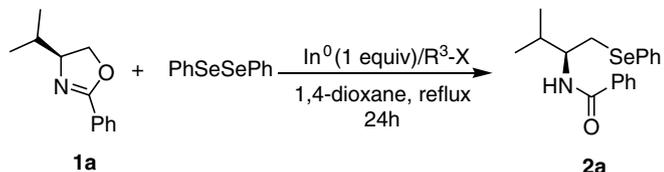
Entry	R^3-X	In^0 (equiv)	Yield (%)[a]
1	*t*-BuCl	1.0	70
2	BnCl	1.0	45
3	BnBr	1.0	90
4	AllylBr	1.0	62
5	*p*-ClPhCH$_2$Cl	1.0	98
6	MeI	1.0	–
7	PhBr	1.0	–
8	*p*-ClPhCH$_2$Cl	0	–
9	*p*-ClPhCH$_2$Cl	0.5	46
10[b]	*p*-ClPhCH$_2$Cl	1.0	15
11[c]	*p*-ClPhCH$_2$Cl	1.0	76

[a] Yields refer to those pure isolated products characterized by spectroscopic methods.
[b] Reaction was carried out at room temperature.
[c] 0.8 equiv. of *p*-ClPhCH$_2$Cl was used.

Table 2
Ring-opening reaction of 2-oxazoline **1a** in the presence of different solvents
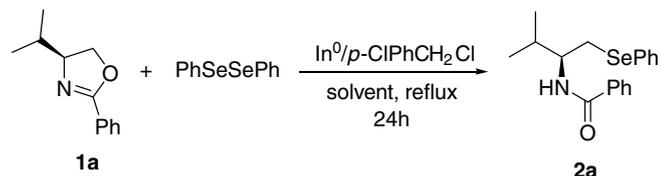
Entry	Solvent	Yield (%)[a]
1	1,4-Dioxane	98
2	DCM	15
3	THF	78
4	Acetonitrile	93
5	DMF	48
6	EtOH	34
7	Toluene	86
8[b]	1,4-Dioxane/H$_2$O	23

[a] Yields refer to those pure isolated products characterized by spectroscopic methods.
[b] 1,4-Dioxane/H$_2$O = 2:1.

yields ranging from 45% to 98% (Table 1, entries 1–5) and the most efficient ring-opening process was achieved when *p*-chloro benzyl chloride was used in the ring-opening process (Table 1, entry 5). On the other hand, no product was observed when the reaction was performed in the presence of a primary alkyl or an aryl halide

(Table 1, entries 6–7). These results are consistent with respect to the stability and reactivity under radical reaction conditions, readily generated from organoyl halides and indium metal [14].

When the reaction was carried out in the absence or in a lower amount of indium metal, the formation of the product was not observed or it was obtained in lower yields (Table 1, entries 8 and 9). The influence of reaction temperature and loading of the corresponding halide were also investigated in the present ring-opening reaction. We could observe a drastic decrease in the yield of the product when the reaction was performed at room temperature, probably due to a decreasing in the efficiency of the ring-opening step in a less energetic system (Table 1, entry 10). The reaction was also evaluated in the presence of 0.8 equivalent of *p*-ClPhCH$_2$Cl. However, a significant decrease in the product yield was observed (Table 1, entry 11).

With these results in hand, the efficiency of the solvent to promote the present process was examined (Table 2). When the reaction was carried out in dichloromethane, quite disappointing results were observed (Table 2, entry 2). By increasing the polarity

Table 3
Ring-opening reaction of 2-oxazolines
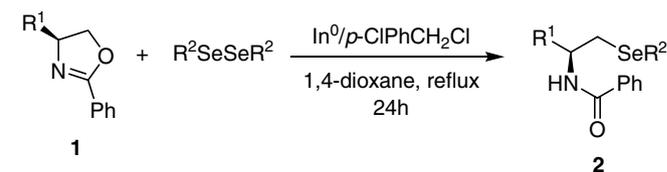
Entry	Oxazoline	R^1	R^2	**2**, Yield (%)[a]
1	**1a**	iPr	Ph	**2a**, 98
2	**1b**	Bn	Ph	**2b**, 94
3	**1c**	Ph	Ph	**2c**, 86
4	**1d**	iBu	Ph	**2d**, 81
5	**1a**	iPr	*p*-ClPh	**2e**, 97
6	**1a**	iPr	*p*-MeOPh	**2f**, 94
7	**1a**	iPr	*o*-MePh	**2g**, 83
8	**1a**	iPr	Bn	**2h**, 88
9	**1a**	iPr	*n*Bu	**2i**, 44
10	**1a**	iPr	Et	**2j**, 58

[a] Yields refer to those pure isolated products characterized by spectroscopic methods.

Table 4
Ring-opening reaction of 2-oxazolines in the presence of sulfur and tellurium nucleophiles
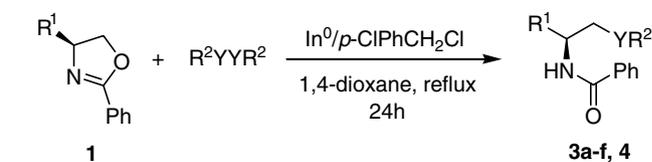
Entry	Oxazoline	R^1	R^2	Y	Product, yield (%)[a]
1	**1a**	iPr	Ph	S	**3a**, 79
2	**1b**	Bn	Ph	S	**3b**, 71
3	**1a**	iPr	*p*-ClPh	S	**3c**, 92
4	**1a**	iPr	*p*-MeOPh	S	**3d**, 94
5	**1a**	iPr	Bn	S	**3e**, 50
6	**1a**	iPr	Et	S	**3f**, 40
7	**1a**	iPr	Ph	Te	**4**, 12

[a] Yields refer to those pure isolated products characterized by spectroscopic methods.
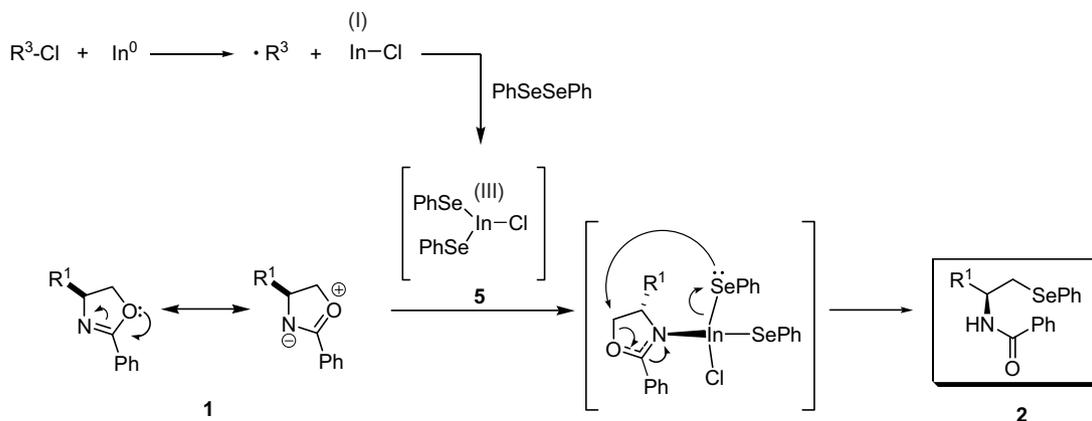
Scheme 2. Ring-opening reaction of 2-oxazoline mediated by indium metal.

and boiling point of the solvent system in comparison with DCM, better yields of **2a** were achieved (Table 2, entries 3–6), probably due to a higher efficiency in the ring-opening step. Toluene was also investigated affording **2a** in very good yield (Table 2, entry 7). However, the best reaction system was achieved using refluxing 1,4-dioxane (Table 2, entry 1) under the standard conditions as established in Table 1. Concerning the high stability of organic indium compounds in water compared with other metals, we also evaluated the reaction in a mixture of dioxane/H_2O, but unfortunately the product was obtained in very low yield (Table 2, entry 8).

After determine the optimum conditions, the present reaction was further expanded to a broader range of oxazolines and diorganoyl dichalcogenides in order to evaluate the scope and limitations of the reaction procedure.

As delineated in Table 3, all the β-seleno amides were obtained in good to excellent yields for the oxazolines studied. The ring-opening reaction permits a series of different lipophilic groups R^1 attached to the oxazoline ring, since the respective products were obtained in up to 98% yield (Table 3, entries 1–4). The present method also tolerates organodiselenides bearing electron-withdrawing (R^2 = p-ClPh) and electron-donating groups (R^2 = p-MeOPh) as well as substituents attached to different positions of the ring (R^2 = o-MePh), furnishing the corresponding chiral organoselenides **2e–g** in excellent yields (Table 3, entries 5–7). Moreover, the reaction was performed with dialkyl diselenides as nucleophilic source of selenium, furnishing the products **2h–j** in moderate to good yields (Table 3, entries 8–10).

Based on the successful approach developed in the preparation of a wide range of chiral β-selenium amides by ring-opening reaction, we decided to extend our studies in order to prepare a series of chiral organochalcogenide compounds using sulfur and tellurium nucleophilic species (Table 4).

Chiral β-thio amides **3a–f** were obtained in yields ranging from 40% to 94% (Table 4, entries 1–6). Once again, the ring-opening reaction tolerates the presence of different R^1 groups presented at the oxazoline ring (Table 4, entries 1 and 2) as well as substituents attached at the aromatic ring of the organosulfur moiety (Table 4, entries 3 and 4) or even the use of dialkyl disulfides as nucleophilic source of sulfur (Table 4, entries 5 and 6). At despite of observed for sulfur and selenium derivatives, β-telluro amide 4 was obtained in very unsatisfactory yield (entry 7).

The reaction pathway for the formation of the β-seleno amides (Scheme 2) is believed to occur first through the single-electron transfer (SET) from indium[14a–d] to alkyl halide with generation of an alkyl radical and indium(I) chloride. The indium salt thus formed reacts with PhSeSePh through oxidative insertion into the

Se–Se bond [15] to generate the complex bis(organoylseleno)chloroindium-(III) 5, responsible for the nucleophilic selenium transferring step. At this point, this indium selenolate promotes the oxazoline ring-opening reaction by the coordination of the indium(III) complex with the nitrogen on the oxazoline moiety given the charged nature of the second resonance structure [16], acting itself as a Lewis acid [10,12]. Because of the double bond character in both C–O and C–N bonds in oxazoline ring, we believe that the intermediate formed between indium (III) complex and oxazoline is non-planar, and this geometric aspect allow the selenium transferring step. By this way, the preparation of β-seleno-amides proceeds through the regio- and chemoselective nucleophilic attack of the phenyl selenide anion at C(5) position of the ring, leads to the C(5)–O(1) bond cleavage and furnishes the desired product, without any loss of enantiomeric purity, as determined by chiral HPLC.

3. Conclusions

In summary, a simple efficient and broadly applicable general method with metallic indium system for the preparation of modular chiral β-chalcogen amides were developed. 2-Oxazolines was used as inexpensive and easily accessible chiral pool starting materials. Features of this method include the following: (i) easily accessible reagents; (ii) stability of indium metal towards air and moisture, its nontoxic, available in pure form and less expensive than indium(I); (iii) excellent yields of β-chalcogen amides were obtained. Studies dealing with the application of this methodology in the synthesis of selenocysteine derivatives and other biologically relevant selenium compounds are currently in progress in our laboratory.

4. Experimental

4.1. General procedures

Melting points are uncorrected. Optical rotations were recorded on a Perkin–Elmer 341 Polarimeter. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with tetramethylsilane as internal standard. High-resolution mass spectra were recorded on a Bruker BioApex 70 eV spectrometer. Column chromatography was performed using Merck Silica Gel (230–400 mesh) following the methods described by Still [17]. Thin layer chromatography (TLC) was performed using Merck Silica Gel GF$_{254}$, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin.

THF was dried over sodium benzophenone ketyl and distilled prior to use. Dichloromethane, 1,4-dioxane and acetonitrile were distilled from phosphorus pentoxide. All other solvents were ACS or HPLC grade unless otherwise noted. Air- and moisture-sensitive reactions were conducted in flame-dried or oven dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry argon. Reagents and solvents were handled using standard syringe techniques. Temperatures above room temperature were maintained by use of a mineral oil bath with an electrically heated coil connected to a Variac controller. Oxazolines were prepared according to the procedures described in the literature [18].

4.2. General procedure for the synthesis of chiral β-chalcogen amides

Indium powder (0.5 mmol, 57.5 mg), *p*-chloro benzyl chloride (0.5 mmol, 80.5 mg), appropriate dichalcogenide (0.5 mmol), appropriate oxazoline (0.5 mmol) and dry 1,4-dioxane (4 mL) were placed in a 25 mL two-necked flask. The resulting suspension was heated at reflux and stirred for 24 h. After cooled to r.t., the mixture was quenched with HCl 1 M, extracted with CH_2Cl_2 and the combined organic fractions were collected, dried over $MgSO_4$ and filtered; the solvent was then removed *in vacuo* yielding crude β-chalcogen amides which were purified by flash chromatography. Spectroscopic data were in good agreement with literature [12,13].

4.2.1. (S)-N-(3-methyl-1-(phenylselanyl)butan-2-yl)benzamide (**2a**)

The enantiomeric purity was determined by HPLC analysis (column Chiralcel-OD, eluent hexane/isopropanol 90:10, flow rate 1.0 ml min^{-1}, *R* isomer, t_R 9.33 min, *S* isomer, t_R 13.47 min and found to be 99.9%; yield 0,322 g (93%); white solid; m.p. 101–103 °C; $[\alpha]_D^{20} = +210$ ($c = 1.0$, CH_2Cl_2); IR (KBr) 3313, 2965, 1633, 1533, 1470, 1178, 733, 693; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60–7.35 (m, 7H); 7.25–7.19 (m, 3H); 6,29 (d, $J = 8.4$, 1H); 4.22 (m, 1H); 3.25–3.23 (m, 2H); 2.05–2.00 (m, 1H); 0.98–0.96 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.04; 134.58; 132.73; 131.17; 129.98; 129.11; 128.32; 126.99; 126.77; 54.74; 31,73; 31.69; 19.33; 18.50; ^{77}Se NMR ($CDCl_3$) δ 251,54; HRMS-ESI *m/z* calc. for $C_{18}H_{21}NOSe + Na^+$ 370.0680, found 370.0677.

Acknowledgements

References

[1] (a) For organoselenium compounds see: K.C. Nicolaou, N.A. Petasis, Selenium in Natural Products Synthesis, CIS, Inc., Pennsylvania, 1984. and references therein;
(b) D.L. Klayman, W.H.H. Günter, Organoselenium Compounds: Their Chemistry and Biology, Wiley, New York, 1973;
(c) A.L. Braga, A. Reckziegel, C.C. Silveira, J.V. Comasseto, Synth. Commun. 24 (1994) 1165;
(d) . For organosulfur compounds, see:S.R. Dabbaka, P. Vogel, Angew. Chem., Int. Ed. Engl. 44 (2005) 7674. and references therein.
[2] (a) For selenium-containing chiral ligands, see: T. Wirth, Angew. Chem., Int. Ed. Engl. 39 (2000) 3740;
(b) A.L. Braga, D.S. Lüdtke, F. Vargas, Curr. Org. Chem. 10 (2006) 1921;
(c) A.L. Braga, D.S. Lüdtke, F. Vargas, R.C. Braga, Synlett (2006) 1453;
(d) . For sulfur-containing chiral ligands, see:J.C. Anderson, R. Cubbon, M. Harding, D.S. James, Tetrahedron: Asymmetr. 9 (1998) 3461;
(e) M. Mellah, A. Voituriez, E. Schulz, Chem. Rev. 107 (2007) 5133;
(f) H. Pellissier, Tetrahedron 63 (2007) 1297;
(g) A.L. Braga, F.Z. Galetto, O.E.D. Rodrigues, C.C. Silveira, M.W. Paixão, Chirality 20 (2008) 839.
[3] (a) G. Heppesh, J. Martens, K. Praefcke, H. Simon, Angew. Chem., Int. Ed. Engl. 16 (1977) 318;
(b) R. Cristiano, F. Ely, H. Gallardo, Liq. Cryst. 32 (2005) 15;
(c) R. Cristiano, E. Westphal, I.H. Bechtold, A.J. Bortoluzzi, H. Gallardo, Tetrahedron 63 (2007) 2851;
(d) D.R. Gamota, P. Brazis, K. Kalyanasundaram, J. Zhang, Printed Organic and Molecular Electronics, Kluwer Academic Publishers, New York, 2004;
(e) V. Balzani, A. Credi, F. M Raymo, J.F. Stoddart, Angew. Chem., Int. Ed. 39 (2000) 3348;
(f) K.L. Woon, M.P. Aldred, P. Vlachos, G.H. Mehl, T. Stirner, S.M. Kelly, M. O'Neill, Chem. Mater. 18 (2006) 2311;
(g) H. Gallardo, C. Zucco, L. Da Silva, Mol. Cryst. Liq. Cryst. 373 (2002) 181;
(i) J. Yamada, H. Akutsu, H. Nishikawa, K. Kikuchi, Chem. Rev. 104 (2004) 5057.
[4] (a) G. Mugesh, W.-W. du Mont, H. Sies, Chem. Rev. 101 (2001) 2125;
(b) C.W. Nogueira, G. Zeni, J.B.T. Rocha, Chem. Rev. 104 (2004) 6255;
(c) J. Perottoni, O.E.D. Rodrigues, M.W. Paixão, G. Zeni, L.P. Lobato, A.L. Braga, J.B.T. Rocha, T. Emanuelli, Food Chem. Toxicol. 42 (2004) 17.
[5] (a) A.L. Braga, O.E.D. Rodrigues, M.W. Paixão, H.R. Appelt, C.C. Silveira, D.P. Bottega, Synthesis (2002) 2338;
(b) A.L. Braga, M.W. Paixão, D.S. Lüdtke, C.C. Silveira, O.E.D. Rodrigues, Org. Lett. 5 (2003) 2635;
(c) A.L. Braga, S.J.N. Silva, D.S. Lüdtke, R.L. Drekener, C.C. Silveira, J.B.T. Rocha, L.A. Wessjohann, Tetrahedron Lett. 43 (2002) 7329;
(d) A.L. Braga, M.W. Paixão, G. Marin, Synlett (2005) 1975;
(e) A.L. Braga, D.S. Lüdtke, J.A. Sehnem, E.E. Alberto, Tetrahedron 61 (2005) 11664;
(f) C. Santi, T. Wirth, Tetrahedron: Asymmetr. 10 (1999) 1019;
(g) T. Wirth, Tetrahedron Lett. 36 (1995) 7849;
(h) J. Sprinz, M. Kiefer, G. Helmchen, M. Reggelin, G. Huttner, O. Walter, L. Zsolnai, Tetrahedron Lett. 35 (1994) 1523;
(i) M. Zielinska-Blajet, R. Siedlecka, J. Skarzewski, Tetrahedron: Asymmetr. 18 (2007) 131.
[6] (a) I. Andreadou, W.M.P.B. Menge, J.N.M. Commandeur, E.A. Worthington, N.P.E. Vermeulen, J. Med. Chem. 39 (1996) 2040;
(b) M. Sakakibara, K. Katsumata, Y. Watanabe, T. Toru, Y. Ueno, Synthesis (1992) 377;
(c) K.K. Bhasin, N. Singh, R. Kumar, D.G. Deepali, S.K. Metha, T.M. Klapoetke, M.J. Crawford, J. Organomet. Chem. 689 (2004) 3327;
(d) D. Crich, D. Grant, J. Org. Chem. 70 (2005) 2384.
[7] (a) O.S. do Rego Barros, E.S. Lang, C.A.F. de Oliveira, C. Peppe, G. Zeni, Tetrahedron Lett. 43 (2002) 7921;
(b) C. Peppe, E.S. Lang, G.N. Ledesma, L.B. de Castro, O.S. do Rego Barros, P.D. Mello, Synlett (2005) 3091.
[8] B.C. Ranu, A. Das, Adv. Synth. Catal. 347 (2005) 712.
[9] O.S. do Rego Barros, A.B. de Carvalho, E.S. Lang, C. Peppe, Lett. Org. Chem. 1 (2004) 43.
[10] A.L. Braga, P.H. Schneider, M.W. Paixão, A.M. Deobald, C. Peppe, D.P. Bottega, J. Org. Chem. 71 (2006) 4305.
[11] (a) B.C. Ranu, T. Mandal, S. Samanta, Org. Lett. 5 (2003) 1439;
(b) B.C. Ranu, T. Mandal, J. Org. Chem. 69 (2004) 5793;
(c) B.C. Ranu, Eur. J. Org. Chem. (2000) 2343;
(d) A.L. Braga, P.H. Schneider, M.W. Paixão, A.M. Deobald, Tetrahedron Lett. 47 (2006) 7195.
[12] A.L. Braga, F. Vargas, F.Z. Galetto, M.W. Paixão, R.S. Schwab, P.S. Taube, Eur. J. Org. Chem. (2007) 5327.
[13] (a) A.L. Braga, F. Vargas, J.A. Sehnem, R.C. Braga, J. Org. Chem. 70 (2005) 9021;
(b) F. Vargas, J.A. Sehnem, F.Z. Galetto, A.L. Braga, Tetrahedron 64 (2008) 392.
[14] (a) P. Cintas, Synlett (1995) 1087;
(b) C.-J. Li, Tetrahedron 52 (1996) 5643;
(c) C.-J. Li, T.H. Chan, Tetrahedron 55 (1999) 11149;
(d) B.C. Ranu, Eur. J. Org. Chem. (2000) 2347;
(e) D.O. Jang, D.H. Cho, Synlett (2002) 631;
(f) W. Munbunjong, E.H. Lee, W. Chavasiri, D.O. Jang, Tetrahedron Lett. 46 (2005) 8769;
(g) M. Ueda, H. Miyabe, A. Nishimura, O. Miyata, Y. Takemoto, T. Naito, Org. Lett. 5 (2003) 3835;
(h) M. Sugi, D. Sakuma, H. Togo, J. Org. Chem. 68 (2003) 7629;
(i) H. Miyabe, M. Ueda, A. Nishimura, T. Naito, Org. Lett. 4 (2002) 131;
(j) H. Miyabe, A. Nishimura, M. Ueda, T. Naito, Chem. Commun. (2002) 1454;
(k) T. Huang, C.C.K. Keh, C.-J. Li, Chem. Commun. (2002) 2440.
[15] C. Peppe, D.G. Tuck, Can. J. Chem. 62 (1984) 2798.
[16] H.R. Hoveyda, V. Karunaratne, S.J. Rettig, C. Orvig, Inorg. Chem. 31 (1992) 5408.
[17] W.C. Still, M. Kahn, A. Mitra, J. Org. Chem. 43 (1978) 2923.
[18] (a) T.G. Gant, A.I. Meyers, Tetrahedron 50 (1994) 2297;
(b) A.L. Braga, R.M. Rubim, H.S. Schrekker, L.A. Wessjohann, M.W.G. de Bolster, G. Zeni, J.A. Sehnem, Tetrahedron: Asymmetr. 14 (2003) 3291.