Available online at www.sciencedirect.com
ScienceDirect
Journal of Organometallic Chemistry 692 (2007) 545–549
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Efficient synthetic protocol for substituted guanidines via copper(I)-mediated intermolecular amination of isothiourea derivatives

Hitoshi Ube, Daisuke Uraguchi, Masahiro Terada *

Department of Chemistry, Graduate School of Science, Tohoku University, Aoba-ku, Sendai 980-8578, Japan

Received 21 April 2006; received in revised form 2 June 2006; accepted 2 June 2006
Available online 3 September 2006

Abstract

Amination of *S*-methyl-*N*,*N*′-bis-Boc-isothiourea with either primary or sterically hindered secondary amines promoted by copper(I) chloride and K_2CO_3 gave *N*,*N*′-bis-Boc protected guanidines in good to excellent yields under mild reaction conditions.

Keywords: Copper(I); Guanidine; Thiourea; Isothiourea; Amination

1. Introduction

Guanidine is a ubiquitous element in natural products and plays a key role in many biological activities. In peptides, guanidine, a residue of arginine, exists in the protonated form as guanidinium ion, which functions as an efficient recognition moiety of anionic substrates such as carboxylate, phosphate, and nitronate functionalities [1]. The guanidinium ion also participates in numerous enzymatic transformations, as it is able to adopt a transition state assembly with the substrates to reduce the activation energy or to stabilize anionic intermediates, and is able to orient specific substrates based on their electronic properties [2]. These characteristics of the guanidinium ion originate from electrostatic attraction and the formation of two parallel hydrogen bonds. In addition to their biological role, guanidine derivatives are widely utilized in synthetic organic chemistry as strong bases—a property that results from the resonance stability of their conjugated acids [3]. It is anticipated that the strong basic character of guanidine derivatives coupled with their ability to act as recognition elements will lend them to application as asymmetric base catalysts. In fact, we recently demonstrated enantioselective 1,4-addition reactions catalyzed by a novel chiral guanidine base catalyst (**1**) bearing axial chirality [4] (Fig. 1). During the course of the preparation of **1**, we established an efficient synthetic protocol for guanidine derivatives via the copper(I)-mediated intermolecular amination of isothiourea derivatives [5]. The method is operationally simple, allows the reaction to proceed under mild conditions, and dose not require use of highly toxic mercury(II) salts that are commonly used for the transformation of thiourea derivatives to guanidine moieties via carbodiimide intermediates [6]. Herein we disclose the generality of the intermolecular amination of (iso)thiourea derivatives mediated by copper(I) salts to offer an efficient and promising protocol for the preparation of guanidine derivatives.

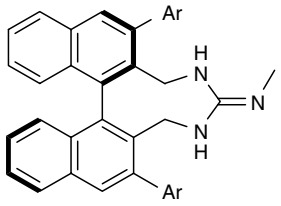
2. Results and discussion

2.1. Amination of isothiourea leading to axially chiral guanidine

In our continuous effort directed toward the development of efficient chiral guanidine base catalysts, we initially examined the direct amination of axially chiral thiourea derivative (**2**) with a binaphthyl backbone. However, the instability of thiourea (**2**) made the desired transformation difficult under currently available dehydrosulfurization

* Corresponding author. Tel./fax: +81 22 795 6602.
E-mail address: mterada@mail.tains.tohoku.ac.jp (M. Terada).

0022-328X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2006.06.046



(R)-**1** (Ar=3,5-(3,5-t-Bu_2Ph)$_2$Ph)

Fig. 1. Novel axially chiral guanidine base catalyst (**1**).

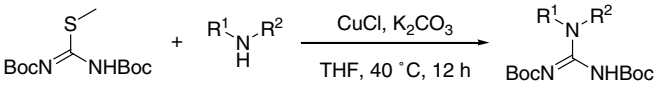
conditions [7]. Therefore, we turned our attention to the utilization of more stable isothiourea derivatives (**3**), which are readily obtained by the methylation of **2** with methyl iodide, as the precursor of guanidine (**1**). At the outset, we searched for a thiophilic metal salt that is not highly toxic and efficiently promotes the intermolecular amination of isothiourea derivatives (**3**) (Scheme 1). We employed $NiBr_2$ salt as a promoter of the reaction of isothiourea (**3**) with methylamine hydrochloride in the presence of an organic or inorganic base [8]. However, the desired guanidine product (**1**) was obtained in low to moderate yield, even though the reaction mixtures were exposed to prolonged periods (80 °C, 40 h). In the synthesis of monosubstituted guanidine by reacting methylisothiourea intermediate with a primary amine, Keszler and co-workers employed copper(II) carbonate to promote the displacement reaction of the thiomethyl moiety, leading to guanidine derivatives in moderate yields [5]. Stimulated by their report, we employed a highly thiophilic copper(I) salt as the promoter of the amination of isothiourea (**3**) in the presence of K_2CO_3, because the advantages of using copper(I) salt for the amination of thiourea derivatives were reported by Senanayake and co-workers [9]. The reaction of isothiourea (**3**) with methylamine hydrochloride proceeded well within 6 h even at 60 °C and the corresponding guanidine (**1**) was isolated in moderate yield. The result obviously indicates that copper(I) salts function as an efficient promoter of the amination of *S*-methylisothiourea to produce guanidine derivatives.

2.2. Amination of isothiourea and thiourea

Next, we demonstrated the generality of the present copper(I)-salt-mediated amination of isothiourea with variety of amines (**5**) including sterically hindered secondary ones and less nucleophilic anilines. The initial experiment was performed with *S*-methyl-*N*,*N*′-bis-Boc-isothiourea (**4**) and diisopropyl amine (**5a**) under the influence of 2 equivalent of CuI and K_2CO_3 in THF at 40 °C for 9 h. As expected, copper(I) iodide worked well to yield guanidine derivative (**6a**) in excellent conversion (>90%) even when sterically hindered secondary amine (**5a**) was used. Unfortunately, however, guanidine (**6a**) thus obtained was contaminated by inseparable impurities that might have arisen from the counter anion of copper(I) salts, iodide. We therefore changed the counter anion from iodide to chloride. To our delight, in the presence of CuCl, guanidine (**6a**) was obtained in nearly quantitative yield and isolated in pure form by column chromatography (Table 1, entry 1).

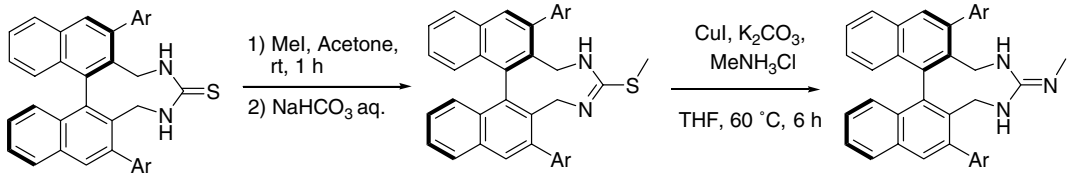
The present copper(I) chloride method is applicable to a broad range of amines including sterically hindered ones. As shown in Table 1, primary amines, either α-mono- or di-substituted amines (**5b–d**), were efficiently transformed into the corresponding guanidines (**6b–d**) (entries 2–4). It is noteworthy that the sterically hindered *tert*-butylamine (**5d**) also gave product (**6d**) in excellent yield (entry 4). As highlighted in entry 5, excellent yield was obtained irrespective of the steric demand of the amines used. Thus, the present method was applicable to the sterically congested secondary amine, 2,2,6,6-tetramethylpiperidine (**5e**). Less nucleophilic anilines (**5f**,**g**) were also useful reactants in this copper(I)-salt-mediated amination and aromatic substituted guanidines were obtained in acceptable yields. It

Table 1
Amination of thiourea mediated by copper(I) chloride



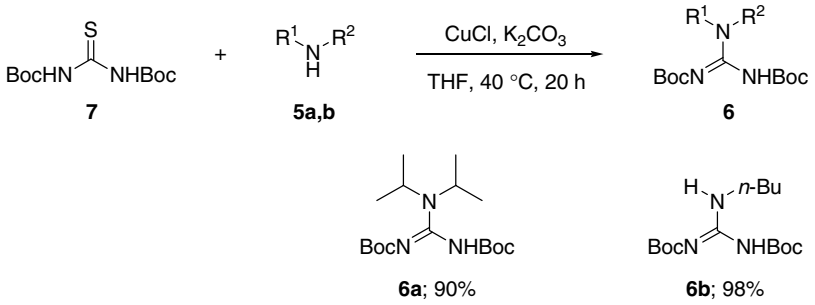
4 **5a-g** **6a-g**

Entry	Amine	Guanidine	Yield (%)
1	Diisopropylamine (**5a**)	**6a**	98
2	*n*-Butylamine (**5b**)	**6b**	95
3	Cyclohexylamine (**5c**)	**6c**	87
4	*t*-Butylamine (**5d**)	**6d**	98
5	2,2,6,6-Tetramethylpiperidine (**5e**)	**6e**	95
6	*o*-Anisidine (**5f**)	**6f**	77
7	4-Nitroaniline (**5g**)	**6g**	64



2 (Ar=3,5-(3,5-*t*-Bu_2Ph)$_2$Ph) **3** **1** 58% from **2**

Scheme 1.



Scheme 2.

should be noted that desired guanidine (**6g**) was obtained in moderate yield even by using electron-withdrawing nitro group substituted aniline (**5g**). Although the precise reaction mechanism has not been clarified yet, the reaction presumably proceeded through the copper–amide complex derived from copper(I) salts and bis-Boc-isothiourea (**4**), because, in the absence of amines (**5**), neither the dehydrosulfurization product, and thus the carbodiimide intermediate, nor other unknown products were detected by TLC analysis during the course of this experiment.

The present method is also applicable to the reaction of *N*,*N*′-bis-Boc-thiourea (**7**) with either primary or secondary amine (**5a**,**b**) (Scheme 2). In either case, the corresponding guanidines (**6a**,**b**) were obtained in excellent yields.

3. Conclusion

In summary, we have demonstrated an efficient synthetic protocol for substituted guanidines using the Copper(I)-mediated intermolecular amination of *S*-methyl-*N*,*N*′-bis-Boc-isothiourea (**4**) and *N*,*N*′-bis-Boc-thiourea (**7**). The elimination of highly toxic metal salts as well as the mild reaction conditions to obtain bis-Boc protected guanidines from a variety of primary/secondary amines and anilines would benefit the preparation of related compounds.

4. Experimental

Infrared spectra were recorded on a Shimazu FTIR-8200PC spectrometer. ^{1}H NMR spectra were recorded on a JEOL GSX-270 (270 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, br = broad, m = multiplet) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL GSX-270 (67.8 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance as the internal standard. Mass spectra analysis was performed at the Instrumental Analysis Center for Chemistry, Graduate School of Science, Tohoku University. Analytical thin-layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was performed on silica gel 60N (spherical, neutral, 100–210 μm; Kanto Chemical Co., Inc.). All reactions were carried out under a nitrogen (N_2) atmosphere in dried glassware. All substrates were purified by column chromatography or distillation prior to use. THF was supplied from Kanto Chemical Co., Inc. as ''Dehydrated solvent system''. Other solvents and other simple chemicals were purchased and used as such. *S*-methyl-*N*,*N*′-bis(*tert*-butoxycarbonyl)isothiourea (**4**) and *N*,*N*′-bis(*tert*-butoxycarbonyl)thiourea (**7**) were prepared according to the literature procedure [10,11], respectively.

4.1. Synthesis of axially chiral guanidie (*1*)

To a solution of thiourea (**2**) (126 mg, 0.10 mmol) in acetone (1 mL) was added MeI (12.5 μL, 0.3 mmol) and the solution was stirred for 1 h at room temperature. The reaction was quenched by saturated Na_2CO_3 aq., and the organic phase was separated. The solvents were washed with brine, and dried over anhydrous Na_2SO_4. After removal of solvents, crude isothiourea (**3**) was obtained, that was used for subsequent reaction without further purification. To a mixture of crude isothiourea (**3**), CuI (40.0 mg, 0.21 mmol), K_2CO_3 (207 mg, 1.5 mmol) in THF, (4 mL), $MeNH_3Cl$ (67.5 mg, 1.0 mmol) was added and stirred for 6 h at 60 °C. After cooling to room temperature, the reaction was quenched by 1 N $NaHSO_4$ aqueous solution and extracted with ethyl acetate. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. After being concentrated, the guanidine salt was purified by column chromatography (hexane/AcOEt = 4/1 to 1/1 as eluent). The guanidinium salt was neutralized by Amberite IRA-400 (OH^- form, EtOH as eluent) to give guanidine (**1**) (73 mg, 0.058 mmol, 58% (2 steps)) as white solid; $[\alpha]_D^{34}$ +42.9 (*c* 0.29, $CHCl_3$); ^{1}H NMR (270 MHz, methanol-d_4) δ 1.36 (72H, s), 2.18 (3H, s), 4.26 (2H, d, J = 15.3 Hz), 4.56 (2H, d, J = 15.3 Hz), 7.21 (2H, d, J = 8.1 Hz), 7.34 (2H, ddd, J = 8.1, 6.8, 1.4 Hz), 7.49 (4H, t, J = 1.9 Hz), 7.52 (8H, d, J = 1.9 Hz), 7.55 (2H, ddd, J = 8.4, 6.8, 1.1 Hz), 7.70 (4H, d, J = 1.6 Hz), 7.83 (2H, t, J = 1.6 Hz), 8.06 (2H, d, J = 8.4 Hz), 8.12 (2H, s); ^{13}C NMR (67.8 MHz, methanol-d_4/$CDCl_3$ = 2/1) δ 31.9, 35.6, 45.2, 122.5, 122.7,

126.7, 127.4, 128.0, 128.4, 129.0, 131.0, 133.5, 133.8, 135.6, 135.8, 141.1, 141.3, 143.0, 144.4, 152.3, 161.5; IR (KBr): 3449, 3057, 2963, 2903, 2866, 1655, 1649, 1585, 1475, 1362, 1248, 1202, 1026, 866, 748, 714 cm^{-1}; HRMS (ESI) calcd for $C_{92}H_{110}N_3$ ($[M+H]^+$) 1256.8694. Found: 1256.8700.

4.2. General procedure for amination of S-methyl-N,N′-bis-Boc-isothiourea

To a suspension of K_2CO_3 (55.3 mg, 0.4 mmol), CuCl (20.8 mg, 0.21 mmol), and *S*-methyl-*N*,*N*′-bis-Boc-isothiourea (**4**) (29.0 mg, 0.1 mmol) in THF (0.5 mL), was added *n*-butylamine (**5a**) (19.8 μL, 0.2 mmol). The resulting mixture was stirred for 12 h at 40 °C. After cooling to room temperature, solids were removed through a pad of Celite, and washed with ethyl acetate. The solution was washed with saturated NH_4Cl aq., saturated $NaHCO_3$ aq., and brine. The organic phase was dried over anhydrous Na_2SO_4 and filtered. After removal of solvents, residue was purified by column chromatography to afford **6b** (30.0 mg, 95%).

4.3. General procedure for amination of N,N′-bis-Boc-thiourea

To a dried glassware were weighted K_2CO_3 (55.3 mg, 0.4 mmol), CuCl (20.8 mg, 0.21 mmol), and *N*,*N*′-bis(*tert*-butoxycarbonyl)thiourea (**7**) (27.6 mg, 0.1 mmol), and the resulting mixture was dissolved in THF (0.5 mL). After turning the suspension into yellow, diisopropylamine (28 μL, 0.2 mmol) was added to the mixture, and the solution was heated to 40 °C for 20 h. After cooling to room temperature, the reaction was quenched by saturated NH_4Cl aq., and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and filtered through a pad of Celite. After removal of solvents, the residue was purified by column chromatography (hexane/AcOEt = 20:1) to afford guanidine (**6a**) (30.8 mg, 90% yield).

4.4. Spectra data for N,N′-bis-Boc-guanidines

4.4.1. N,N′-Bis-Boc-N″,N″-diisopropylguanidine (*6a*)

^1H NMR (270 MHz, $CDCl_3$): δ 1.32 (12H, d, $J = 6.8$ Hz), 1.47 (18H, m), 3.92 (2H, sept., $J = 7.8$, 3.8 Hz), 8.31 (1H, br d, $J = 7.8$ Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 20.8, 28.2, 48.5, 78.8 (br), 81.2 (br), 151.6, 161.8 (br); IR (KBr): 3366, 2980, 2932, 1744, 1655, 1603, 1132 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{34}N_3O_4$ ($[M+H]^+$) 344.2544. Found: 344.2545.

4.4.2. N,N′-Bis-Boc-N″-n-butylguanidine (*6b*)

^1H NMR (270 MHz, $CDCl_3$): δ 0.92 (3H, t, $J = 7.2$ Hz), 1.30–1.60 (22H, m), 3.40 (2H, br q, $J = 6.4$ Hz), 8.28 (1H, br s) 11.50 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 13.8, 20.1, 28.0, 28.3, 31.0, 40.7, 79.2, 82.9, 153.3, 155.3, 156.1, 163.7; IR (KBr): 3348, 2981, 2934, 2876, 1717, 1638, 1616, 1570, 1128, 1053, 812, 772 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{30}N_3O_4$ ($[M+H]^+$) 316.2231. Found: 316.2233.

4.4.3. N,N′-Bis-Boc-N″-cyclohexylguanidine (*6c*)

^1H NMR (270 MHz, $CDCl_3$): δ 1.17–1.80 (27H, m), 1.90–1.95 (2H, m), 4.03 (1H, dq, $J = 7.8$, 3.8 Hz), 8.31 (1H, br d, $J = 7.8$ Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 24.4, 25.5, 28.1, 28.3, 32.8, 48.5, 79.0, 82.8, 153.3, 155.3, 163.9; IR (KBr): 3323, 2982, 2934, 2856, 1732, 1653, 1616, 1140, 758 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{32}N_3O_4$ ($[M+H]^+$) 342.2387. Found: 342.2386.

4.4.4. N,N′-Bis-Boc-N″-t-butylguanidine (*6d*)

^1H NMR (270 MHz, $CDCl_3$): δ 1.43 (9H, s), 1.47 (18H, s), 8.26 (1H, br s), 11.4 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 28.1, 28.4, 28.9, 52.0, 78.4, 82.6, 153.4, 154.4, 163.5; IR (KBr): 3323, 2986, 2932, 1722, 1647, 1618, 1163, 768 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{30}N_3O_4$ ($[M+H]^+$) 316.2231. Found: 316.2232.

4.4.5. 1-(N,N′-Bis(t-butoxycarbonyl)carboxamidino)-2,2,6,6-tetramethylpiperidine (*6e*)

^1H NMR (270 MHz, $CDCl_3$): δ 1.39 (12H, m), 1.45 (9H, s), 1.49 (1H, s), 1.60–1.72 (6H, m), 6.83 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 15.6, 28.0, 28.1_6, 28.2_2, 29.5, 37.7, 56.8, 79.3, 81.4, 150.3, 150.8, 160.1; IR (KBr): 3256, 2982, 2934, 1744, 1701, 1610, 1499, 1151, 1047 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{38}N_3O_4$ ($[M+H]^+$) 384.2857. Found: 384.2859.

4.4.6. N,N′-Bis-Boc-N″-(2-methoxyphenyl)guanidine (*6f*)

^1H NMR (270 MHz, $CDCl_3$): δ 1.54 (18H, br s), 7.85 (2H, d, $J = 9.0$ Hz), 4.03 (1H, d, $J = 9.0$ Hz), 10.77 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 28.0, 80.4, 84.5, 121.2, 124.8, 142.9, 143.6, 153.1, 163.0; IR (KBr): 3265, 3001, 270, 2934, 1736, 1643, 1618, 1599, 1580, 1406, 1128, 1059, 735 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{28}N_3O_5$ ($[M+H]^+$) 366.2023. Found: 366.2021.

4.4.7. N,N′-Bis-Boc-N″-(4-nitrophenyl)guanidine (*6g*)

^1H NMR (270 MHz, $CDCl_3$): δ 1.54 (18H, br s), 7.85 (2H, d, $J = 9.0$ Hz), 4.03 (1H, d, $J = 9.0$ Hz), 10.77 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 28.0, 80.4, 84.5, 121.2, 124.8, 142.9, 143.6, 153.1, 163.0; IR (KBr): 3134, 2978, 2932, 1719, 1653, 1578, 1406, 1246, 1151, 852 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{25}N_4O_6$ ($[M+H]^+$) 381.1769. Found: 381.1768.

Acknowledgement

This work was partially supported by Grants-in-Aid for Scientific Research (No. 16033210 "Reaction Control of Dynamic Complexes") from the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Sumitomo Foundation.

References

[1] C.L. Hannon, E.V. Anslyn, Bioorganic Chemistry Frontiers, vol. 3, Springer-Verlag, Berlin, 1993;
F.P. Schmidtchen, M. Berger, Chem. Rev. 97 (1997) 1609–1646.

[2] A. Fersht, Enzyme Structure and Mechanism, Freeman, San Francisco, 1985;
J. Kraut, Science 242 (1988) 533–540;
H. Dugas, Bioorganic Chemistry. A Chemical Approach to Enzyme Action, third ed., Springer, New York, 1996.

[3] For a review, see: Y. Yamamoto, S. Kojima, in: S. Patari, Z. Rappoport (Eds.), The Chemistry of Amidines and Imidates, vol. 2, Wiley, New York, 1991.

[4] M. Terada, H. Ube, Y. Yaguchi, J. Am. Chem. Soc. 128 (2006) 1454–1455.

[5] Copper(II) carbonate promoted the amination of isothiourea with primary amine. J. Wityak, S.J. Gould, S.J. Hein, D.A. Keszler, J. Org. Chem. 52 (1987) 2179–2183;
The intermolecular amination of *N*-cyanothiourea using CuCl was reported. See: T. Suyama, T. Iwaoka, T. Yatsurugi, E. Ichikawa, Nihonkagakukaishi (1986) 1192–1195.

[6] Selected recent examples of guanidine synthesis from (iso)thiourea using mercury(II) salts. See: J. Shimokawa, T. Ishiwata, K. Shirai, H. Koshino, A. Tanatani, T. Nakata, Y. Hashimoto, K. Nagasawa, Chem. Eur. J. 11 (2005) 6878–6888;
U. Scheffer, A. Strick, V. Ludwig, S. Peter, E. Kalden, M.W. Gobel, J. Am. Chem. Soc. 127 (2005) 2211–2217;
C. Dahmen, J. Auernheimer, A. Meyer, A. Enderle, S.L. Goodman, H. Kessler, Angew. Chem., Int. Ed. 43 (2004) 6649–6652.

[7] Thiourea (**2**) can be stored under refrigeration, whereas it was gradually decomposed into unknown mixtures at room temperature.

[8] L. Bhat, G.I. Georg, US 6100428 A 20000808 Patent.

[9] X. Wang, L. Zhang, Y. Xu, D. Krishnamurthy, C.H. Senanayake, Tetrahedron Lett. 45 (2004) 7167–7170.

[10] R.J. Bergeron, J.S. McManis, J. Org. Chem. 52 (1987) 1700–1703.

[11] A. Exposito, M. Fernandez-Suarez, T. Iglesias, L. Munoz, R. Riguera, J. Org. Chem. 66 (2001) 4206–4213.