ELSEVIER

Available online at www.sciencedirect.com
ScienceDirect

Tetrahedron Letters 47 (2006) 8771–8775

Tetrahedron
Letters

The first example of γ-chloromagnesio γ-lactones: their generation from γ-tolylsulfinyl γ-lactones with isopropylmagnesium chloride, stability, and reaction with electrophiles

Shimpei Sugiyama, Hitomi Shimizu and Tsuyoshi Satoh*

Department of Chemistry, Faculty of Science, Tokyo University of Science, Ichigaya-funagawara-machi,
Shinjuku-ku, Tokyo 162-0826, Japan

Received 12 September 2006; revised 28 September 2006; accepted 29 September 2006

Abstract—The treatment of γ-lactones having a sulfinyl group at the γ-position, which were synthesized from 1-chlorovinyl *p*-tolyl sulfoxides with lithium enolate of carboxylic esters, with isopropyl magnesium chloride in THF at −78 °C gave γ-chloromagnesio γ-lactones by the sulfoxide–magnesium exchange reaction in high yields. The generated γ-chloromagnesio γ-lactones were found to be stable at below −50 °C for at least 2 h. The reaction of these γ-chloromagnesio γ-lactones with electrophiles and the stereochemistry of the reactions were investigated.

Organomagnesium compounds, the Grignard reagents, are one of the most important reagents for the formation of a carbon–carbon bond with carbonyl compounds or alkyl halides.[1] As the carbon–magnesium bond is highly reactive, it has long been generally recognized that the presence of electrophilic functional groups, such as esters, nitriles, and ketones, cannot be compatible in the Grignard reagents. However, recently, the preparation of functionalized Grignard reagents and their properties have been studied and reported by Knochel[2] and some other chemists.

The functionalized Grignard reagents are those for functionalized arylmagnesium reagents,[3] polyfunctional heteroaryl-magnesium reagents,[4] functionalized alkenylmagnesium reagents.[5] These functionalized magnesium reagents have ester, nitrile, halogen, and amide as the functional groups. However, those functional groups are usually present directly on the aromatic ring or on the sp^2-carbon, which means that there is no acidic α-hydrogen, although some exceptions are also reported.[6]

In previous studies, we have found that various ester lithium enolates reacted with 1-chlorovinyl *p*-tolyl sulfoxides **1** to give adducts **2** in high yields. Furthermore, we also reported a novel method for the synthesis of lactones having a sulfinyl group at γ-position **3** from adducts **2** in two steps in high overall yields.[7] We thought that if Grignard reagents react with the sulfinyl group in lactones **3**, γ-chloromagnesio γ-lactone **4** could be generated via sulfoxide–magnesium exchange reaction.[8] We also anticipated that the continuous reaction of **4** with various electrophiles would afford lactones **5** having a carbon–carbon bond at the γ-position. Herein, we report the generation of the first example of γ-chloromagnesio γ-lactones and investigation of their property and the reaction with electrophiles (Scheme 1).

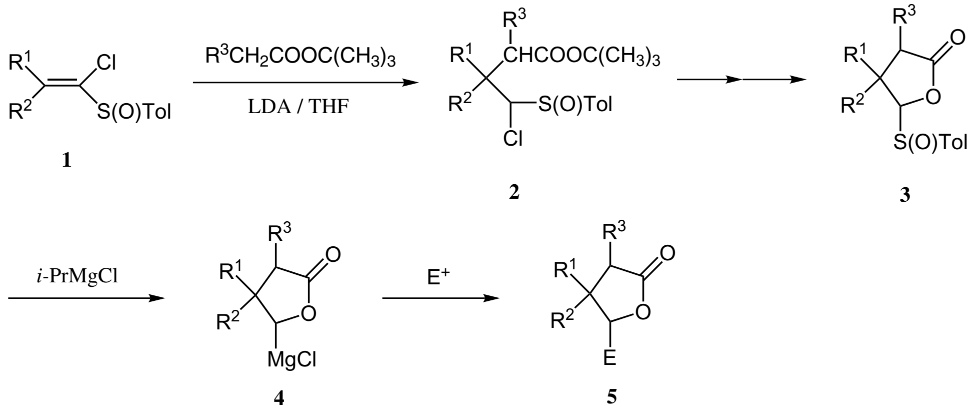
First, 1-chlorovinyl *p*-tolyl sulfoxide **6** was selected as a representative example of the 1-chlorovinyl *p*-tolyl sulfoxide in this study and was synthesized from ethylene glycol in five steps in a 54% overall yield (Scheme 2). Lithium ester enolate of *tert*-butyl 4-phenylbutyrate was generated in THF at −78 °C and to this solution was added 1-chlorovinyl *p*-tolyl sulfoxide **6**. The desired addition reaction took place within 5 min to afford adduct **7** in a quantitative yield. Adduct **7** has three chiral centers and theoretically four diastereomers would be

---

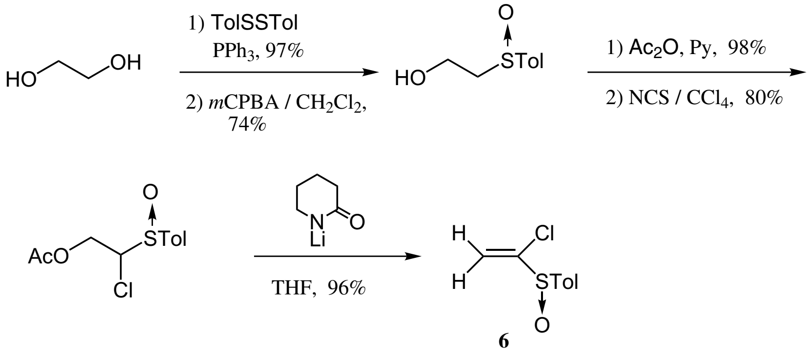
Keywords: Sulfoxide; Sulfoxide–magnesium exchange; Grignard reagents; γ-Chloromagnesio γ-lactone; γ-Lactone.

* Corresponding author. Tel.: +81 3 5228 8272; fax: +81 3 3235 2214; e-mail: tsatoh@ch.kagu.tus.ac.jp

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.09.165



Scheme 1.



Scheme 2.

produced; however, adduct **7** was obtained as a single diastereomer.[9]

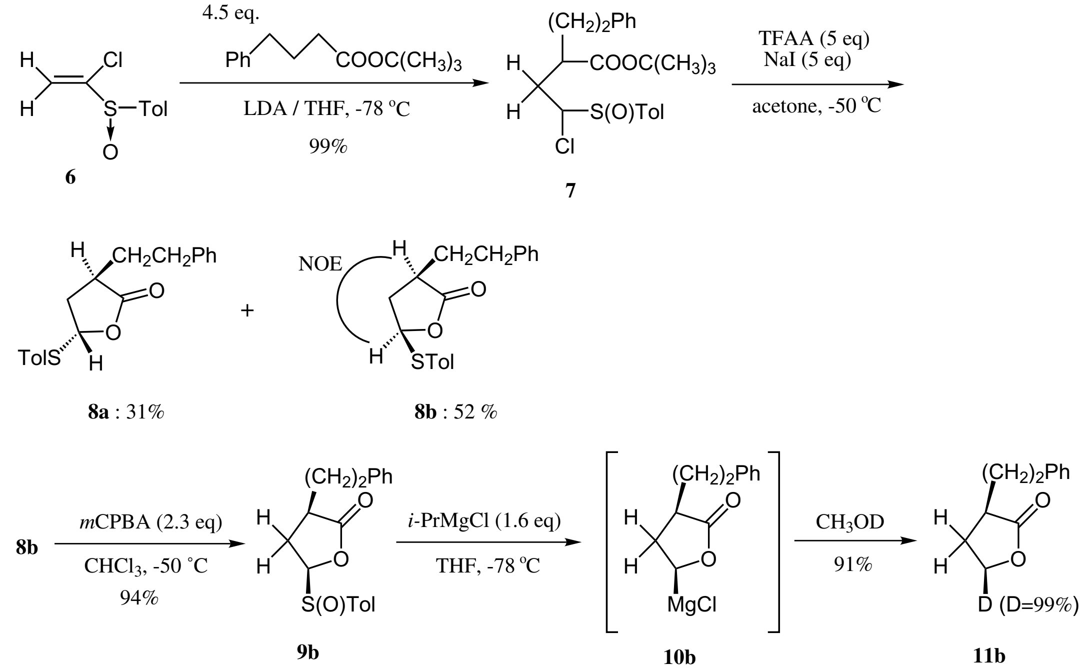
Next, trifluoroacetic anhydride (TFAA) was added to a solution of adduct **7** in the presence of NaI in acetone to give γ-lactone **8** having a tolylsulfanyl group at the γ-position (Scheme 3).[7] γ-Lactone **8** has two chiral centers and, theoretically, two diastereomers are possible. On silica gel TLC, two products could be observed and they could be separated by silica gel column chromatography as a less polar (expressed as **8a**; 31%) and a more polar product (expressed as **8b**; 52%).

In order to determine the configuration of **8a** and **8b**, the NOESY spectrum of both lactones was measured. From the detailed inspection of the spectra, we were able to determine unambiguously the cis-structure of **8b** as shown in Scheme 3. The main isomer **8b** was used in the following studies. Sulfide **8b** was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) at −50 °C to give sulfoxide **9b** as a mixture of two diastereomers in a good yield.

Finally, **9b** was treated with 1.6 equiv of *i*-PrMgCl at −78 °C for 10 min (a solution of **9b** in THF was added to a solution of *i*-PrMgCl in THF) to give the desulfinylated product **11b** in a 91% yield via sulfoxide–magnesium exchange reaction without a trace of the starting sulfoxide **9b**. Quenching this reaction with CH_3OD gave γ-lactone deuterated at γ-position **11b** with 99% deuterium incorporation. This result showed that the intermediate of this reaction was γ-chloromagnesio γ-lactone **10b** (see Scheme 3).

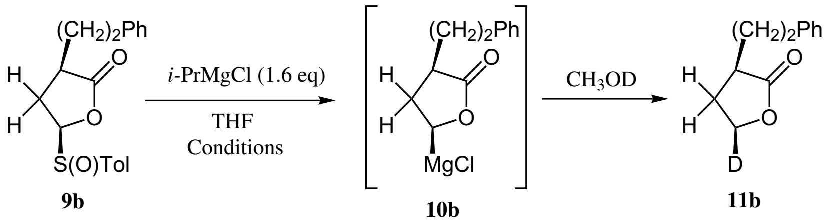
At this stage, we were worried about an intermolecular or an intramolecular proton abstraction, because **10b** has a relatively acidic hydrogen on the α-position. However, no deuterium incorporation at the α-position of γ-lactone **11b** was observed on its ^{1}H NMR.

Next, we investigated the stability of γ-chloromagnesio γ-lactone **10b** by the chemical yield and the rate of deuterium incorporation and the results are summarized in Table 1. The γ-sulfinylated lactone **9b** was treated with 1.6 equiv of *i*-PrMgCl and the reaction mixture was stirred at −78 °C for 1 h, and the reaction was quenched with CH_3OD (Table 1, entry 1). The result was almost the same as the result in Scheme 3. Next, the reaction mixture was stirred at −78 °C for 2 h and the reaction was quenched with CH_3OD (entry 2). The result was almost the same compared with that in entry 1. These results show that γ-chloromagnesio γ-lactone **10b** is stable at −78 °C for at least 2 h. Next, the reaction mixture was slowly allowed to warm to −50 °C for over 50 min and



Scheme 3.

Table 1. Generation of γ-chloromagnesio γ-lactone **10b** form **9b** and quenching with deuterio methanol

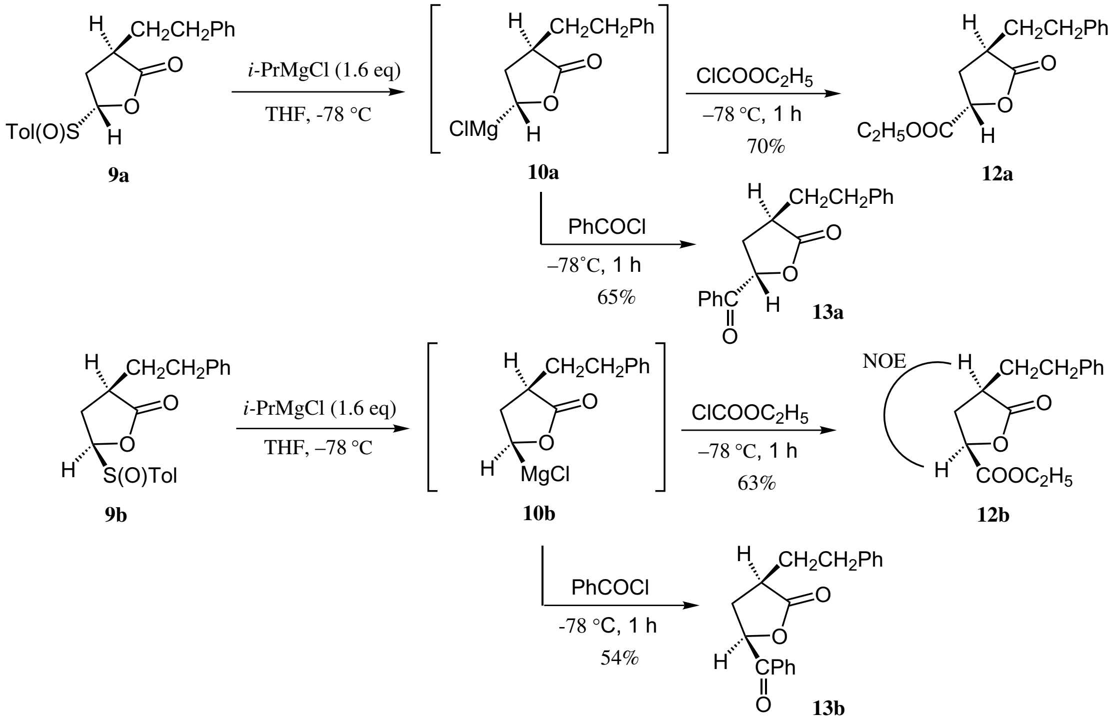


Entry	Conditions	**11b** Yield (%)/D-content (%)
1	−78 °C, 60 min	91/94
2	−78 °C, 120 min	85/91
3	−78 to −50 °C, 50 min, then −50 °C for 60 min	80/91
4	−78 to −50 °C, 50 min, then −50 °C for 120 min	80/88
5	−78 to −30 °C, 90 min, then −30 °C for 10 min	63/93
6	−78 to 0 °C, 150 min, then 0 °C for 10 min	54/53

the reaction mixture was further stirred at −50 °C for 1 h (entry 3). In addition, the reaction was further left to stand at −50 °C for 2 h (entry 4). Both reactions showed the chemical yield and deuterium content were the same within an experimental error. Furthermore, the reaction temperature was slowly allowed to rise to −30 °C over 1.5 h and the reaction mixture was further stirred at −30 °C for 10 min (entry 5). Marked decomposition of γ-chloromagnesio γ-lactone **10b** was observed. The yield of **11b** was markedly diminished when this reaction was carried out at 0 °C (entry 6). From these studies, the γ-chloromagnesio γ-lactone has been found to be stable at below −50 °C for at least 2 h.

In order to extend this unprecedented Grignard reagent to a new synthetic method for γ-substituted γ-lactones, we tried to trap γ-chloromagnesio γ-lactone **10** with several electrophiles. As a preliminary result, the reaction of **10a** and **10b** with ethyl chloroformate at −78 °C for 1 h gave a good yield of ester **12a** and**12b** (Scheme 4). Interestingly, both products, **12a** and **12b**, were obtained as a single diastereomer. Configuration of the products was again confirmed by NOESY experiment and this reaction was found to be highly stereospecific as shown in Scheme 4. Namely, the stereochemistry of the anionic carbon was retained throughout the sequence. The reaction of **10a** and **10b** with benzoyl chloride at −78 °C for 1 h gave the products **13a** and **13b** in 65% and 54% yields, respectively, as a single diastereomer. Unfortunately, propanal did not react at all with γ-chloromagnesio γ-lactone **10**.

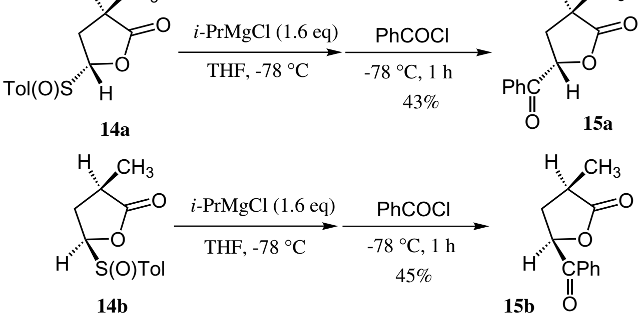
In order to investigate the generality of these reactions, **14a** and **14b** were used in the following studies. The



Scheme 4.

same treatment of **14a** and **14b** with *i*-PrMgCl followed by benzoyl chloride resulted in the formation of γ-lactones **15a** and **15b** via γ-chloromagnesio γ-lactones, again highly stereospecifically (Scheme 5).

We further investigated this reaction with β-monosubstituted γ-lactones **16a**[10] and **16b**, and β,β-disubstituted γ-lactones, **16c** and **16d** (Table 2). The γ-sulfinylated γ-lactones **16** were treated with 1.6 equiv of *i*-PrMgCl at −78 °C to give γ-chloromagnesio γ-lactone **17** in quantitative yields, which was confirmed by quenching the reactions with deuterated methanol. The reaction gave γ-deuterated γ-lactones **18** in quantitative yields with 95–99% deuterium incorporation (entries 1, 6 and 10). The reaction of **17a** and **17b** with ethyl chloroformate at −78 °C for 1 h gave the products having an ethoxycarbonyl group in 36% and 46% yields (entries 2 and 4). In the same manner, the reaction of the γ-chloromagnesio γ-lactones derived from **16a** and **16b** with benzoyl chloride gave γ-lactones having a benzoyl group at the γ-position up to 61% yield (entries 3 and 5). The yields of both reactions were not satisfactory and steric hindrance was thought to be the reason for the low yield. Interestingly, the products were obtained as a single diastereomer, respectively, and again the reaction proceeded in a highly stereospecific manner.

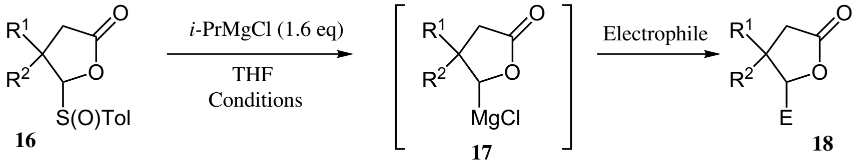


Scheme 5.

Entries 6–11 show the results concerning the γ-chloromagnesio γ-lactones generated from β,β-disubstituted γ-lactones, **16c** and **16d**. As shown in the results in entries 6–8, the γ-chloromagnesio γ-lactones generated from β,β-disubstituted γ-lactones **16c** were found to be stable at below −50 °C. The reactivity of the γ-chloromagnesio γ-lactones generated from **16c** and**16d** was investigated; however, both ethyl chloroformate and benzoyl chloride, and propanal did not react at all with the alkylmagnesiums. Steric hindrance (neopentyl position) was thought to be the reason for the low reactivity with the electrophiles.

In conclusion, we were able to generate, for the first time, the γ-chloromagnesio γ-lactones from γ-lactones having a tolylsulfinyl group at the γ-position by sulfoxide–magnesium exchange reaction. The γ-chloromagnesio γ-lactones were found to be stable at below −50 °C for several hours and were reactive with some electrophiles to give γ-lactones having multi-substituents. We are continuing to investigate the scope and limitation of this reaction and development for the asymmetric synthesis of highly substituted γ-lactones.

Table 2. Generation of γ-chloromagnesio γ-lactone **17** form **16** and quenching with electrophiles



Entry		R^1	R^2	Electrophile	Conditions	**18**	Yield (%)
1	**16a**[a]	$Ph(CH_2)_2$	H	CH_3OD	−78 °C, 10 min	95	(D-content, 98%)
2	**16a**[a]	$Ph(CH_2)_2$	H	ClCOOEt	−78 °C, 60 min	36[b]	
3	**16a**[a]	$Ph(CH_2)_2$	H	PhCOCl	−78 °C, 60 min	36[b]	
4	**16b**[a]	$CH_3(CH_2)_5$	H	ClCOOEt	−78 °C, 60 min	46[b]	
5	**16b**[a]	$CH_3(CH_2)_5$	H	PhCOCl	−78 °C, 60 min	61[b]	
6	**16c**	$-(CH_2)_{14}-$		CH_3OD	−78 °C, 10 min	99	(D-content, 95%)
7	**16c**	$-(CH_2)_{14}-$		CH_3OD	−78 °C, 60 min	90	(D-content, 91%)
8	**16c**	$-(CH_2)_{14}-$		CH_3OD	−78 to −50 °C, 60 min	85	(D-content, 94%)
9	**16c**	$-(CH_2)_{14}-$		ClCOOEt	−78 °C, 60 min	0	
10	**16d**[a]	$4\text{-}CH_3C_6H_4(CH_2)_2$	CH_3	CH_3OD	−78 °C, 10 min	99	(D-content, 99%)
11	**16d**[a]	$4\text{-}CH_3C_6H_4(CH_2)_2$	CH_3	ClCOOEt	−78 °C, 60 min	0	

[a] The main isomer of the γ-lactone having a tolylsulfanyl group at the γ-position was used in this study.

[b] Some amount of protonated lactone was contaminated and the yield was determined from its ^1H NMR.

Acknowledgments

This work was supported by Tokyo University of Science, Joint Study Program in Graduate Course, which is gratefully acknowledged.

References and notes

1. (a) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995; (b) *Grignard Reagents New Developments*; Richey, H. G., Jr., Ed.; John Wiley and Sons: Chichester, 2000.
2. Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414.
3. (a) Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701; (b) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481; (c) Lee, J.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428; (d) Delacroix, T.; Berillon, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 8108; (e) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333; (f) Dohle, W.; Lindsay, D. M.; Knochel, P. *Org. Lett.* **2001**, *3*, 2871; (g) Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390; (h) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565; (i) Sugimoto, O.; Aoki, K.; Tanji, K. *Tetrahedron Lett.* **2004**, *45*, 1915.
4. (a) Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449; (b) Abarbri, M.; Knochel, P. *Synlett* **1999**, 1577; (c) Abarbri, M.; Thibonnet, J.; Berillon, L.; Dehmel, F.; Rottlander, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618; (d) Kneisel, F. F.; Knochel, P. *Synlett* **2002**, 1799.
5. (a) Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 3983; (b) Rottlander, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080; (c) Sapountzis, I.; Dohle, W.; Knochel, P. *Chem. Comm.* **2001**, 2068; (d) Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 3319; (e) Vu, V. A.; Berillon, L.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 6847; (f) Thibonnet, J.; Vu, V. A.; Berillon, L.; Knochel, P. *Tetrahedron* **2002**, *58*, 4787.
6. (a) Avolio, S.; Malan, C.; Marek, I.; Knochel, P. *Synlett* **1999**, 1820; (b) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 351.
7. (a) Satoh, T.; Sugiyama, S.; Ota, H. *Tetrahedron Lett.* **2002**, *43*, 3033; (b) Satoh, T.; Sugiyama, S.; Kamide, Y.; Ota, H. *Tetrahedron* **2003**, *59*, 4327.
8. (a) Satoh, T. J. *Syn. Org. Chem. Jpn.* **1996**, *54*, 481; (b) Satoh, T. *J. Syn. Org. Chem. Jpn.* **2003**, *61*, 98.
9. Sugiyama, S.; Kido, M.; Satoh, T. *Tetrahedron Lett.* **2005**, *46*, 6771.
10. Sugiyama, S.; Satoh, T. *Tetrahedron: Asymmetry* **2005**, *16*, 665.