Note

Journal of Labelled Compounds and Radiopharmaceuticals

Received 1 May 2009, Revised 17 June 2009, Accepted 1 July 2009 Published online 11 August 2009 in Wiley Interscience

(www.interscience.wiley.com) DOI: 10.1002/jlcr.1667

[^{14}C]Dimethyltitanocene and [^{14}C]Methyl(methyltrimethylsilyl) titanocene – Reagents for the [^{14}C]olefination of carbonyl compounds: synthesis of [^{14}C]Aprepitant

M. A. Wallace,* D. C. Dean, and D. G. Melillo

A neurokinin (NK-1) receptor antagonist, [^{14}C]Aprepitant, was synthesized using two labeled olefination reagents: [^{14}C]dimethyltitanocene 1 and [^{14}C]methyl (methyltrimethylsilyl)titanocene 7. Both reagents can be readily prepared from [^{14}C]methyllithium and have been shown to convert a variety of carbonyls to [^{14}C]methylenes in good radiochemical yields.

Keywords: [^{14}C]dimethyltitanocene; [^{14}C]methyl(methyltrimethylsilyl)titanocene; olefination; NK-1; organometallic

Introduction

Potential clinical applications of a substance P inhibitor include treatment for pain, depression, and chemotherapy-induced nausea and vomiting, for which Aprepitant was approved.[1] While several syntheses have been previously described,[2] we envisioned that installing the label in the methyl position would allow for accurate determination of the metabolic fate of Apprepitant, via ADME studies, with minimal loss of label (Scheme 1). Although several titanium based reagents could be useful to perform this transformation (i.e. Tebbe[3] or Grubbs[4] reagents), their difficult preparation has excluded them as practical methods to introduce a carbon-14 label. Petasis has shown that dimethyltitanocene, conveniently generated from dichlorotitanocene and methyllithium, can be used to convert a variety of carbonyl compounds to methylenes.[5] Requests for a tracer labeled in a methyl group along with the availability of intermediates prompted our investigation into utilizing carbon-14-labeled dimethyltitanocene, as a method to introduce the labeled methylene, as shown in Scheme 1.

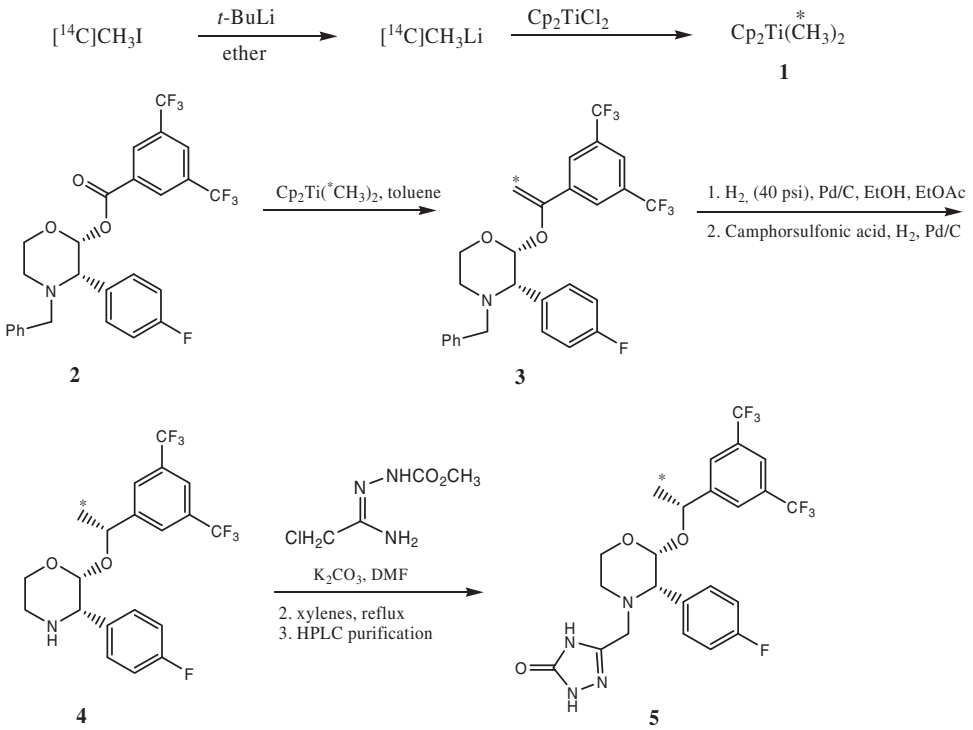
Results and discussion

The synthesis of [^{14}C]dimethyltitanocene (**1**) was accomplished by addition of 2.3 equivalents of [^{14}C]methyllithium, freshly prepared from [^{14}C]methyl iodide and *t*-butyl lithium to commercially available dichlorotitanocene. The stability and reactivity of the resulting [^{14}C]dimethyltitanocene (**1**) was dependent on the reagents specific activity. Attempts to convert carbonyls to carbon-14-labeled olefins using [^{14}C]dimethyltitanocene with a specific activity greater than 40 mCi/mmol resulted in poor yields (~2%); presumably due to rapid radiolytic decomposition of the reagent. Attempts to purify the reagent by recrystallization from hexane, also led to decomposition. Further investigation found that dilution of the [^{14}C]methyl iodide with unlabeled carrier, followed by formation of the lithiate and addition to dichlorotitanocene, produced a viable reagent (specific activity ~10.7 mCi/mmol), which could be used without further purification. With the labeled reagent in hand, [^{14}C]olefination of highly functionalized ester **2** proceeded using 3 equivalents of **1** at 85°C in toluene over 16 h to afford [^{14}C]vinyl ether **3** in an isolated overall 30% radiochemical yield. Although the chemical conversion from ester to the labeled vinyl ether is quite clean, radiochemical detection reveals the formation of highly polar titanium-oxide byproducts, which Petasis hypothesizes quenches unreacted [^{14}C]dimethyltitanocene.[5] This results in the need for three equivalents of **1** to achieve good conversion to [^{14}C]vinyl ether **3**. Hydrogenation of the vinyl ether **3** with Pd/C afforded a 9:1 mixture of diastereomers. Removal of the benzyl protecting group by hydrogenation in the presence of camphorsulfonic acid afforded **4** as the camphorsulfonic acid salt in 85% yield. The triazole ring was formed by treatment of **4** with chloroamidrazone over potassium carbonate, then, following workup, the crude mixture was heated to reflux in xylene, to give crude **5**. Preparative chromatography afforded pure carbon-14-labeled apprepitant **5**, which was used in carry out ADME studies.

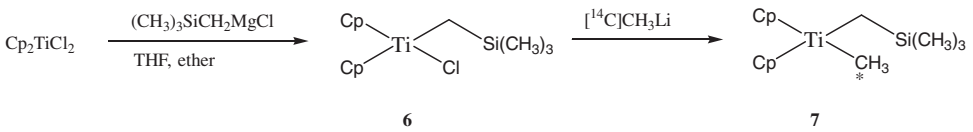
While [^{14}C]dimethyltitanocene provided a viable synthetic route to the target tracer, the breakdown of [^{14}C]dimethyltitanocene to the postulated reactive carbene intermediate[6] results in the loss of [^{14}C]methane[7], intrinsically reducing the overall yield to a maximum of 50%.[6] To address this issue, we had hoped that generation of a mixed titanocene could increase the overall yield based on [^{14}C]methyl iodide. Petasis has shown that several types of alkyl groups, including benzyl,[8]

Department of Drug Metabolism, Merck Research Laboratories, 126 Lincoln Ave., P.O. Box 2000, Rahway, NJ 07065, USA

**Correspondence to: M. A. Wallace, RY80R-104, P.O. Box 2000, Rahway, NJ 07065, USA.*
E-mail: mike_wallace@merck.com



Scheme 1.



Scheme 2.

cyclopropyl,[9] and methyltrimethylsilyl[10,11] will react with carbonyls to afford benzylidenes, cyclopropenes, and vinylsilanes, respectively. The different reaction conditions for each complex suggests that alkyl transfer rates could be manipulated through control of the reaction conditions. Petasis also has described the sequential addition of organometallics to dichlorotitanocene.[12] Based on this methodology, we have developed a novel mixed reagent, [^{14}C]methyl(methyltrimethylsilyl)titanocene (**7**) as shown in Scheme 2. Treatment of dichlorotitanocene with methyltrimethylsilyl magnesium chloride at −60°C afforded chloro(methyltrimethylsilyl)titanocene **6** in 90% isolated yield. This stable intermediate was then treated with 1.1 equivalents of [^{14}C]methyllithium to afford the desired [^{14}C]methyl(methyltrimethylsilyl)titanocene **7** in 50% isolated radiochemical yield.

Investigation of the ability of **7** to convert esters, ketones, and aldehydes to [^{14}C]methylenes found that when **7** is heated to 140°C in xylenes in the presence of carbonyl compounds, both [^{14}C]methylenes and the corresponding unlabeled vinylsilanes were detected. Similar to Petasis' bis and tris silyl-titanium complexes, the generation of titanium-oxide byproducts was suppressed,[9] resulting in much cleaner radiochemical conversions. Good radiochemical yields could be obtained using 2 equivalents of **7**. Yields for representative carbonyl compounds are summarized in Table 1.

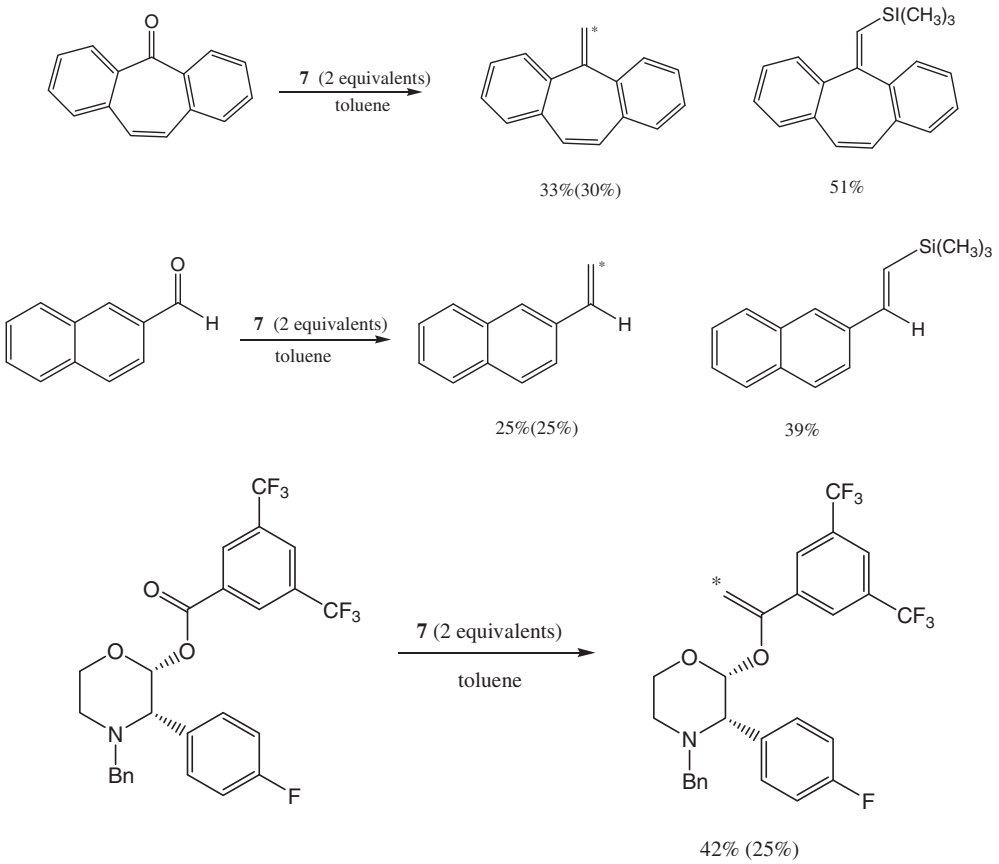
Experimental

Radioactivity measurments were carried out using Packard Tricarb 1000 TR liquid scintillation spectrometer with Scintiverse 1™ as scintillation medium. Analytical HPLC analyses were performed using a Dupont Zorbax RX C-8 (4.6 mm × 25 cm), Rainin UV-1 detector at 254 nm, Radiomatic radioactivity monitor, Spectra-Physics SP8810 LC pump and controller, and software run on an IBM PS/2 computer. Preparative HPLC were carried out using Altex pumps with a Beckman UV detector at 254 nm and either a Whatman M20 (22.1 mm × 25 cm) Partisil or Dupont (22.1 mm × 25 cm) Zorbax RX C-8 column. The identities of appropriate labeled intermediates as well as the final product were established by co-elution via HPLC with authentic material.

[^{14}C]Dimethyltitanocene (1)

[^{14}C]methyl iodide (25 mCi, 0.454 mmol) was transferred by vacuum line to 2 mL of ether containing 64 mg (0.454 mmol) unlabeled methyl iodide. The ethereal mixture was warmed to −78°C, *t*-butyl lithium (1.7 M, 575 μL) was added dropwise, and the mixture aged at −78°C for 30 min. Dichlorotitanocene (112 mg, 0.454 mmol) was slurried into ether (4 mL) and cooled to 0°C. The [^{14}C]methyllithium was transferred by cannula, and the mixture aged for 30 min at 0°C. Unlabeled methyllithium

Table 1. Carbon-14 olefinations with [^{14}C]Methyl(methyltrimethylsilyl)titanocene



* overall radiochemical assay yields shown in ( ).

(1.6 M, 50 μL) was added until the yellow color persisted. The mixture was aged an additional 15 min and quenched with water (5 mL). The mixture was diluted with ether (10 mL) and the layers separated. The organic phase was washed with water (5 mL), brine (5 mL), dried over MgSO4, filtered, and concentrated to afford 98 mg (9.5 mCi, 10.7 mCi/mmol) of [^{14}C]dimethyltitanocene. The [^{14}C]dimethyltitanocene was redissolved in toluene and used as a stock solution (14% w/w) without the need for further purification.[13]

[^{14}C]methyl(methyltrimethylsilyl)titanocene (7)

Monochloro(trimethylsilyl methyltitanocene) was generated as described by Petasis.[4] [^{14}C]methyl iodide (25 mCi, 0.454 mmol) was transferred by vacuum line into 2 mL of ether. The ether was warmed to −78°C and *t*-butyl lithium (1.7 M, 275 μL) was added dropwise. The mixture was aged for 30 min at −78°C. The monochlorotitanocene **6** (139 mg, 0.454 mmol) was dissolved in 6 ml of ether and cooled to 0°C. The [^{14}C]methyl lithium was transferred by cannula and the flask rinsed with ether (1 mL). The mixture was aged for 30 min at room temperature (reddish to orange color) and then unlabeled methyllithium (300 μL, 1.0 M) was added dropwise. The mixture was aged an additional 15 min at 0°C (orange to yellow color) and then quenched with water (5 mL). The mixture was diluted with ether (10 mL) and the layers separated. The organic phase was washed with water (5 mL), brine (5 mL), dried over MgSO4, filtered, and concentrated to afford 119 mg of [^{14}C]methyl-methyltrimethylsilyltitanocene (**7**). The titanocene was redissolved in toluene (7.764 mCi, specific activity 18.2 mCi/mmol) and could be used without further purification.

Methylenation of ester 2 with [^{14}C]dimethyltitanocene: Synthesis of Apprepitant

Ester **2** (10.5 mg, 0.08 mmol) was dissolved in 800 μL of toluene and 350 μL of THF and [^{14}C]dimethyltitanocene (50 mg, 0.24 mmol, 3 equivalents, 4.5 mCi) was added. The mixture was aged at 86°C for 18 h. HPLC (Zorbax RX-C8, 65A/35B, A = CH3CN, B = 0.1% H3PO4) indicated complete consumption of ester (25% radiochemical yield). Liquid scintillation counting of the reaction mixture indicated 2.2 mCi remained. The reaction mixture was concentrated and the residue redissolved in methanol/water. The mixture was filtered, to remove titanocene-oxide byproducts, and concentrated. The crude residue was purified by silica gel chromatography (hexanes) to afford [^{14}C]vinyl ether **3** (500 μCi, spec. act. 16 μCi/mg, 12% radiochemical yield). The [^{14}C]vinylether **3** was dissolved in methanol and 15%, by weight, of Pd/C (10%) was added. The mixture was stirred under 40 psi H_2 for 4 h upon which HPLC showed [^{14}C]vinyl ether **3** was consumed. *R*-Camphorsulfonic acid (1.1 equivalents) was added and the mixture aged under 40 psi of H_2 for 16 h. The mixture was filtered and concentrated. The amine **4** (35 mg, 0.06 mmol) was treated with chloroamidrazone (12 mg, 0.064 mmol, 1.2 equivalents) over potassium carbonate (17 mg, 0.12 mmol, 2 equivalents) in DMF (1 mL). The reaction mixture was diluted

with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The organic phase was dried and concentrated and the resulting oil was dissolved in xylenes (2 mL) and the mixture refluxed for 6 h. Following concentration, the crude tracer was purified by preparative HPLC (Zorbax RX C8, 40A/60B, A = CH3CN, B = 0.1% H3PO4). Isolation by extraction, followed by recrystallization from methanol/water 2/1 (3 mL), afforded 200 μCi (4% from [^{14}C]methyl iodide) of 98.7% radiochemically pure apprepitant **5**.

Olefination of ester 2 with [^{14}C]methyl-methyltrimethylsilyltitanocene (7)

Ester **2** (10.5 mg, 0.019 mmol) was dissolved in 300 μL of xylenes and [^{14}C]methyl (methyltrimethylsilyl)titanocene (**7**) (16 mg, 0.057 mmol, 3 equivalents, 1.2 mCi) was added. The mixture was aged at 150°C for 4 h. HPLC analysis (Zorbax RX C8, 65A/35B, A = CH3CN, B = 0.1% H3PO4) showed the mixture contained starting ester (2%), [^{14}C]methylene product (42% (19% radiochemical yield)), and vinyl silane product (55%). Liquid scintillation counting of the reaction mixture indicated 390 μCi of the desired [^{14}C]vinyl ether that had a radiochemical purity of 60%.

Olefination of Dibenzosurbenone with 7

Dibenzosurbenone (5.9 mg, 0.028 mmol) was dissolved in 300 μL of xylenes. [^{14}C]methyl(methyltrimethylsilyl)titanocene **7** (stock solution toluene, 15.8 mg, 0.056 mmol, 2 equivalents, 1.2 mCi) was added and the mixture aged at 150°C for 4 h. HPLC analysis (Zorbax RX C8, 50A/50B, A = CH3CN, B = 0.1 % H3PO4) showed the reaction mixture contained starting dibenzosurbenone (15%), [^{14}C]methylene product (33% (30% radiochemical yield.)), and vinyl silane product (51%). A count of reaction mixture indicated 400 μCi (33%) remained of which 95% was the desired [^{14}C]methylene compound.

Olefination of 2-Napthaldehyde with 7

2-Napthaldehyde (1.0 mg, 0.0064 mmol) was dissolved in 300 μL of xylenes. [^{14}C]methyl-methyltrimethylsilyltitanocene **7** (stock solution toluene, 11.9 mg, 0.013 mmol, 2 equivalents, 225 μCi) was added and the mixture aged at 150°C for 2 h. (prolonged heating results in several radiochemical impurities). HPLC analysis (Zorbax RX C8, 50A/50B, A = CH3CN, B = 0.1 % H3PO4) showed the mixture contained starting aldehyde (38%), [^{14}C]methylene product (22% (25% radiochemical yield.)), and vinyl silane product (39%). A count of reaction mixture indicated 75 μCi (33%) remained of which 90% was the desired [^{14}C]methylene product.

Conclusion

As our investigation into titanium mediated [^{14}C]olefinations continues, we have shown that both [^{14}C]dimethyltitanocene (**1**) and [^{14}C]methyl(methyltrimethylsilyl) titanocene (**7**) can be readily prepared and are quite capable of converting carbonyls to [^{14}C]methylenes in reasonable radiochemical yields. Although **1** provides usable radiochemical yields in many instances, **7** does offer several advantages: Most importantly, generation of the mixed titanocene **7** requires only one equivalent of [^{14}C]methyllithium, reducing the necessary amount of [^{14}C]methyl iodide. Good radiochemical yields of [^{14}C]olefination products can be achieved with 2 equivalents of **7,** as opposed to 3 equivalents needed with reagent **1**. Lastly, although **5** may generate significant amounts of undesired vinyl silanes, their non-polar nature generally make them separable from the desired carbon-labeled methylene products. Also, **7** provides access to potentially higher specific activity tracers as the reagents oxidation/decomposition was not observed. Further experiments are underway using different complexes in an attempt to influence the reaction pathway to favor olefination and further increase overall label incorporation.

References

[1] R. M. Navari, R. R. Reinhardt, R. J. Gralla, M. G. Kris, P. J. Hesketh, A. Khojasteh, H. Kindler, T. H. Grote, K. Pendergrass, S. M. Grunberg, A. D. Carides, B. J. Gertz, *N. Engl. J. Med.* **1999**, *340*, 190–195. M. S. Kramer, N. Cutler, J. Feighner, R. Shrivastava, J. Carman, J. J. Sramek, S. A. Reines, G. Liu, D. Snavely, E. Wyatt-Knowles, J. J. Hale, S. G. Mills, M. MacCoss, C. J. Swain, T. Harrison, R. G. Hill, F. Hefti, E. M. Scolnick, M. A. Cascieri, G. G. Chicchi, S. Sadowski, A. R. Williams, L. Hewson, D. Smith, E. J. Carlson, R. J. Hargreaves, N. M. J. Rupniak, *Science* **1998**, *281*, 1640–1645.

[2] K. M. J. Brands, S. W. Krska, T. Rosner, K. M. Conrad, E. G. Corley, M. Kaba, R. D. Larsen, R. A. Reamer, Y. Sun, F. R. Tsay, *Org. Process Res. Dev.* **2006**; *10*: 109–117. M. Journet, D. Cai, D. L. Hughes, J. J. Kowal, R. D. Larsen, P. J. Reider, *Org. Process Res. Dev.* **2005**, *9*, *490*–498. K. M. J. Brands, J. F. Payack, J. D. Rosen, T. D. Nelson, A. Candelario, M. A. Huffman, M. M. Zhao, J. Li, B. Craig, Z. J. Song, D. M. Tschaen, K. Hansen, P. N. Devine, P. J. Pye, K. Rossen, P. G. Dormer, R. A. Reamer, C. J. Welch, D. J. Mathre, N. N. Tsou, J. M. McNamara, P. J. Reider, *J. Am. Chem. Soc.* **2003**, *125*, 2129–2135. C. C. Cowden, R. D. Wilson, B. C. Bishop, I. F. Cottrell, A. J. Davies, U. H. Dolling, *Tetrahedron Lett.* **2000**, 8661–8664. C. S. Elmore, D. C. Dean, Y. Zhang, D. G. Melillo, *J. Label. Compd. Radiopharm.* **2004**, *47*, 837–846. J. J. Hale, S. G. Mills, M. MacCoss, P. E. Finke, M. A. Cascieri, S. Sadowski, E. Ber, G. G. Chicchi, M. Kertz, J. Metzger, G. Eiermann, N. N. Tsou, F. D. Tattersall, N. M. J. Rupniak, A. R. Williams, W. Rycroft, R. Hargreaves, D. E. MacIntyre, *J. Med. Chem.* **1998**, *41*, 4607–4614. J. F. Payack, M. A. Huffman, D. Cai, D. L. Hughes, P. C. Collins, B. K. Johnson, I. F. Cottrell, L. D. Tuma, *Org. Process Res. Dev.* **2004**, *8*, 256–259.

[3] F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**; *100*; 3611–3613. S. H. Pine, *Org. React. (NY)* **1993**, *43*, 1–91 (review).

[4] T. R. Howard, J. B. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **1980**, *102*, 6876–6878. K. C. Ott, R. H. Grubbs, *J. Am. Chem. Soc.* **1981**, *103*, 5922–5923. D. Strauss, R. H. Grubbs, *Organometallics* **1982**, *1*, 1658–1661. E. V. Anslyn, R. H. Grubbs, *J. Am. Chem. Soc.* **1987**, *109*, 4880–4890.

[5] N. A. Petasis, E. I. Bzowej. *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394. N. A. Petasis, S. P. Lu, *Tetrahedron Lett.* **1995**, *36*, 2393–2396. N. A. Petasis, E. I. Bzowej. U.S. Patent No. 5,087,790, Feb. 11, **1992**. N. A. Petasis, Y.-H. Hu, *Tetrahedron Lett.* **1995**, *36*, 6001–6004. N. A. Petasis, M. A. Patane, *Tetrahdron Lett.* **1990**, *31*, 6799.

[6] D. L. Hughes, J. F. Payack, D. Cai, T. R. Verhoeven, P. J. Reider, *Organometallics* **1996**, *15*, 663–667.

[7] As labeled methane is generated during the reaction, periodic venting should be used to prevent pressure buildup, especially on large scale.

[8] N. A. Petasis, E. I. Bzowej, *J. Org. Chem.* **1992**, *57*, 1327–1330.

[9] N. A. Petasis, E. I. Bzowej, *Tetrahedron Lett.* **1993**, *34*, 943–946.

[10] N. A. Petasis, I. Akritopoulou, *Synlett* **1992**, 665–667.

[11] N. A. Petasis, J. P. Staszzewski, D.-K. Fu, *Tetrahedron Lett.* **1995**, *36*, 3619–3622.

[12] N. A. Petasis, D.-K. Fu, *J. Am. Chem. Soc.* **1993**, *115*, 7208–7214.

[13] Dimethyltitanocene will decompose if stored in solid form. Dimethyltitanocene kept in toluene solution is stable for several months.