

# SYNLETT Spotlight 299

## Petasis Reagent

Compiled by Carine Vaxelaire

Carine Vaxelaire was born in Remiremont, France, in 1982. She studied chemistry at the engineering school CPE-Lyon and at the University of Lyon, France. Currently, she is pursuing her Ph.D. under the supervision of Professor Janick Ardisson and Dr. Ange Pancrazi at the Paris Descartes University, France. Her research is focused on the total synthesis of a natural molecule using multistep synthesis.

Faculté des Sciences Pharmaceutiques et Biologiques, Avenue de l'Observatoire 4, 75270 Paris, France  
E-mail: carine.vaxelaire@univ-paris5.fr



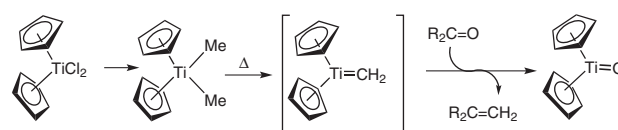
This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

### Introduction

The Petasis reagent<sup>1</sup> (dimethyl titanocene,  $\text{Cp}_2\text{TiMe}_2$ ) is readily prepared by the reaction of methylmagnesium chloride<sup>2</sup> or methyllithium<sup>3</sup> with titanocene dichloride. It is used for transforming carbonyl groups to terminal alkenes,<sup>4</sup> like the Tebbe reagent or Wittig reaction. Unlike the Wittig reaction, the Petasis reagent can react with a wide range of carbonyls, such as aldehydes, ketones, esters, and lactones including enolizable and acid-labile substrates. The Petasis reagent is also non-pyrophoric, rel-

atively air- and water-stable, and can be used directly as a solution in toluene–THF.

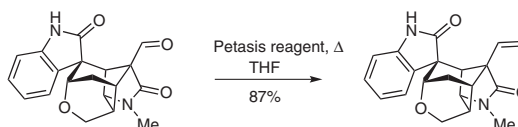
The active olefinating reagent,  $\text{Cp}_2\text{TiCH}_2$ , can be prepared by heating the Petasis reagent in toluene or THF to 60–75 °C. The Petasis reaction can also be promoted by microwave irradiation.



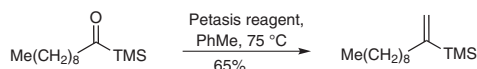
Scheme 1

### Abstracts

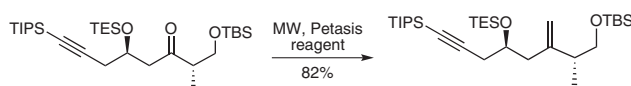
(A) Aldehydes and ketones can be selectively methylenated in the presence of less electrophilic carbonyl groups such as esters<sup>1a,5</sup> and amides.<sup>6</sup>



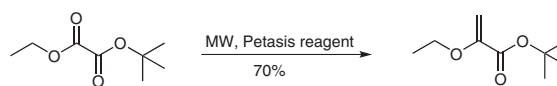
(B) Reaction of dimethyl titanocene with heteroatom-substituted carbonyls,<sup>1b</sup> such as silyl esters, lactones,<sup>7</sup> thioesters, selenoesters, and acylsilanes gives the corresponding heteroatom-substituted alkenes.



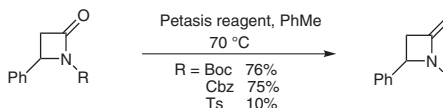
(C) Petasis methylenation can be accomplished in the presence of many protecting groups, like silyl ethers,<sup>8</sup> benzyl ethers,<sup>9</sup> and acetals.<sup>10</sup> The reaction in the presence of an unprotected hydroxyl group<sup>11</sup> can also be efficient when an excess of the reagent is used.



(D) The selectivity of this reaction has been extended to unsymmetrical oxalates<sup>12</sup> and oxalate monoesters or monoamides. Improvement of the methylenation can be promoted by microwave irradiation.<sup>13</sup>



(E) The reaction of  $\beta$ -lactams with  $\text{Cp}_2\text{TiMe}_2$  can be realized in good yields as long as the lactams are properly activated by N-protection.<sup>14</sup>



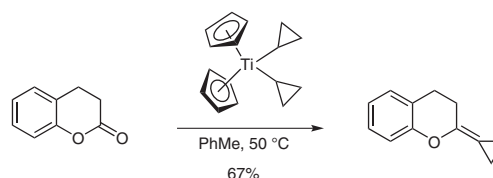
SYNLETT 2009, No. 19, pp 3221–3222

Advanced online publication: 13.11.2009

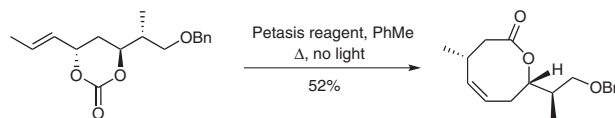
DOI: 10.1055/s-0029-1218382; Art ID: V30509ST

© Georg Thieme Verlag Stuttgart · New York

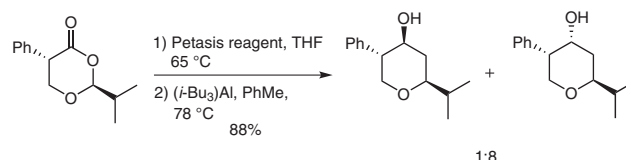
(F) Homologue dialkyltitanocene derivatives of the Petasis reagent can be prepared from titanocene dichloride and alkyllithium or Grignard reagents,<sup>15</sup> with the exception of compounds that undergo facile  $\beta$ -hydride elimination.



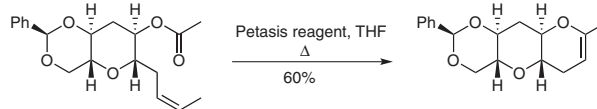
(G) The Petasis reagent has been utilized in a tandem methylenation–Claisen rearrangement to give ring extension<sup>16</sup> or contraction.<sup>17</sup>



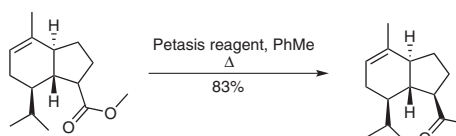
(H) One application of the Petasis reagent is the Petasis–Ferrier rearrangement,<sup>18</sup> which involves methylenation of a 1,3-dioxan-4-one to give an enol ether which yields in the presence of a trialkylaluminum reagent a 2,6-*syn*-disubstituted tetrahydropyranone. This method has been utilized as an exceptional powerful tool for the total synthesis of complex natural product.<sup>19</sup>



(I) A one-pot methylenation–RCM procedure has been developed by Nicolaou<sup>20</sup> using Petasis reagent as both methylenation reagent and RCM catalyst.



(J) A one-carbon homologation was achieved using Petasis methylenation followed by acid hydrolysis.<sup>21</sup>



## References

- (1) (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392. (b) Petasis, N. A.; Lu, S. P. *Tetrahedron Lett.* **1995**, *36*, 2393.
- (2) Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Synth.* **2002**, *79*, 19.
- (3) Clauss, K.; Bestian, H. *Justus Liebigs Ann. Chem.* **1962**, 654, 8.
- (4) Hartley, R. C.; McKiernan, G. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2763.
- (5) Colson, P. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918.
- (6) Atarashi, S.; Choi, J. K.; Ha, D. C.; Hart, F. J.; Kuzmich, D.; Lee, C. S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226.
- (7) (a) Morency, L.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 8841. (b) Smith, A. B. III.; Simon, V. *Org. Lett.* **2006**, *8*, 3315.
- (8) (a) Lambert, W. T.; Hanson, G. H.; Benayoud, F.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 9382. (b) Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Tanner, H. R.; Hook, D. F.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4819.
- (9) Heskamp, B. M.; Veeneman, G. H.; van der Marel, G. A.; Van Boeckel, C. A. A.; Van Boom, J. H. *Tetrahedron* **1995**, *51*, 8397.
- (10) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856.
- (11) Li, X.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Synlett* **2001**, 1885.
- (12) (a) Chenault, H. K.; Chafin, L. F. *J. Org. Chem.* **1994**, *59*, 6167. (b) Chenault, H. K.; Castro, A.; Chafin, L. F.; Yang, J. *J. Org. Chem.* **1996**, *61*, 5024.
- (13) Cook, M. J.; Fleming, D. W.; Gallagher, T. *Tetrahedron Lett.* **2005**, *46*, 297.
- (14) Martinez, I.; Howell, A. R. *Tetrahedron Lett.* **2000**, *41*, 5607.
- (15) (a) Petasis, N. A.; Bzowej, E. I. *J. Org. Chem.* **1992**, *57*, 1327. (b) Petasis, N. A.; Akritopoulou, I. *Synlett* **1992**, 665. (c) Petasis, N. A.; Bzowej, E. I. *Tetrahedron Lett.* **1993**, *34*, 943.
- (16) (a) Davidson, J. E. P.; Anderson, E. A.; Buhr, W.; Harrison, J. R.; O'Sullivan, P. T.; Collins, I.; Green, R. H.; Holmes, A. B. *Chem. Commun.* **2000**, 629. (b) Anderson, E. A.; Davidson, J. E. P.; Harrison, J. R.; O'Sullivan, P. T.; Burton, J. W.; Holmes, A. B. *Tetrahedron* **2002**, *58*, 1943.
- (17) Petasis, N. A.; Bzowej, E. I. *Tetrahedron Lett.* **1993**, *34*, 1721.
- (18) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141.
- (19) Few examples: (a) Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292. (b) Smith, A. B. III.; Simov, V. *Org. Lett.* **2006**, *8*, 3315. (c) Smith, A. B. III.; Minibiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913.
- (20) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565.
- (21) (a) Taber, D. F.; Kong, S.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 7953. (b) Panda, J.; Ghosh, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3013. (c) Donohoe, T. J.; Guillermin, J.-B.; Frampton, C.; Walter, D. S. *Chem. Commun.* **2000**, 465.