Carbocyclization Reaction of Active Methine Compounds with Unactivated Alkenyl or Alkynyl Groups Mediated by $TiCl_4$−Et_3N

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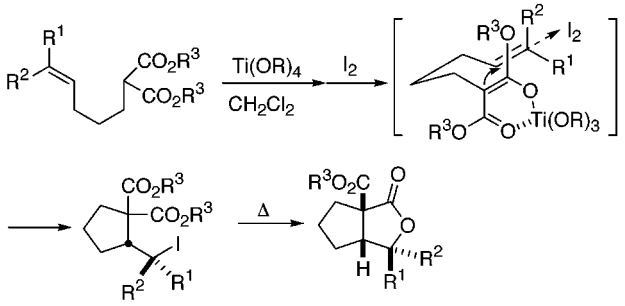
In the presence of $TiCl_4$, Et_3N, and I_2, iodocarbocyclization reaction of various active methine compounds having alkenyl groups gave iodocycloalkane derivatives in good yields. On the other hand, $TiCl_4$ and Et_3N promote the carbocyclization of active methine compounds with 4-alkynyl groups in the absence of I_2 to give methylenecyclopentane derivatives in good yields. This reaction proceeds with high streoselectivity through a *cis*-addition of trichlorotitanium enolates of active methine compounds to alkynes, and the resulting vinyltitanium intermediates can be further functionalized by the reaction with various electrophiles.

Introduction

The addition reaction of stabilized carbanions prepared from active methylene and methine compounds to the activated C−C π-bond is commonly known as the Michael reaction, while a limited number of examples has been reported on the addition of these to unactivated alkenes and alkynes.[1−3] On the other hand, in the cases of unstabilized carbanions, many examples of the inter- and intramolecular addition to an unactivated C−C π-bond, such as carbometalation using unstabilized organometallic carbanions, have been reported so far.[4] Thus, the difficulty of the reaction with a stabilized carbanion may be due to an endothermic process involving the conversion of a stabilized enolate anion to an unstabilized sp^3 or sp^2 carbanion.[5]

We previously reported iodocarbocyclization reaction of a malonate derivative having unreactive alkenyl or alkynyl groups which proceeds in a highly stereospecific manner through the *trans*-addition of I_2 and a malonate enolate to the C−C π-bond in the presence of $Ti(OR)_4$ and I_2 (Scheme 1).[6] In this reaction, iodine is a proper electrophile to activate the C−C π-bond, while $Ti(OR)_4$ acts as a basic reagent to enhance the nucleophilicity of the malonate moiety through the formation of a titanium enolate. Other bases, in particular, a strong base such as *tert*-BuOK and NaH, resulted in a marked decrease in the chemical yield, because dimerization and α-iodination reaction of the malonate anions occurs at the same time; thus, a mild base such as $Ti(OR)_4$ may be required to get the product in a good yield.[6b,7] Furthermore, we have also succeeded in the development of highly enantioselective iodocarbocyclization using a chiral titanium alkoxide, Ti(TADDOLate)$_2$ catalyst.[8] A limitation of the present reaction is the choice of only malonate derivatives as substrates, and it could not be applied to a variety of active methine compounds.

Scheme 1



In this paper, we report the result of iodocarbocyclization reaction mediated by $TiCl_4$, Et_3N, and I_2 which is applicable to various unsaturated active methine compounds (Scheme 2). In addition, in the course of the related experiment, we found that without the addition of I_2, $TiCl_4$ and Et_3N promote the carbocyclization of

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(1) Examples of intramolecular carbometalation reactions of enolates with unactivated olefins or alkynes: (a) Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1990**, *46*, 7763−7773. (b) Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1991**, *47*, 6293−6304. (c) Yeh, M.-C. P.; Chuang, L.-W.; Ueng, C. H. *J. Org. Chem.* **1996**, *61*, 3874−3877. (d) Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* **1998**, *39*, 2157−2158. (e) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett* **1998**, 446−448. (f) Lorthiois, E.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1998**, *63*, 2442−2450 and references therein.

(2) Examples of intermolecular carbometalation reactions of enolates to unactivated olefins or alkynes: (a) Bertrand, M. T.; Courtois, G.; Miginiac, L. *Tetrahedron Lett.* **1974**, 1945−1948. (b) Ehrhardt, H.; Mildenberger, H. *Liebigs Ann. Chem.* **1982**, 989−993. (c) Stack, J. G.; Simpson, R. D.; Hollander, F. J.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1990**, *112*, 2716−2729. (d) Yamaguchi, M.; Hayashi, A.; Hirama, M. *J. Am. Chem. Soc.* **1993**, *115*, 3362−3363. (e) Yamaguchi, M.; Hayashi, A.; Hirama, M. *J. Synth. Chem. Org. Jpn.* **1996**, *54*, 267−279. (f) Kubota, K.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2491−2493.

(3) An example of palladium-catalyzed addition of activated methylene compounds to allenes: Yamamoto, Y. Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019−6020.

(4) (a) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; New York, Pergamon Press: 1991; Vol. 4, pp 865−911. (b) Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080−3090 and references therein. (c) Marek, I.; Normant, J. F. *Cross Coupling Reactions*; Diederich, D., Stang, P., Eds.; VCH: New York, 1998.

(5) Nakamura, E. Kubota, K. *Tetrahedron Lett.* **1997**, *38*, 7099−7102.

(6) (a) Kitagawa, O.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, *33*, 2167−2170. (b) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106−3112. (c) Taguchi, T.; Kitagawa, O.; Inoue, T.; *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 770−779. (d) Kitagawa, O.; Inoue, T. Taguchi, T. *Rev. Heteroat. Chem.* **1996**, *15*, 243−262.

(7) (a) Curran D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *62*, 3140. (b) Cossy, J.; Thellen, A. *Tetrahedron Lett.* **1990**, *31*, 1427−1428. (c) Beckwith, A. L.; Zozer, M. J. *Tetrahedron Lett.* **1992**, *33*, 4975−4978.

(8) Inoue, T.; Kitagawa, O.; Saito, A.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7384−7389 and references therein.

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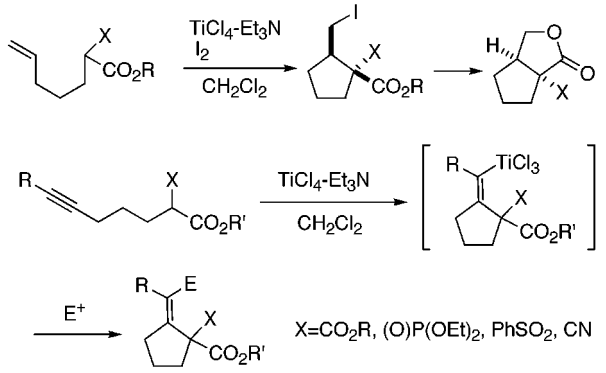
Scheme 2



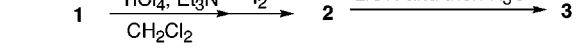
active methine compounds with a 4-alkynyl group (Scheme 2).[9] This reaction proceeds with high stereoselectivity through an intramolecular *cis*-addition of trichlorotitanium enolates of active methine compounds to alkynes, and the resulting vinyltitanium intermediate can be further functionalized by the reaction with various electrophiles. As far as we know, carbometalation reaction of a titanium enolate to an unactivated C−C π-bond has not been reported so far. The details of this reaction and stereodivergent synthesis of an (iodomethylene)cyclopentane derivative are also described.

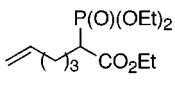
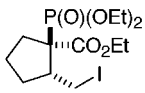
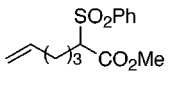
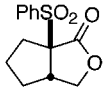
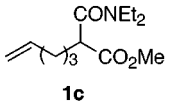
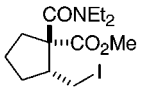
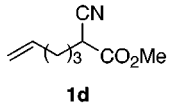
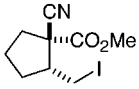
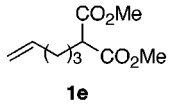
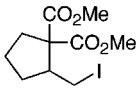
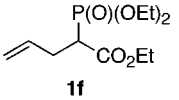
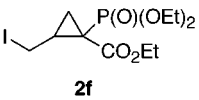
Results and Discussion

Iodocarbocyclization Reaction of Various Active Methine Compounds. In contrast to alkenylmalonate derivatives, the iodocarbocyclization reaction of 4-pentenylphosphonoacetate **1a** did not proceed in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ and I_2 in CH_2Cl_2, and **1a** was quantitatively recovered. Among many additives examined, it was found that when $TiCl_4$ and Et_3N were used in the presence of I_2, an iodocarbocyclized product **2a** was obtained in 78% yield (Table 1, entry 1). As shown in Scheme 3, the individual use of amines or $TiCl_4$, and the combination of Et_3N with $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ or $Ti(O\textit{i}\text{-}Pr)_4$, were ineffective, resulting in a recovery of **1a** together with the formation of an addition product of I_2 to the olefin. On the other hand, the use of basic metal alkoxides such as $LiAl(O\textit{t}\text{-}Bu)_4$ and $La(O\textit{i}\text{-}Pr)_3$ gave an α-iodination product of **1a** and an addition product of I_2 to the olefin without the formation of **2a**. Thus, the combination of $TiCl_4$ and Et_3N is essential for the reaction of **1a**. In addition, the cyclopentane derivative **2a** having a *cis*-relationship between the ester and iodomethyl groups was obtained as a major isomer with relatively high diastereoselectivity (12:1). The stereochemistriy of **2a** was determined on the basis of a lactonization experiment; the major isomer of **2a** easily gave bicyclic lactone **3a** by heating at 140 °C, while the lactone was not obtained from the minor isomer under the same conditions because of the unfavorable process for the formation of the *trans*-fused [3.3.0]-bicyclic ring system (Scheme 4).

The reaction of 4-pentenylsulfonyl acetate **1b** also smoothly proceeded to give (iodomethyl)cyclopentane derivative **2b** in a diastereomeric ratio of 8.6:1 (entry 2). Similar to the case of **1a**, this reaction did not proceed in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ and I_2. **2b** was converted to lactone **3b** in a good yield without the further separation of the diastereomer (Scheme 4),[10] because the lactonization of **2b** partly occurs during the chromatographic purification step (silica gel). Similar to **2a,** although the lactonization of the major isomer easily proceeded, the formation of a bicyclic lactone from the minor isomer was not observed. In the reactions of **1a** and **1b**, the separation of diastereomers of products **2a** and **2b** was very

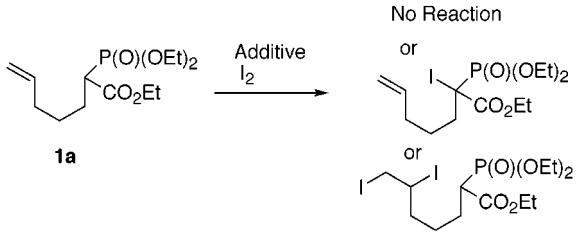
Table 1. Iodocarbocyclization Reaction of Various Unsaturated Active Methine Compounds[a]



Entry	1	2 or 3[b]	stereoisomer ratio	Yield (%)[c]
1	 **1a**	 **2a**	12 : 1[d]	78
2	 **1b**	 **3b**	(8.6 : 1)[d,e] **2b**	81 **3b**
3	 **1c**	 **2c**	> 50 : 1[f]	53
4	 **1d**	 **2d**	1.4 : 1[d]	92
5	 **1e**	 **2e**	—	71
6	 **1f**	 **2f**	2 : 1[g]	78

[a] Iodocarbocyclization: **1** (1 mmol), $TiCl_4$ (1.8 mmol), Et_3N (1.5 mmol), I_2 (1.5 mmol), CH_2Cl_2 (6 mL), rt, 2-3 h. [b] Major streoisomers are shown. [c] Isolated yield. [d] The ratios were determined by 300 MHz ^{1}H-NMR. [e] The diastereomer ratio of the crude iodide **2b** is shown. [f] Minor stereoisomer was not detected. [g] The streochemistries of **2f** were not determined.

Scheme 3



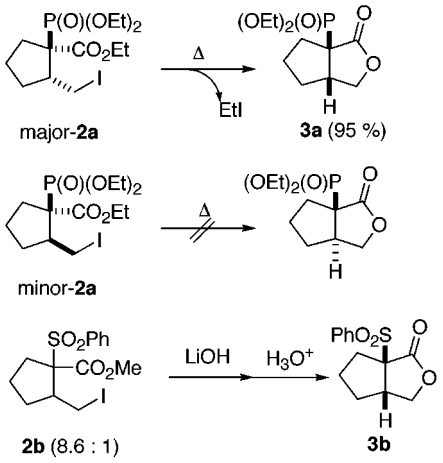
Ineffective additive

$Ti(O\textit{i}\text{-}Pr)_4$, Et_3N, DBU, $TiCl_4$, $Et_3N\text{-}TiCl_2(O\textit{i}\text{-}Pr)_2$, $Et_3N\text{-}Ti(O\textit{i}\text{-}Pr)_4$, $LiAl(O\textit{t}\text{-}Bu)_4$, $La(O\textit{i}\text{-}Pr)_3$

(9) Preliminary communication of this work: Kitagawa, O.; Suzuki, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1998**, *39*, 7357−7360.

(10) In the lactonization of **2b**, when simply heating **2b** as in the case of **2a**, a chemical yield of **3b** was low due to the formation of **1b**. Thus, in this case, the lactonization through alkaline hydrolysis of the ester group was performed.

Scheme 4



difficult, while the bicyclic lactones **3a** and **3b** could be easily obtained as single stereoisomers without difficult separation. The stereochemistry of **3b** having a *cis*-fused bicyclic ring system was confirmed by X-ray analysis (see Supporting Information).

The reactions of malonate-monoamide **1c** and cyanoacetate **1d** also proceeded under the above conditions to give cyclized products **2c** and **2d**, respectively (entries 3, 4). In the reaction of **1c**, almost complete stereoselectivity was observed (entry 3), while the reaction of **1d** gave **2d** with low stereoselectivity (1.4:1, entry 4).[11] The steric factor would be one of the possible explanations for the moderate to high stereoselectivities which were observed in the reactions of **1a**−**1c**. That is, in the transition state, the iodine−olefin π-complex part may favor *trans*-relationship with phosphonyl, sulfonyl, or dialkylamide which are bulkier groups in comparison with the ester group. Therefore, the reaction of **1d** with a sterically less hindered substituent such as nitrile may result in considerable decrease in the stereoselectivity.

Under the same conditions, the reaction of malonate derivative **1e** which underwent the iodocarbocyclization as previously reported,[6] also gave **2e** in a good yield (entry 5). Thus, the present reaction is applicable to various active methine compounds.

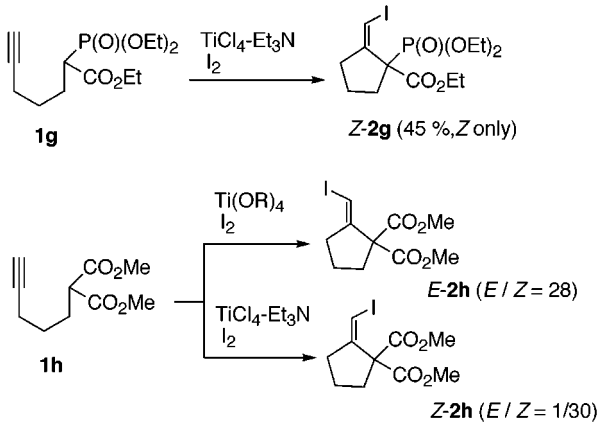
Although high stereoselectivity was not observed, the three-membered ring-forming reaction with allylphosphonoacetate **1f** also smoothly proceeded to give an (iodomethyl)cyclopropane derivative **2f** in a good yield (Entry 6).

Attempts to extend the reaction to the production of cyclohexane or cyclobutane derivatives have not yet been successful. For example, under the above conditions, the reactions of dimethyl 5-hexenylmalonate and dimethyl 4-butenylmalonate gave dimethyl (5,6-diiodohexyl)malonate and dimethyl (3,4-diiodobutenyl)malonate as the major products, respectively, without the formation of 6-*exo* and 4-*exo* iodocarbocyclization products.

All the reactions shown in Table 1 proceeded with complete *exo*-selectivity; the formation of 4- or 6-*endo*-cyclized product was not observed.

Intramolecular Carbotitanation Reaction of Various Active Methine Compounds with Alkynyl Groups. During the experiment in relation to the above reaction, we found that when the reaction of 4-pentynylphosphonoacetate **1g** was performed under the above conditions, (*Z*)-**2g** was obtained with complete stereoselectivity but not the expected iodocarbocyclized product (*E*)-**2g** (Scheme 5).[12,13] The *Z*-selectivity was also observed in the reaction of 4-pentynylmalonate derivative **1h**, which gave (*Z*)-**2h** with high stereoselectivity (*E*/*Z* = 1/30) in the presence of $TiCl_4-Et_3N$ and I_2 (Scheme 5).[14]

Scheme 5



The preferential formation of (*Z*)-**2g** and (*Z*)-**2h** was assumed to follow another reaction pathway which proceeds in a *cis*-selective manner prior to *trans*-selective iodocarbocyclization. Indeed, the cyclization reaction of **1h** smoothly proceeded even in the absence of I_2 to give methylenecyclopentane derivative **4h** in a good yield (82%) after quenching by HCl (Scheme 6, Table 2, entry 1).[15] Thus, it is obvious that the reaction of **1h** with $TiCl_4$ and Et_3N proceeds through intramolecular addition of the trichlorotitanium enolate of **1h** to the alkyne. The stereoselectivity in the carbotitanation process, which completes within 10 min at room temperature, is almost perfect and the following stereospecific iodonolysis of the resulting (*Z*)-vinyltitanium intermediate **1H** gave (*Z*)-**2h** as a single stereoisomer (Scheme 6).[16,17] Since we have already found the stereoselective construction of (*E*)-**2h** through $Ti(OR)_4$-mediated iodocarbocyclization, stereodivergent synthesis of **2h** can be possible by employing either reaction conditions (Scheme 5).

It should be also noted that, despite the existence of $Et_3N{\cdot}HCl$ in the reaction mixture, most of the vinyltita-

(11) The stereochemistries of iodides **2c** and **2d** were determined on the basis of the lactonization experiment in accordance with Scheme 4.

(12) The stereochemistries of **2g** and **4k** were determined on the basis of NOE experiments.

(13) This *Z*-selective reaction, which was carried out at −15 °C (see Supporting Information), also gave an addition product of I_2 to the C−C triple bond as a byproduct. On the other hand, the effect of temperature on the reaction pathways should be noted; that is, when the reaction of **1g** was performed at room temperature, (*E*)- and (*Z*)-**2g** were obtained in a ratio of *E*/*Z* = 4/7 in 78% yield due to a competition of both iodocarbocylization and carbotitanation−iodonolysis processes.

(14) In this reaction, I_2 was immediately added to the solution of **1h** after the addition of $TiCl_4$ and Et_3N.

(15) Excess of $TiCl_4$ (1.8 equiv) to Et_3N is required to get the cyclized product in good yield. Although the reason is not clear, the use of 1.2 equiv of $TiCl_4$ and Et_3N to 1 equiv of the substrates resulted in a considerable decrease in the chemical yield due to the formation of unidentified byproducts.

(16) After the completion of the carbocyclization was confirmed by TLC monitoring, I_2 was added to the reaction solution.

(17) The formation of the (*Z*)-vinyltitanium intermediate **1H** is in remarkable contrast to the palladium-catalyzed carbocylization of **1h**, which exclusively gives the (*E*)-vinylpalladium species via *trans*-addtion of a palladium and a malonate anion.[1b]

Scheme 6

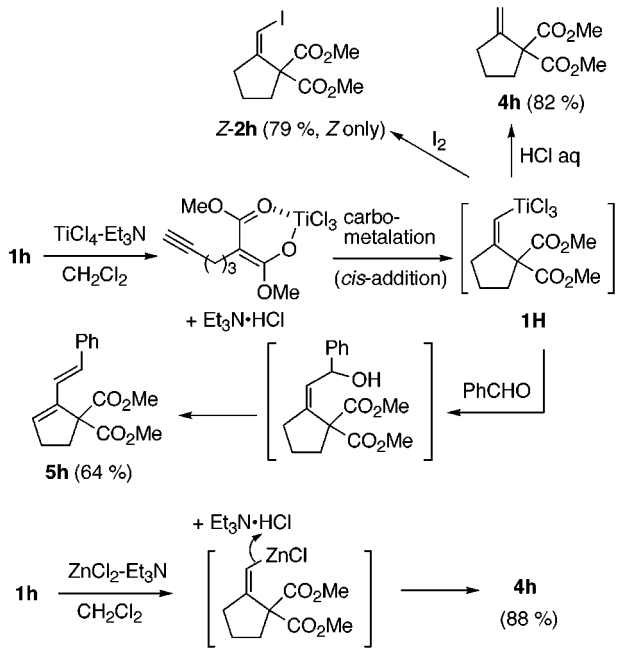
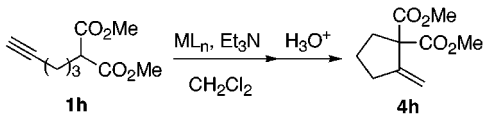


Table 2. Additive Effects in the Carbometalation of 4-Pentynylmalonate 1h[a]



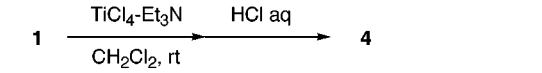
Entry	ML_n	Time	Yield (%)[b]
1	$TiCl_4$	15 min	82
2	$Ti(O\textit{i}\text{-}Pr)_4$	2.5 h	0
3	$Cl_2Ti(O\textit{i}\text{-}Pr)_4$	2h	21
4	$ZnCl_2$	15 min	88
5	BBr_3	3.5 h	0
6	$ZrCl_4$	4 h	0
7	$SnCl_4$	30 min	0

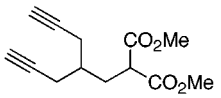
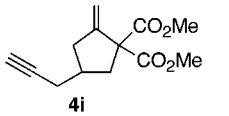
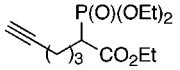
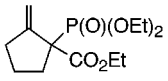
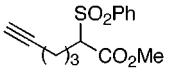
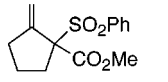
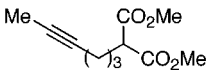
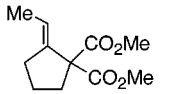
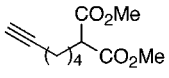
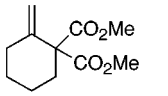
[a] Carbometalation: **1h** (1 mmol), ML_n (1.8 mmol), Et_3N (1.4 mmol), CH_2Cl_2 (8 mL), rt. [b] Isolated yield.

nium intermediate **1H** is not protonated within 10 min at room temperature and can be further functionalized by the reaction with an electrophile. The strong intramolecular coordination of two ester groups to the titanium atom may stabilize the resulting **1H**. As an example of the C−C bond-forming reaction of **1H**, the reaction of **1H** with benzaldehyde gave diene **5h** in 64% via the addition to aldehyde and the following dehydration (Scheme 6).

In contrast to $TiCl_4-Et_3N$, the cyclized product **4h** could not be obtained by the use of $Ti(O\textit{i}\text{-}Pr)_4$ or Et_3N and $Ti(O\textit{i}\text{-}Pr)_4$ (Table 2, entry 2). The reaction of **1h** with $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ and Et_3N gave **4h** in a poor yield (21%, entry 3). Thus, it is obvious that the strong Lewis acidity of the titanium atom is required for the efficient activation of the alkyne part. Although prolonged reaction time is required (14 h), the present reaction proceeded even in the absence of Et_3N to give **4h** in a good yield (80%). In this case, however, further functionalization of vinyltitanium intermediate **1H** could not be performed, because during the cyclization reaction a rapid protonation of **1H** by the resulting HCl occurs. Thus, Et_3N acts not only as a basic reagent for the deprotonation but also as an effective HCl scavenger to prevent the protonation of the vinyltitanium intermediate **1H**.

Table 3. Intramolecular Carbotitanation Reaction[a]



Entry	1	Time (h)	4	Yield (%)[b]
1	 **1i**	0.5	 **4i**	83
2	 **1g**	1.5	 **4g**	83
3	 **1j**	1	 **4j**	86
4	 **1k**	12	 **4k** (*E* only)[c]	65
5	 **1l**	1	 **4l**	34

[a] Carbotitanation: **1** (1 mmol), $TiCl_4$ (1.8 mmol), Et_3N (1.0 mmol), CH_2Cl_2 (8 mL), rt. [b] Isolated yield. [c] *Z*-isomer was not detected by 300 MHz ^{1}H-NMR.

Among the other metallic reagents examined here, the use of $ZnCl_2$ was also effective for the cyclization reaction. That is, the reaction of **1h** with $ZnCl_2$ and Et_3N gave **4h** in good yield (88%, entry 4), while the following iodination of vinylzinc intermediate failed, because the vinylzinc intermediate is easily protonated by Et_3N·HCl in the reaction mixture (Scheme 6). In the reaction of **1h** with Et_3N and other metallic reagents such as BBr_3, $ZrCl_4$, or $SnCl_4$, the cyclized product **4h** could not be obtained (entries 5−7). In the reaction with $SnCl_4$, although the complete disappearance of **1h** and the formation of an olefinic hydrogen indicated the progress of the carbocyclization, the product **4h** could not be obtained because of the difficulty of cleavage of the Sn−vinyl bond (entry 7).

The results of carbotitanation of various alkynylated active methine compounds are shown in Table 3. The reaction of bisalkynylated malonate **1i** proceeded without any side reaction at an unreacted alkynyl group to give **4i** in a good yield (83%, entry 1). Similar to malonate derivatives **1h** and **1i**, the reaction of active methine compounds **1g** and **1j** with phosphonyl and sulfonyl groups also gave the products **4g** and **4j** in good yields (entries 2, 3). On the other hand, the use of $ZnCl_2-Et_3N$, which gave a good result in the reaction of malonate **1h**, was not effective for **1g**, and the formation of cyclized product **4g** was not observed. This reaction can be also applied to disubstitued alkyne; that is, although the reaction required prolonged time in comparison with

those of 1-alkyne **1g**−**j**, 4-hexynylmalonate **1k** gave the product **4k** with complete stereoselectivity (*cis*-addition, entry 4).[12] In the six-membered ring-forming reaction with 5-hexynylmalonate **1l**, a considerable decrease in the chemical yield was observed (34%, entry 5). In all the reactions shown in Scheme 6 and Table 3, the *exo*-cyclized products were obtained as a single regioisomer without the formation of *endo*-cyclized products.

Carbotitanation reaction of an active methine compound with an alkenyl group has not been yet successful. For example, the reaction of 4-pentenylmalonate **1e** did not proceed under the same conditions, and **1e** was quantitatively recovered. Thus, the reactions in Table 1 should proceed through an iodocarbocyclization process but not the carbotitanation and following iodination process.

In conclusion, by using $TiCl_4$, Et_3N, and I_2, we have succeeded in the development of an iodocarbocyclization reaction which is applicable to various unsaturated active methine compounds. In addition, we have also found that $TiCl_4$ and Et_3N promote the carbotitanation reaction of 4-alkynylated active methine compounds which proceeds with high stereoselectivity through an intramolecular *cis*-addition of trichlorotitanium enolates of active methine compounds to alkynes. These reactions should be widely utilized as new methodology for the synthesis of cyclopentanoid compounds.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 300-MHz spectrometer. In ^1H and ^{13}C NMR spectra, chemical shifts were expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm), respectively. Mass spectra were recorded by electron impact or chemical ionization. Column chromatography was performed on silica gel (75−150 μm). Medium-pressure liquid chromatography (MPLC) was performed on a 30 × 4 cm i.d. prepacked column (silica gel, 50 μm) with a UV detector.

Starting Materials. Starting materials **1a**−**1l** were prepared according to reported procedures.[1a,b,18]

Typical Procedure of Iodocarbocyclization. To phosphonoacetate **1a** (292 mg, 1 mmol) in CH_2Cl_2 (6 mL) were added Et_3N (0.21 mL, 1.5 mmol) and $TiCl_4$ (0.2 mL, 1.8 mmol) under argon atmosphere at room temperature. After the mixture was stirred for 10 min, I_2 (381 mg, 1.5 mmol) was added, and then the reaction mixture was stirred for 2h at room temperature. The mixture was poured into 2% HCl and extracted with Et_2O. The Et_2O extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave a mixture of **1a** and major- and minor-**2a** (major-**2a**/minor-**2a** = 12). Further purification by MPLC (hexane/AcOEt = 1.5) gave minor-**2a** (less polar, 5 mg, 1%), a mixture of major- and minor-**2a** (201 mg, 48%) and major-**2a** (more polar, 121 mg, 29%), respectively.

(1*R,2*R**) and (1*R**,2*S**)-1-(Diethylphosphono)-1-(ethoxycarbonyl)-2-(iodomethyl)cyclopentane (major-2a and minor-2a).** Major-**2a**: colorless oil; IR (neat) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10−4.26 (6H, m), 3.73 (1H, dd, J = 3.1, 9.4 Hz), 3.04 (1H, dd, J = 9.4, 11.6 Hz), 2.72 (1H, m), 2.50 (1H, m), 2.22−2.38 (2H, m), 1.82 (1H, m), 1.68 (1H, m), 1.52 (1H, m), 1.33 (6H, t, J = 7.0 Hz), 1.29 (3H, dt, J = 1.0, 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 170.1, 62.9 (d, J_{C-P} = 7 Hz), 62.5 (d, J_{C-P} = 7 Hz), 61.5, 56.7 (d, J_{C-P} = 144.7 Hz), 49.4, 33.8, 33.2 (d, J_{C-P} = 11.1 Hz), 22.6 (d, J_{C-P} = 8.2 Hz), 16.5 (d, J_{C-P} = 4.4 Hz), 16.4 (d, J_{C-P} = 5.3 Hz), 14.1, 6.6; MS (*m*/*z*) 419 (M^+ + 1), 373; HRMS Calcd for $C_{13}H_{24}IO_5P$ (M^+) 418.0406, Found 418.0417. Minor-**2a**: colorless oil; IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.08−4.26 (6H, m), 3.90 (1H, dd, J = 3.2, 9.4 Hz), 3.33 (1H, dd, J = 9.4, 12.2 Hz), 2.88 (1H, m), 2.28−2.50 (2H, m), 2.10 (1H, m), 1.60−1.92 (3H, m), 1.20−1.35 (9H, m); MS (*m*/*z*) 419 (M^+ + 1), 373;

(3a*R,6a*S**)-Tetrahydro-3a(3*H*)-diethylphosphono-1*H*-cyclopenta[*c*]furan-3-one (3a).** Major-**2a** (209 mg, 0.5 mmol) was heated for 2h at 140 °C. Purification of the reaction mixture by column chromatography (hexane/AcOEt = 1) gave **3a** (124 mg, 95%). **3a**: colorless oil; IR (neat) 1768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.51(1H, dd, J = 7.4, 9.2 Hz), 4.10−4.30 (6H, m), 4.03 (1H, dd, J = 2.1, 9.2 Hz), 3.23 (1H, m), 2.00−2.32 (3H, m), 1.52−1.88 (3H, m), 1.36 (3H, t, J = 6.7 Hz), 1.33 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 176.3, 72.7 (d, J_{C-P} = 3.3 Hz), 63.2 (2 carbons, d, J_{C-P} = 6.8 Hz), 54.8 (d, J_{C-P} = 146.2 Hz), 43.4, 34.3, 34.1 (d, J_{C-P} = 4.8 Hz), 26.0 (d, J_{C-P} = 10 Hz), 16.4 (d, J_{C-P} = 3.9 Hz), 16.3 (d, J_{C-P} = 5.7 Hz); MS (*m*/*z*) 263 (M^+ + 1), 262 (M^+). Anal. Calcd for $C_{11}H_{19}O_5P$: C, 50.38; H, 7.30. Found: C, 50.26; H, 7.40.

(3a*R,6a*S**)-Tetrahydro-3a(3*H*)-(phenylsulfonyl)-1*H*-cyclopenta[c]furan-3-one (3b).** **2b** was prepared from **1b** (282 mg, 1 mmol) in accordance with general procedure of iodocarbocyclization. Purification of the residue by column chromatography (hexane/EtOAc = 3) gave a mixture of major-**2b**, minor-**2b**, and **1b** (major-**2b**/minor-**2b** = 8.6). To the mixure in THF (3 mL) and H_2O (1 mL) was added $LiOH·H_2O$ (105 mg, 2.5 mmol). After being stirred for 24 h at room temperature, the mixture was poured into 2% HCl and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 2) gave **3b** (215 mg, 81%). **3b**: colorless solid; mp 135−136 °C; IR (KBr) 1771 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (2H, d, J = 7.5 Hz), 7.70 (1H, t, J = 7.5 Hz), 7.57 (2H, t, J = 7.5 Hz), 4.50 (1H, dd, J = 8.0, 9.2 Hz), 4.05 (1H, dd, J = 2.2, 9.2 Hz), 3.67 (1H, m), 2.15−2.37 (2H, m), 2.05 (1H, m), 1.88 (1H, m), 1.75 (1H, m), 1.61 (1H, m); ^{13}C NMR ($CDCl_3$) δ 172.5, 135.6, 134.6, 130.3, 128.9, 78.3, 72.8, 42.3, 34.6, 34.4, 25.8; MS (*m*/*z*) 266 (M^+). Anal. Calcd for $C_{13}H_{14}O_4S$: C, 58.63; H, 5.30. Found: C, 58.98; H, 5.32.

(1*S,2*R**)-*N*,*N*-Diethyl 1-(Methoxycarbonyl)-2-(iodomethyl)cyclopentane-1-carboxamide (2c).** **2c** was prepared from **1c** (241 mg, 1 mmol) in accordance with general procedure of iodocarbocyclization. Purification of the residue by column chromatography (hexane/EtOAc = 5) gave **2c** (196 mg, 53%). **2c**: colorless oil; IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (3H, s), 3.61 (1H, dd, J = 3.3, 9.0 Hz), 3.36 (1H, q, J = 7.0 Hz), 3.35 (1H, q, J = 7.0 Hz), 3.15 (1H, m), 3.30−3.10 (2H, m), 2.68 (1H, dd, J = 9.0, 11.4 Hz), 2.60 (1H, m), 2.23 (1H, m), 1.82−1.96 (2H, m), 1.65 (1H, m), 1.43 (1H, m), 1.09 (6H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.6, 169.5, 62.2, 52.1, 50.7, 40.9, 39.6, 34.8, 31.3, 22.1, 13.1, 12.0, 7.4; MS (*m*/*z*) 367 (M^+), 295. Anal. Calcd for $C_{13}H_{22}INO_3$: C, 42.52; H, 6.04; N, 3.81. Found: C, 42.79; H, 6.20; N, 3.88.

Typical Procedure of an Intramolecular Carbotitanation. To alkynylmalonate **1h** (198 mg, 1 mmol) in CH_2Cl_2 (8 mL) were added Et_3N (0.14 mL, 1 mmol) and $TiCl_4$ (0.2 mL, 1.8 mmol) under argon atmosphere at room temperature. After being stirred for 15 min at room temperature, the mixture was poured into 2% HCl and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 30) gave **4h** (163 mg, 82%).

Dimethyl 2-Methylenecyclopentane-1,1-dicarboxylate (4h). ^1H NMR data of **4h** coincided with that reported in the literature.[18]

1-(Methoxycarbonyl)-1-(phenylsulfonyl)-2-methylenecyclopentane (4j). **4j** was prepared from **1j** (281 mg, 1 mmol) in accordance with general procedure of the intramolecular carbotitanation. Purification of the residue by column chromatography (hexane/EtOAc = 7) gave **4g** (241 mg, 86%). **4j**: colorless oil; IR (neat) 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (2H, d, J = 7.3 Hz), 7.65 (1H, t, J = 7.3 Hz), 7.52 (2H, t, J = 7.3

(18) Monteiro, N.; Gore, J.; Balme, *G. Tetrahedron* **1992**, *48*, 10103−10114.

Hz), 5.38 (1H, t, J = 2.1 Hz), 5.36 (1H, t, J = 2.1 Hz), 3.72 (3H, s), 2.41−2.73 (4H, m), 1.90 (1H, m), 1.69 (1H, m); ^{13}C NMR ($CDCl_3$) δ 167.6, 144.3, 136.4, 133.9, 131.0, 128.2, 116.6, 80.0, 53.1, 34.6, 34.0, 24.0; MS (*m*/*z*) 280 (M^+), 241. Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 59.84; H, 5.87.

(*Z*)-Dimethyl 2-iodomethylenecyclopentane-1,1-dicarboxylate [(*Z*)-2h]. To alkynylmalonate **1h** (198 mg, 1 mmol) in CH_2Cl_2 (8 mL) was added Et_3N (0.14 mL, 1 mmol) and $TiCl_4$ (0.2 mL, 1.8 mmol) under argon atmosphere at room temperature. After the mixture was stirred for 15 min, I_2 (508 mg, 2 mmol) was added, and then the reaction mixture was stirred for 30 min at room temperature. The mixture was poured into 2% HCl and extracted with Et_2O. The Et_2O extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 20) gave (*Z*)-**2h** (256 mg, 79%). ^{1}H NMR data of (*Z*)-**2h** coincided with that reported in the literature.[6b]

(*E*)-Dimethyl 2-(2′-Phenylethenyl)-2-cyclopentene-1,1-dicarboxylate (5h). To alkynylmalonate **1h** (198 mg, 1 mmol) in CH_2Cl_2 (8 mL) were added Et_3N (0.14 mL, 1 mmol) and $TiCl_4$ (0.2 mL, 1.8 mmol) under argon atmosphere at room temperature. After the mixture was stirred for 15 min, benzaldehyde (0.1 mL, 1 mmol) was added, and then the reaction mixture was stirred for 45 min at room temperature. The mixture was poured into 2% HCl and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 30) gave **5h** (183 mg, 64%). **5h**; colorless oil; IR (neat) 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40 (2H, d, J = 7.2 Hz), 7.28−7.33 (2H, t, J = 7.2 Hz), 7.22 (1H, t, J = 7.2 Hz), 6.80 (1H, d, J = 16.5 Hz), 6.74 (1H, d, J = 16.5 Hz), 6.22 (1H, t, J = 2.6 Hz), 3.77 (6H, s), 2.53−2.66 (4H, m); ^{13}C NMR ($CDCl_3$) δ 171.6, 139.7, 137.4, 134.2, 130.3, 128.5, 127.5, 126.4, 122.6, 66.6, 52.7, 35.2, 31.0; MS (*m*/*z*) 286 (M^+), 227; HRMS calcd for $C_{17}H_{18}O_4$ (M^+) 286.1205, found 286.1207.

Supporting Information Available: Characterization data and experimental pocedures of **2d**−**g**, **4i**, **4g**, **4k**, and **4l**, and X-ray crystal data of **3b** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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