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[2 + 2 + 1] Cycloaddition between Alkynes, Acrylates, and Titanocene(II): Regioselective Formation of 5-Alkoxycarbonyltitanacyclopent-2-enes and Their Addition to Carbonyls

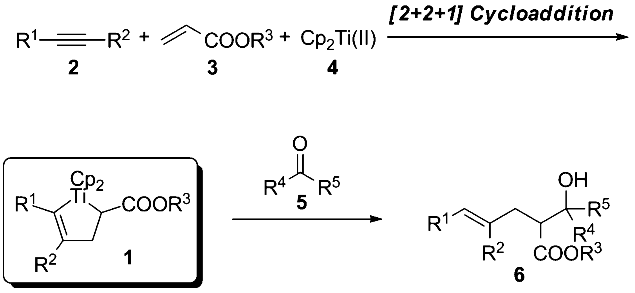
Shigeki Oishi, Kaoru Ohomika, Akira Tsubouchi, and Takeshi Takeda*
Department of Applied Chemistry, Graduate School of Engineering,
Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588

(Received April 16, 2010; CL-100373; E-mail: takeda-t@cc.tuat.ac.jp)

5-Alkoxycarbonyltitanacyclopent-2-enes were produced regioselectively by the [2 + 2 + 1] cycloaddition between alkynes, acrylates, and titanocene(II) reagent $Cp_2Ti[P(OEt)_3]_2$. Although the titanacycles were inactive toward carbonyl compounds, their addition proceeded in the presence of titanocene(II).

Five-membered metallacycles of group 4 metals play important roles in organic synthesis. For instance, metallacyclopentadienes are utilized for the synthesis of biologically active compounds[1a–1c] and organic functional materials such as acenes[1d–1f] and π-conjugated polymers.[1g] Therefore, the elucidation of their structures and reactivities is significant in early-transition-metal chemistry, and much effort has focused on the preparation and isolation of five-membered group 4 metallocene complexes such as metallacyclopentanes,[2] -pent-3-enes,[3] -pentadienes,[4] -pentynes,[5] and -pentatrienes.[6] As for the construction of titanacyclopent-2-enes, a variety of protocols have been disclosed.[7] They include the ring enlargement of a titana[3]-radialene,[7a] dimerization of a titanacyclocumulene,[7b] and the [2 + 2 + 1] cycloaddition of alkynes, alkenes, and divalent titanium species.[7c–7f] Although the third approach is apparently most versatile and straightforward, only ethylene[7c,7d] and some symmetric strained olefins have been employed.[7e,7f]

Our group is studying the formation of titanacycles by [2 + 2][8] and [2 + 2 + 1][9] cycloadditions and their application to organic synthesis. The [2 + 2 + 1] process between alkynes, alkenes bearing a leaving group such as vinyl pivalate and alkenyl sulfones, and titanocene(II)–triethyl phosphite complex affords titanacyclopentenes bearing a leaving group β to titanium as transient intermediates. Simultaneous β-elimination produces dienyltitaniums. This finding prompted us to pursue an alternative regioselective mode of formation of functionalized titanacyclopentenes. We describe here the regioselective formation of 5-alkoxycarbonyltitanacyclopent-2-enes **1** by the [2 + 2 + 1] cycloaddition between alkynes **2**, acrylates **3**, and titanocene(II) reagent $Cp_2Ti[P(OEt)_3]_2$ **4** and their reactivity as enolate equivalents (Scheme 1).



Scheme 1.

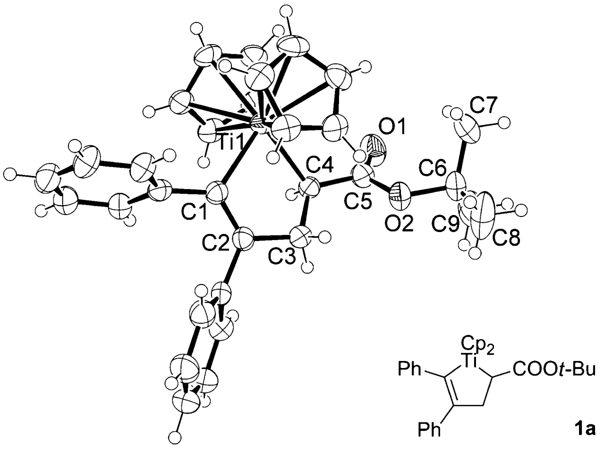
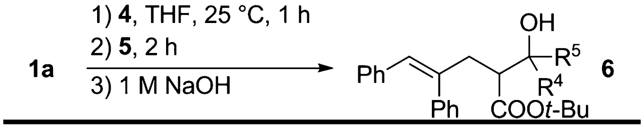


Figure 1. The ORTEP view of molecular structure of **1a**. Selected bond distances (Å) and angles (°): Ti1–C1 2.178(3), Ti1–C4 2.238(3), C1–C2 1.348(5), C2–C3 1.517(4), C3–C4 1.530(5); C1–Ti1–C4 79.23(12), Ti1–C1–C2 113.1(2), C1–C2–C3 119.4(3), C2–C3–C4 110.8(3), C3–C4–Ti1 105.4(2).

The treatment of diphenylacetylene (**2a**) with *tert*-butyl acrylate (**3a**) in THF at 25 °C for 3 h in the presence of titanocene(II) reagent **4** produced the titanacyclopent-2-ene **1a** with perfect regioselectivity. Although **1a** was found to be susceptible to both air and moisture, it could be isolated as a dark red powder in 61% yield by alumina column chromatography under N_2. The molecular structure of **1a** was unambiguously determined by X-ray diffraction analysis (Figure 1).[10] The bond lengths of Ti–C1 and Ti–C4 are in the typical region,[7b] and the structure further shows the expected C–C bond lengths of a five-membered ring.

The metallacycle **1a** showed interesting reactivity toward carbonyl compounds.[11] The titanium enolate equivalent **1a** was completely inactive toward ketones and aldehydes **5** even at elevated temperature (Table 1, Entry 1). By contrast, the reaction of **1a** with carbonyl compounds carried out in the presence of an equimolar amount of the low-valent titanium reagent **4** at 25 °C for 2 h gave 2-(hydroxymethyl)alk-4-enoates **6**. Thus the successive treatment of **1a** with titanocene(II) reagent **4** (1 equiv) and ketones **5a**–**5d** (2 equiv) produced (*Z*)-2-(1-hydroxymethyl)-4,5-diphenylpent-4-enoates **6a**–**6d** in 45–88% yields (Table 1). Decreasing the loading of **4** to 0.5 equiv

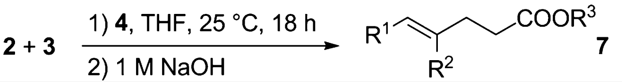
Table 1. The reaction of titanacyclopentene **1a** with carbonyl compounds **5**



Entry	5	R^4	R^5	6	Yield/%^{a}
1^{b}	**5a**	$-(CH_2)_2CHPh(CH_2)_2-$		**6a**	0
2^{c}	**5a**	$-(CH_2)_2CHPh(CH_2)_2-$		**6a**	63^{d}
3	**5a**	$-(CH_2)_2CHPh(CH_2)_2-$		**6a**	88^{d}
4	**5b**	Et	Et	**6b**	73
5	**5c**	$Ph(CH_2)_2$	$Ph(CH_2)_2$	**6c**	68
6	**5d**	*i*-Pr	Me	**6d**	45^{e}
7	**5e**	$Ph(CH_2)_2$	H	**6e**	72^{f}

^{a}Isolated yield based on the titanacyclopentene **1a** used. ^{b}Carried out without **4** in the presence and absence of $MgCl_2$. ^{c}Carried out with 0.5 equiv of **4**. ^{d}Single isomer. ^{e}The ratio of diastereoisomers = 63:37. ^{f}The ratio of diastereoisomers = 65:35.

Table 2. The cross-coupling between alkynes **2** and acrylates **3**

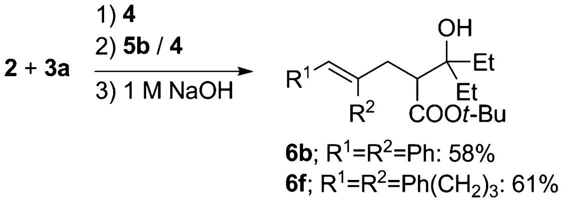


Entry	2	R^1	R^2	3	R^3	7	Yield/%^{a}
1	**2a**	Ph	Ph	**3a**	*t*-Bu	**7a**	74
2^{b}	**2b**	$Ph(CH_2)_3$	$Ph(CH_2)_3$	**3a**	*t*-Bu	**7b**	64
3	**2c**	Me	Pent	**3a**	*t*-Bu	**7c**	62^{c}
4	**2d**	Bu	Ph	**3a**	*t*-Bu	**7d**	64^{c}
5	**2e**	2-Thienyl	Hex	**3a**	*t*-Bu	**7e**	59^{c}
6	**2f**	Ph	Ph	**3b**	Me	**7f**	54

^{a}Isolated yield based on alkyne **2** used. ^{b}Quenching the reaction with excess D_2O produced the dideuterated ester (C2; 93%D, C5; 91%D). ^{c}The ratios of regioisomers = 62:38 (**7c**), 80:20 (**7d**), 82:18 (**7e**). The structures of major isomers are given.

resulted in the formation of **6a** in 63% yield (Entry 2). Although we have no experimental evidence for the role of additional titanocene(II) reagent **4**, we tentatively assume that certain organotitanium species would be formed by the treatment of **1** with **4**. The aldehyde **5e** also reacted with **1a** to produce **6e** in good yield (Entry 7). When unsymmetrical carbonyl compounds were employed, mixtures of diastereomers were produced (Entries 6 and 7). The double bond formation in these reactions was found to be completely stereoselective: the NOE experiment of all the adducts indicated that two phenyl groups originating from **2a** were completely *cis* to each other.

The formation of titanacyclopent-2-enes **1** also proceeded by using various alkynes **2**. The titanacycles **1** other than **1a** were too unstable to be isolated and hence transformed into the unsaturated esters **7** by hydrolysis (Table 2). This suggests that the unusual stability of **1a** is due to the kinetic stabilization provided by the bulky two Cp rings and C1-phenyl group. When unsymmetrical alkynes were employed, the interesting regioselectivity was observed. The reaction of 1-phenyl-1-hexyne (**2d**) produced the 4-phenylnon-4-enoate **7d** as a major product (Entry 4) whereas the reaction of 1-(2-thienyl)-1-octyne (**2e**) gave the 5-(2-thienyl)pent-4-enoate **7e** preferentially (Entry 5). These results might indicate that the regioselectivity of the formation of titanacyclopenetene **1** is controlled by the coordination of a heteroatom to titanium.



6b; R^1=R^2=Ph: 58%
6f; R^1=R^2=$Ph(CH_2)_3$: 61%

Scheme 2.

Based on the above results, the one-pot, three-component coupling of alkynes **2**, acrylates **3**, and carbonyl compounds **5** was examined (Scheme 2). After the preparation of **1a** by the reaction of **2a** with **3a**, the resulting titanacycle **1a** was further treated with pentan-3-one (**5b**) and the titanocene(II) species **4** to produce **6b** in good yield. A comparable result was also obtained using **2b** as a coupling component.

In conclusion, we found that the [2 + 2 + 1] cycloaddition between alkynes, acrylates, and titanocene(II) reagent produced 5-alkoxycarbonyltitanacyclopent-2-enes regioselectively.[12] We have succeeded in the isolation of a monocyclic titanacyclopent-2-ene and elucidated its molecular structure and unique reactivity toward carbonyl compounds. Further study on the regioselective preparation of a variety of functionalized titanacyclopentenes and their synthetic application is currently underway.

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10 Crystal data for titanacyclopent-2-ene **1a**: $C_{31}H_{32}O_2Ti$, $M_r = 484.47$, $0.50 \times 0.01 \times 0.01\,\text{mm}^3$, monoclinic, $P2_1/c$, $a = 7.55713(14)$, $b = 24.3338(4)$, $c = 14.7771(3)\,\text{Å}$, $\beta = 110.7360(10)°$, $V = 2541.40(8)\,\text{Å}^3$, $Z = 4$, $T = 193\,\text{K}$, $D = 1.266\,\text{g cm}^{-3}$, $\mu(\text{Cu K}\alpha) = 3.040\,\text{mm}^{-1}$, $R_{\text{int}} = 0.0462$, number of measured/independent reflections = 47169/4606, $R = 0.0469$ and $wR = 0.1319$ (all data). Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-760628. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U.K.; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

11 Similar reactivity of titanacyclopentenes, generated by the intramolecular cyclization of alk-2-en-7-ynoates and alk-2-en-8-ynoates with (η^2-propene)Ti(O*i*-Pr)$_2$, reacted with carbonyl compounds at α to the ester group was reported: H. Urabe, K. Suzuki, F. Sato, *J. Am. Chem. Soc.* **1997**, *119*, 10014.

12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.