DOI: 10.1002/ejoc.200500976

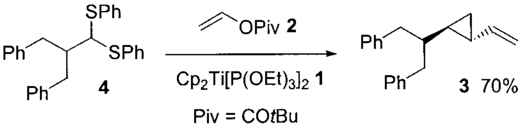
Titanocene(II)-Promoted Cross-Coupling of Unsaturated Compounds

**Akitoshi Ogata,[a] Masami Nemoto,[a] Koutarou Arai,[a] Kenji Kobayashi,[a]
Akira Tsubouchi,[a] and Takeshi Takeda*[a]**

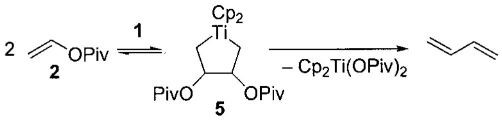
Keywords: Allylic alcohols / Cross-coupling / Conjugated dienes / Metallacycles / Titanium

Vinyl pivalate in the presence of the titanocene(II) reagent $Cp_2Ti[P(OEt)_3]_2$ reacts both with nonpolar C≡C triple bonds and with polar C=O double bonds, to produce conjugated dienes and allylic alcohols, respectively. Similar alkenylation also takes place when (Z)-alkenyl sulfones are treated with alkynes and carbonyl compounds.

We recently reported two methods for the transformation of thioacetals into cyclopropanes. Alkyl-substituted cyclopropanes are produced through reactions between thioacetals and vinyl pivalate (**2**) promoted by the titanocene(II) reagent $Cp_2Ti[P(OEt)_3]_2$ (**1**), whilst vinylcyclopropanes are obtained by treatment of thioacetals with the titanocene(II) reagent **1** and buta-1,3-dienes.[1] During this study we found that the vinylcyclopropane **3** was produced when the pivalate **2** (3 equiv.) was treated successively with excess quantities of **1** (7 equiv.) and the thioacetal **4** at 25 °C for 2 h (Scheme 1). The formation of **3** indicates that buta-1,3-diene is formed by the self-coupling of **2**, probably via the titanacyclopentane intermediate **5**, in which equilibrium of the formation of titanacycle **5** would be favored by elimination of titanocene dipivalate (Scheme 2). This result prompted us to investigate a new titanocene(II)-promoted intermolecular cross-coupling of unsaturated compounds via a similar titanacycle intermediate.

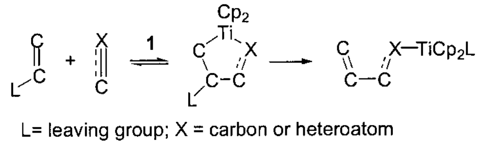


Scheme 1. Formation of vinylcyclopropanes.



Scheme 2. Self-coupling of vinyl pivalate (**2**).

Transition-metal-catalyzed reactions between alkenyl halides or sulfonates and alkenylmetal compounds[2] – such as Suzuki coupling,[3] Stille coupling,[4] and Hiyama coupling[5] – are frequently employed for carbon–carbon bond formation between two sp^2 carbon atoms. A major synthetic route to the alkenylmetal compounds used in these reactions is hydrometallation of alkynes. Direct cross-coupling between alkenes containing a leaving group and alkynes, promoted by a low-valent metal species **1** as depicted in Scheme 3, would therefore be advantageous: the procedure should give conjugated dienes, the products of the above conventional cross-couplings, without the need for prior transformation of alkynes into any alkenylmetal species. Another advantage of this methodology is that it should also be applicable to reactions of compounds possessing a carbon–heteroatom multiple bond.



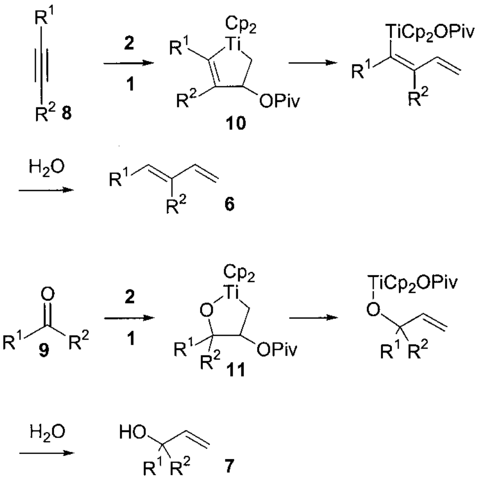
Scheme 3. Titanocene(II)-promoted cross-coupling of unsaturated compounds.

In this context, we have studied titanocene(II)-promoted cross-couplings between vinyl pivalate (**2**) and unsaturated compounds, and here we describe the preparation of conjugated dienes **6** and allylic alcohols **7** through reactions between **2** and alkynes **8** or carbonyl compounds **9**, via the titanacycle intermediates **10** and **11** (Scheme 4). These reactions are useful in that vinyl pivalate (**2**), a poor substrate for transition-metal-catalyzed cross-couplings, is available as a coupling component.

Treatment of alkynes **8** with vinyl pivalate (**2**) (3 equiv.) in the presence of titanocene(II) reagent **1** (3 equiv.) at 0–25 °C for 2.5 h produced the conjugated dienes **6** in good yields (Table 1). Although the reactions of unsymmetrical alkynes generally proceeded with mixed regioselectivity, high selectivity was observed when phenylacetylene deriva-

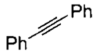
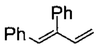
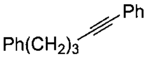
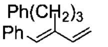
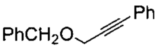
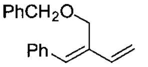
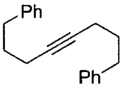
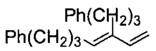
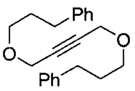
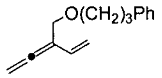
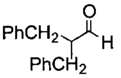
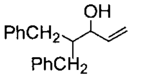
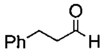
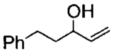
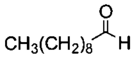
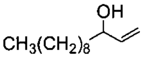
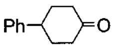
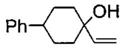
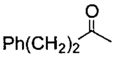
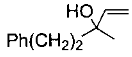
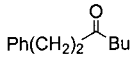
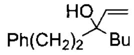
---

[a] Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology,
Koganei, Tokyo 184-8588, Japan
Fax: +81-42-388-7034,
E-mail: takeda-t@cc.tuat.ac.jp

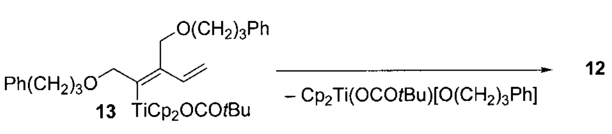


Scheme 4. Titanocene(II)-promoted vinylation of alkynes and carbonyl compounds.

Table 1. Reactions between unsaturated compounds and vinyl pivalate (**2**).

Entry	Unsaturated Compound		Product (Yield / %)	
1		**8a**		**6a** (82[a])
2		**8b**		**6b** (83)
3		**8c**		**6c** (72)
4		**8d**		**6d** (37)
5		**8e**		**12** (73)
6		**9a**		**7a** (82)
7		**9b**		**7b** (72)
8		**9c**		**7c** (72)
9[b]		**9d**		**7d** (70)
10[b]		**9e**		**7e** (65)
11[b]		**9f**		**7f** (51)

[a] Contaminated with **8a**. Yield was determined by NMR analysis. [b] Carried out at –10 °C overnight.

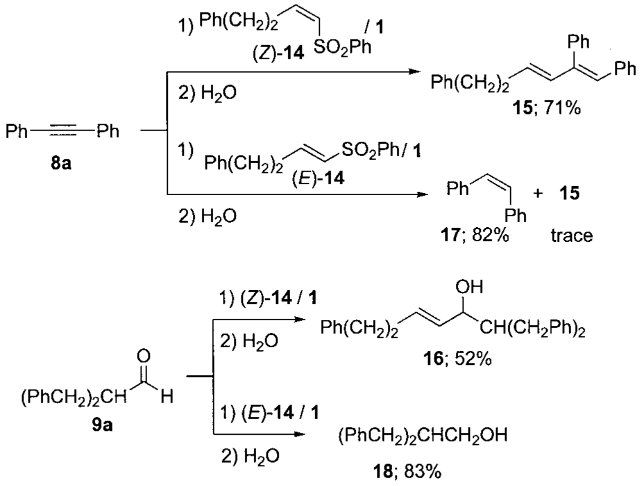


Scheme 5. Formation of vinylallenes.

tives were employed; only the regioisomers in which a vinyl group was attached at the carbon atom β to the phenyl group were produced (Entries 2 and 3). The formation of the vinylallene **12** (Entry 5) supports the hypothetical reaction pathway depicted in Scheme 4 because it is reasonable to assume that β-elimination of the initially produced dienyltitanium intermediate **13** affords the allene **12** (Scheme 5). Aliphatic aldehydes **9** also reacted with vinyl pivalate (**2**) under the same reaction conditions to produce allylic alcohols **7** (Entries 6–8). Reactions between aliphatic ketones and **2** also produced the alcohols **7** at lower reaction temperatures (Entries 9–11). It was found, however, that aromatic and α,β-unsaturated carbonyl compounds were inappropriate substrates for this reaction; treatment of these compounds with the pivalate **2** and titanocene(II) reagent **1** resulted in the formation of complex mixtures.

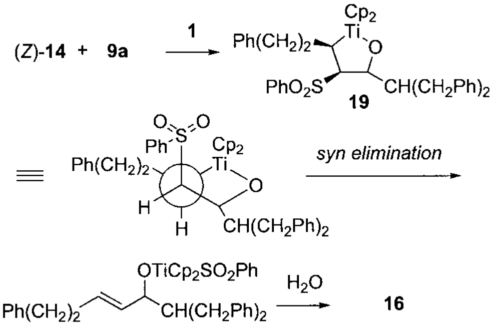
Some synthetic reactions that involve the formation of five-membered titana-[6] and zirconacycles[7] and their subsequent β-elimination have been investigated. The diethylzirconocene-promoted intermolecular reactions between ethyl vinyl ether and alkynes proceed through the formation of zirconacyclopentenes and subsequent elimination of an ethoxy group, similarly to the present reaction.[8] Couplings of unsaturated compounds via three-membered titanacycles have been reported; in the presence of the divalent titanium alkoxide complex, alkynes react with allyl[9] and propargyl[10] carbonates intermolecularly.

It is noteworthy that this reaction is a versatile method for the intermolecular vinylation of both polar and nonpolar multiple bonds, and this methodology could be extendable to alkenylation of multiple bonds. Such idea has been partly substantiated with the (*Z*)-alkenyl sulfone (*Z*)-**14** (Scheme 6). Treatment of diphenylacetylene (**8a**) with (*Z*)-**14** (2 equiv.) in the presence of **1** (2 equiv.) at 0–25 °C for 2.5 h gave the diene **15**, while a similar reaction between (*Z*)-**14** and the aldehyde **9a** produced the allylic alcohol **16**. It was of great interest that the reduction products **17** and **18**, rather than the alkenylation products, were isolated when the corresponding (*E*) isomer (*E*)-**14** was employed. The formation of these compounds is attributable to the reaction of the unsaturated compounds with the titanocene(II) reagent **1**, without involvement of the (*E*)-alkenyl sulfone. These results imply that the cross-coupling proceeds through a cyclic transition state similar to **10** and **11**, associated with titanocene(II), alkenyl sulfone, and alkyne or carbonyl group, in which the (*E*) isomer may suffer steric hindrance much more than the (*Z*) isomer.



Scheme 6. Alkenylation of alkynes and carbonyl compounds.

The stereochemistry of these reactions is also fascinating; the configuration of the double bond originating from (*Z*)-alkenyl sulfone is (*E*). The observed stereospecificity is completely different from that of the alkenylation of carbonyl compounds with alkenyl halides through the formation of alkenylmetal compounds such as Nozaki–Hiyama–Kishi reaction,[11] which generally proceeds with retention of configuration. The stereospecificity is interpreted in terms of the formation of the titanacycle **19** with retention of configuration and subsequent *syn* elimination as shown in Scheme 7.



Scheme 7. Stereochemical course of alkenylation.

In conclusion, we have established a novel vinylation, promoted by the titanocene(II) reagent, of compounds containing multiple bonds with vinyl pivalate (**2**). As implied in the reaction of alkenyl sulfones, the concept of this cross-coupling could be applicable to the stereoselective alkenylation of a variety of unsaturated compounds and could provide a comprehensive approach for the construction of carbon frameworks. Study along these lines is currently underway.

Experimental Section

Typical Experimental Procedure: Finely powdered molecular sieves (4 Å, 90 mg), magnesium turnings (24 mg, 0.99 mmol), and Cp_2TiCl_2 (224 mg, 0.9 mmol) were placed in a flask and dried by heating with a heat gun in vacuo (2–3 Torr). After the system had cooled, THF (1.5 mL) and $P(OEt)_3$ (0.31 mL, 1.8 mmol) were added successively with stirring under argon at 25 °C. After 3 h, the reaction mixture was cooled to 0 °C. A THF (1 mL) solution of **2** (115 mg, 0.9 mmol) was added dropwise over 5 min to the mixture, which was then stirred for 30 min. After a THF (1 mL) solution of **8b** (66 mg, 0.3 mmol) had been added dropwise over 10 min, stirring was continued at 0 °C for 30 min and then at 25 °C for 2 h. The reaction was quenched by addition of 1 M NaOH. The usual workup and purification by column chromatography on silica gel (hexane) gave **6d** (62 mg, 83%).

Acknowledgments

This work was carried out under the 21th Century COE "Future Nanomaterials" program at Tokyo University of Agriculture and Technology.

---

[1] T. Takeda, K. Arai, H. Shimokawa, A. Tsubouchi, *Tetrahedron Lett.* **2005**, *46*, 775–778.

[2] *Metal-catalyzed Cross-coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[3] a) A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749–1758; b) F. Bellina, R. Carpita, R. Rossi, *Synthesis* **2004**, 2419–2440; c) F. Robert, X. Youjun, *Can. J. Chem.* **2005**, *83*, 266–272; d) A. Suzuki, *Chem. Commun.* **2005**, 4759–4763.

[4] a) J. K. Stille, *Pure Appl. Chem.* **1985**, *57*, 1771–1780; b) E. Pablo, E. M. Antonio, *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734; c) A. M. Echararren, *Angew. Chem. Int. Ed.* **2005**, *44*, 3962–3965.

[5] a) T. Hiyama, Y. Hatanaka, *Pure Appl. Chem.* **1994**, *66*, 1471–1478; b) T. Hiyama, *J. Organomet. Chem.* **2002**, *653*, 58–61.

[6] a) Y. Takayama, S. Okamoto, F. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 3559–3560; b) R. Nakajima, H. Urabe, F. Sato, *Chem. Lett.* **2002**, 4–5; c) Y. Song, S. Okamoto, F. Sato, *Tetrahedron Lett.* **2002**, *43*, 6511–6514; d) Y. Song, Y. Takayama, S. Okamoto, F. Sato, *Tetrahedron Lett.* **2003**, *44*, 653–657.

[7] a) T. Takahashi, D. Y. Kondakov, N. Suzuki, *Chem. Lett.* **1994**, 259–262; b) T. Takahashi, R. Hara, S. Huo, Y. Ura, M. P. Leese, N. Suzuki, *Tetrahedron Lett.* **1997**, *38*, 8723–8726; c) D. B. Millward, R. M. Waymouth, *Organometallics* **1997**, *16*, 1153–1158; d) A. Ligard, J. Kaftanov, H. Chechik, S. Farhat, N. Morlender-Vais, C. Averbuj, I. Marek, *J. Organomet. Chem.* **2001**, *624*, 26–33; e) S. Farhat, I. Marek, *Angew. Chem. Int. Ed.* **2002**, *41*, 1410–1413; f) J. Barluenga, L. Álvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, *Angew. Chem. Int. Ed.* **2004**, *43*, 3932–3935; g) J. Barluenga, F. Rodríguez, L. Álvarez-Rodrigo, F. J. Fañanás, *Chem. Eur. J.* **2004**, *10*, 101–108; h) J. Barluenga, F. Rodríguez, L. Álvarez-Rodrigo, J. M. Zapico, F. J. Fañanás, *Chem. Eur. J.* **2004**, *10*, 109–116; i) S. Farhat, I. Zouev, I. Marek, *Tetrahedron* **2004**, *60*, 1329–1337.

[8] T. Takahashi, D. Y. Kondakov, Z. Xi, N. Suzuki, *J. Am. Chem. Soc.* **1995**, *117*, 5871–5872.

[9] Y. Takayama, Y. Gao, F. Sato, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 851–853.

[10] C. Delas, H. Urabe, F. Sato, *J. Am. Chem. Soc.* **2001**, *123*, 7938–7973.

[11] a) K. Takai, K. Kimura, T. Kuroda, T. Hiyama, H. Nozaki, *Tetrahedron Lett.* **1983**, *24*, 5281–5284; b) Y. Kishi, *Pure Appl. Chem.* **1992**, *64*, 343–350.

Received: December 14, 2005