ORGANIC LETTERS

2007
Vol. 9, No. 15
2875−2878

Titanocene(II)-Promoted, One-Pot, Three-Component Coupling of Thioacetals, Alkynyl Sulfones, and Carbonyl Compounds: Highly Stereoselective Formation of *tert*-Homopropargyl Alcohols

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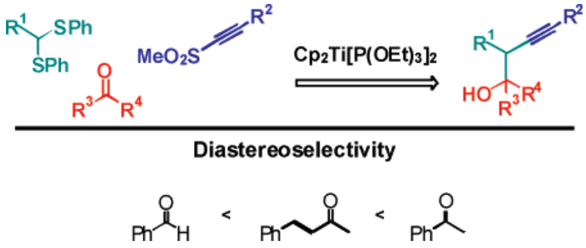
Received May 8, 2007

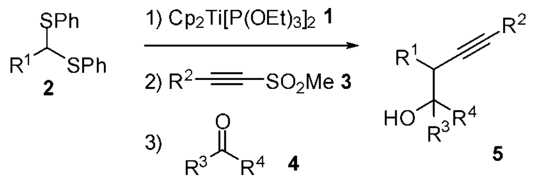
ABSTRACT



Titanocene alkylidene complexes, generated by desulfurizative titanation of thioacetals with $Cp_2Ti[P(OEt)_3]_2$, reacted with alkynyl methyl sulfones to produce organotitanium species, which gave *tert*-homopropargyl alcohols with high diastereoselectivity on treatment with aromatic and α,*β*-unsaturated ketones.

Much attention has been paid to one-pot multistep reactions because of their synthetic efficiency. Recently, we reported preparation of vinylallenes by the titanocene(II)-promoted one-pot multistep reaction utilizing alkynyl sulfones, alkenyl sulfones, and carbonyl compounds.[1] This finding prompted us to further investigate multicomponent coupling using the titanocene(II) and alkynyl sulfones. Here we wish to describe a new $Cp_2Ti[P(OEt)_3]_2$ **1**-promoted three-component coupling between thioacetals **2**, alkynyl sulfones **3**, and carbonyl compounds **4** and unusual diastereoselective formation of *tert*-homopropargyl alcohols **5** (Scheme 1).

Scheme 1



Previously, we reported the formation of conjugated dienes by the reaction of alkylidenetitanocenes **6**, generated by the desulfurizative titanation of thioacetals **2**, with alkynes.[2] The reaction presumably proceeds via the formation of titanacyclobutenes. We anticipated that allenyltitaniums **7** would be produced by the reaction of carbene complexes **6** with alkynyl sulfones **3** via the formation of titanacyclobutene intermediates **8** (Scheme 2).

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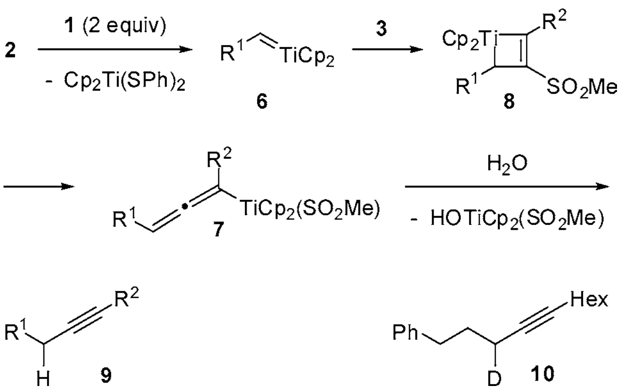
[1] Ogata, A.; Nemoto, M.; Kobayashi, K.; Tsubouchi, A.; Takeda, T. *Chem.*—*Eur. J.* **2007**, *13*, 1320−1325.

[2] Takeda, T.; Shimokawa, H.; Miyachi, Y.; Fujiwara, T. *Chem. Commun.* **1997**, 1055−1056.

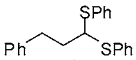
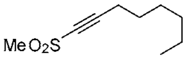
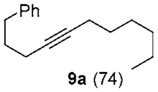
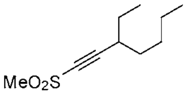
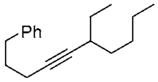
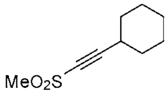
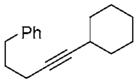
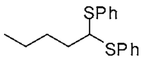
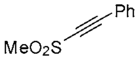
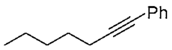
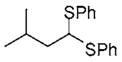
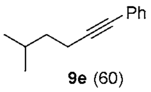
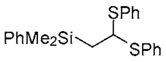
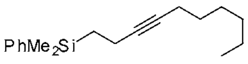
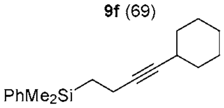
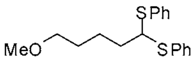
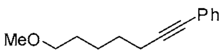
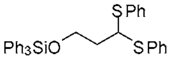
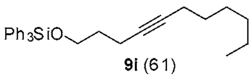
10.1021/ol071077w CCC: $37.00

Scheme 2



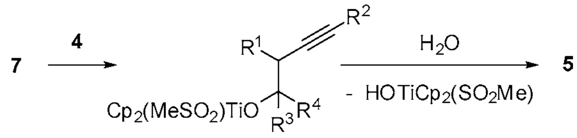
Indeed, the successive treatment of the thioacetal **2a** (1.5 equiv) with the titanocene(II) reagent **1** (4.5 equiv) and the alkynyl sulfone **3a** at 25 °C followed by hydrolysis produced the internal alkyne **9a** in 74% yield (Table 1, entry 1). When the reaction of **2a** with **3a** was quenched with D_2O, the deuterated alkyne **10** (ca. 100% D) was obtained in 68% yield, which suggested the formation of the intermediary allenyltitanium compound **7**. Similarly, various alkynes were obtained by the reaction of alkynyl methyl sulfones **3** with alkylidenetitanocenes **6** generated from thioacetals **2**.

Table 1. Titanocene(II) **1**-Promoted Reaction of Thioacetals **2** with Alkynyl Methyl Sulfones **3**

entry	thioacetal **2**	alkynyl sulfone **3**	alkyne **9** (yield / %)
1	 **2a**	 **3a**	 **9a** (74)
2	**2a**	 **3b**	 **9b** (73)
3	**2a**	 **3c**	 **9c** (75)
4	 **2b**	 **3d**	 **9d** (57)
5	 **2c**	**3d**	 **9e** (60)
6	 **2d**	**3a**	 **9f** (69)
7	**2d**	**3c**	 **9g** (71)
8	 **2e**	**3d**	 **9h** (59)
9	 **2f**	**3a**	 **9i** (61)

Preparation of allenylmetals has been extensively studied,[3] and their reaction with carbonyl compounds provides a useful synthetic route to homopropargyl alcohols. Therefore, the allenyltitanium species **7** generated by the above reaction were expected to react with carbonyl compounds **4** to produce homopropargyl alcohols **5** (Scheme 3). Indeed, treatment of aldehydes (2 equiv) with the organotitanium species generated from thioacetals **2** (1.2 equiv), sulfones **3**, and **1** (3.6 equiv) in THF gave homopropargyl alcohols **5**, and no formation of the isomeric allenyl alcohols was observed (Table 2, entries 1−3).

Scheme 3



Yamamoto et al. first reported preparation of allenyltitaniums by lithiation of alkynes followed by transmetalation with Ti(O^{i}Pr)$_4$.[4] Similar allenyltitaniums have been prepared by the reaction of propargyl substrates with a titanium reagent generated from Ti(O^{i}Pr)$_4$ and ^{i}PrMgBr.[5] Although the 1,3-disubstituted allenyltitanium reagents formed by these methods react with aldehydes at a temperature below −20 °C, ketones do not react with these reagents[5a] with the exception of intramolecular reaction.[5b] In contrast, **7** do react with ketones to produce tertiary alcohols **5**. Considering that Ding et al. reported that the allenyltitanium reagents generated from propargyl acetates and a certain titanocene(II) species react with acetone at 0 °C,[6] it is reasonable to assume that thermal stability of the allenyltitaniums bearing Cp ligands enables them to react with ketones at a rather high temperature.

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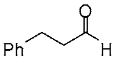
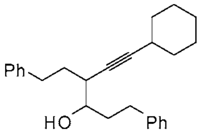
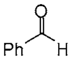
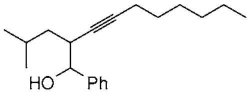
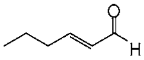
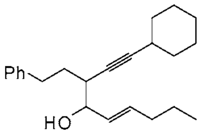
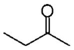
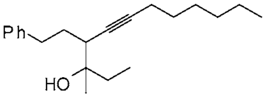
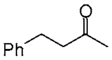
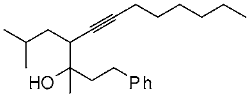
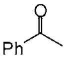
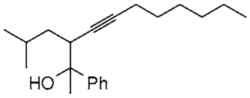
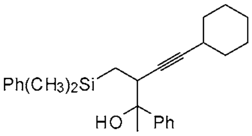
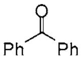
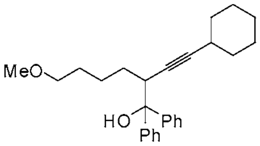
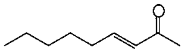
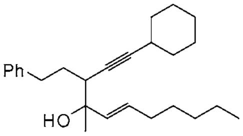
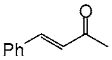
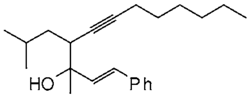
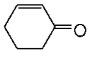
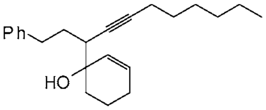
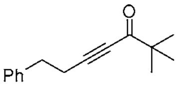
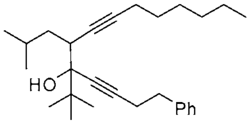
(3) (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 2. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316. (c) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31−47. (d) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163−3185. (e) Marshall, J. A.; Gung, B. W.; Grachan, M. L. In *Modern Allen Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 493−592. For recent examples, see: (f) Lai, C.; Soderquist, J. A. *Org. Lett.* **2005**, *5*, 799−802. (g) Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840−4844. (h) Groth, U.; Kesenheimer, C.; Neidhöfer, J. *Synlett* **2006**, 1859−1862. (i) Hegedus, L. S.; Ranslow, P.; Achmatowicz, M.; de los Rios, C.; Hyland, C.; Gracia-Frutos, E. M.; Salman, S. *Pure Appl. Chem.* **2006**, *78*, 333−339. (j)Vrancken, E.; Alouane, N.; Gérard, H.; Mangeney, P. *J. Org. Chem.* **2007**, *72*, 1770−1779 and references cited therein.

(4) (a) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225−2227. (b) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768−2776.

(5) (a) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835−2886. (b) Yoshida, Y.; Nakagawa, T.; Sato, F. *Synlett* **1996**, 437−438. (c) Hanazawa, T.; Okamoto, S.; Sato, F. *Org. Lett.* **2000**, *2*, 2369−2371. (d) Okamoto, S.; Matsuda, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **2001**, *42*, 6323−6326.

(6) Yang, F.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2001**, *42*, 2839−2841.

Table 2. Three-Component Coupling of Thioacetals **2**, Alkynyl Sulfones **3**, and Carbonyl Compounds **4**

entry	thioacetal **2**	alkynyl sulfone **3**	carbonyl compound **4**	homopropargyl alcohol **5** (yield / %;[a] ratio of diastereomers)
1	**2a**	**3c**	 **4a**	 **5a** (63; 52 : 48[b])
2[c]	**2c**	**3a**	 **4b**	 **5b** (58; 50 : 50[d])
3	**2a**	**3c**	 **4c**	 **5c** (64; 53 : 47[b])
4[c]	**2a**	**3a**	 **4d**	 **5d** (60; 62 : 38[e])
5	**2c**	**3a**	 **4e**	 **5e** (66; 70 : 30[b])
6	**2c**	**3a**	 **4f**	 **5f** (68; single isomer[d,e])
7	**2d**	**3c**	**4f**	 **5g** (70; single isomer[d,e])
8[f]	**2e**	**3c**	 **4g**	 **5h** (68)
9	**2a**	**3c**	 **4h**	 **5i** (68; 89 : 11[e])
10[c]	**2c**	**3a**	 **4i**	 **5j** (66; 90 : 10[d])
11	**2a**	**3a**	 **4j**	 **5k** (70; 90 : 10[d,e])
12	**2c**	**3a**	 **4k**	 **5l** (68; single isomer[d])

[a] Isolated yield. [b] Based on the isolated yields of the diastereomers. [c] 3 equiv of **4** was used. [d] Determined by NMR analysis. [e] Determined by GLC analysis. [f] 1.2 equiv of **4g** was used.

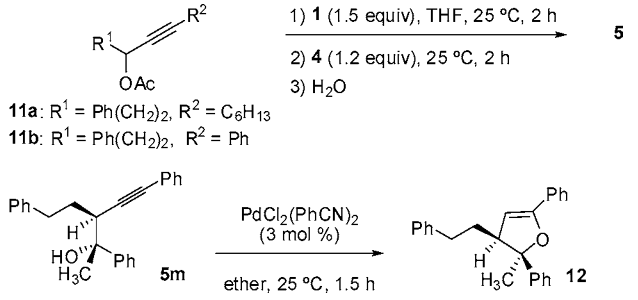
The three-component coupling can also be applied to α,*β*-unsaturated carbonyl compounds. Selective 1,2-additon of the allenyltitanium intermediates **7** takes place in the case of both enals and enones (Table 2, entries 3, 9, and 10−12). Despite the extensive studies on the reactivity of allenylmetal reagents, only a few reactions with enones have been known.

Danheiser et al. reported $TiCl_4$-promoted reaction of allenylsilanes with enones which involves the 1,4-addition process.[7] As far as we know, there is no report on the selective 1,2-addition of allenylmetal species to α,β-unsaturated ketones.

The diastereoselectivity is also dependent on the ligands of allenyltitaniums. The reaction of allenyltitanium reagents bearing ^{i}PrO ligands with aldehydes tends to produce *anti* homopropargyl alcohols with good selectivity.[3,6a] No selectivity, however, was observed in the reaction of the Cp congeners **7** with aldehydes (Table 2, see entries 1−3). In contrast, the reaction of **7** with aliphatic ketones showed moderate diastereoselectivity, and high stereoselectivity was observed when α,β-unsaturated and aromatic ketones were employed. Addition of allylmetal species to carbonyl compounds has been extensively studied as a useful tool for preparation of homoallylic alcohols.[3a,e,8] Reactions of γ-substituted allylmetals with aldehydes generally produce secondary homoallylic alcohols bearing adjacent chiral centers with high diastereoselectivity, but the selectivity tends to decrease when ketones are employed. In this context, recently, much attention has been paid to diastereoselective addition of allylmetals to ketones and several highly diastereoselective reactions with aromatic ketones have been reported.[9] *To the best of our knowledge, however, no reaction which produces tertiary alcohols more diastereoselectively than secondary alcohols has been reported.* Therefore, the selectivity observed in the present reaction is of special interest from the mechanistic as well as synthetic points of view.

The same diastereoselective formation of tertiary alcohols **5** was also observed in the reaction of allenyltitanium species formed by the reductive titanation of propargylic acetates **11** with **1**: the reactions of **11a** with **4j** and **11b** with **4f** gave **5k** (69%, ratio of isomers; 90:10) and **5m** (67%, single isomer), respectively (Scheme 4). The Pd-catalyzed cyclization[10] of **5m** produced the dihydrofuran **12** in 94% yield. A positive NOE observed between 2-CH_3 and 3-H of **12** suggests that the reaction of allenyltitanium species **7** with acetophenone (**4f**) proceeds with *syn* stereochemistry.

Scheme 4



In summary, we have established a new three-component coupling of thioacetals, alkynyl sulfones, and carbonyl compounds promoted by the titanocene(II) reagent providing access to *tert*-homopropargyl alcohols. Further study on the elucidation of high diastereoselectivity observed in the reaction of allenyltitaniums **7** with ketones is currently underway.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 18350018) and Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" (No. 18037017) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and characterization data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071077W

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