Regio- and stereoselective formation of conjugated dienes by titanocene(II)-promoted alkylation of propargyl carbonates[†]

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Conjugated dienes were produced with complete regio- and stereoselectivity by the titanocene(π)-promoted alkylation of propargyl carbonates *via* the formation of 2,3,4-trisubstituted titanacyclobutenes.

Preparation of titanacyclobutenes 1 has been the subject of considerable recent attention because of their unique reactivity and synthetic potential. A variety of titanacyclobutenes 1 bearing two identical substituents at the 2- and 3-positions have been prepared by the reaction of symmetrical alkynes with titanocene methylidene complex.¹ However, poor regioselectivity is observed when unsymmetrical alkynes are employed. We reported the formation of 2,3,4-trisubstituted titanacyclobutenes 1 by the reaction of titanocene-alkylidenes generated by the reductive titanation of thioacetals or 1,1dichlorocyclopropanes with alkynes.² The reaction with unsymmetrical alkynes, however, also lacks regioselectivity. Therefore, the preparation of 1 bearing a variety of substituents at any positions is crucial for the development of unsaturated titanacycle chemistry. In this context, recently we disclosed a new method for the preparation of mono- and disubstituted titanacyclobutenes by the reaction of γ -chloroallylic sulfides with the titanocene(II) reagent Cp₂Ti[P(OEt)₃]₂ 2.³ We have further explored a straightforward and general method for the generation of titanacyclobutenes 1, and here we describe a novel method for the stereoselective preparation of conjugated dienes 3 via the formation of titanacycles 1 starting from propargyl carbonates 4.

Our new approach for the generation of titanacycles **1** is outlined in Scheme 1. We recently reported that allenyltitanocenes **5** were produced by the reductive titanation of propargyl

alcohol derivatives with the titanocene(II) reagent 2.⁴ Further treatment of 5 with 2 generates the titanacyclopropanes 6 which are then alkylated to form gem-dititanium species 7. Elimination of the titanium(IV) species Cp₂TiXY affords titanium carbene complexes 8. As for the formation of titano-titanacycles, Marek and coworkers reported the generation of titano-titanacyclopropenes by the reaction of alkynyl chlorides with Ti(Oi-Pr)₄-i-PrMgBr.⁵ Titanium alkenylcarbene complexes 8 are present in equilibrium with titanacyclobutenes 1 and the position of equilibrium is dependent on their substitution patterns.³ Since the position of equilibrium lies far toward titanacycles 1 when they possess two substituents at the 2- and 3-positions, we expected that the organotitanium species generated from y-monosubstituted propargyl carbonates 4 ($R^1 = H$) according to Scheme 1 exclusively exist as titanacyclobutenes 1 ($R^1 = H$).

Indeed, successive treatment of the organotitanium species, generated by the reductive titanation of the γ -monosubstituted propargyl carbonate **4a** with the titanocene(II) reagent **2** (3 equiv.) at 25 °C for 35 min, with benzyl chloride (**9a**) (3 equiv., 25 °C, 2 h) and D₂O (55 equiv., 25 °C, 18 h) produced the dideuterated Z-alkene **10** with retention of the stereochemistry of the double bond of **1a**. Similar stereoselective formation of alkenes by the protonation of titanacyclobutenes has been observed.^{2b} The formation of **10** clearly indicates that the titanacycle **1a** was formed by the sequential reactions of **4a** (Scheme 2).

The thermal stability of titanacyclobutenes is also dependent on their substitution pattern. As shown in Scheme 3, 2,3,4-trisubstituted titanacyclobutenes 1 having a β -hydrogen on the substituent at the 4-position are thermally unstable and readily decompose through β -elimination to afford conjugated dienes 3 stereoselectively.^{2a,c} We therefore



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 Table 1
 Reaction of the propargyl carbonate 4b with alkylating agents 9

anticipated that 3 would be produced by a similar reaction using α, γ -disubstituted propargyl carbonates 4 via trisubstituted titanacyclobutenes 1 illustrated in Scheme 3. Then the generation of organotitanium species by the treatment of α, γ -disubstituted propargyl carbonates 4 with the titanocene(II) reagent 2 and the following reaction with various alkylating agents 9 were examined. As was expected, the conjugated E,E-diene 3a was produced with complete regio- and stereoselectivity by the treatments of 4b with 2 (3 equiv.) at 25 °C for 35 min and then with methallyl chloride (9b) (3 equiv.) for 2 h (Table 1, entry 1).[‡] In a similar fashion, the titanocene(II) 2-promoted reactions of 4b with various alkylating agents 9 were examined. The reaction using benzyl chloride (9a) gave the corresponding diene 3b in good yield (entry 2). In contrast, a similar reaction of 4b with benzyl bromide (9c) was complicated and the formation of only a trace amount of 3b was observed (entry 3). Although the reaction with the secondary chloride 9d produced the diene **3c**, the alkene **11** was produced as the only isolable product when butyl chloride (9e) was employed (entry 5). The formation of 11 could be explained by the difference between the modes of alkylation: the dititanium species 6a acts as an allyltitanium species toward the primary halide 9e exclusively and the subsequent hydrolysis of the resulting titanacyclopropene 12 affords the Z-alkene 11^6 (Scheme 4). Styrene



oxide (9f) could also be employed for the alkylation of dititanium species 6a and the dienyl alcohol 3d was obtained (entry 6).

Regio- and stereoselective formation of a variety of conjugated dienes **3** was also achieved by using various α,γ -disubstituted propargyl carbonates **4**. As shown in Table 2, the carbonates **4** having a primary alkyl or aryl substituent at the γ -position reacted with alkylating agents **9** to give the conjugated dienes **3** in good yields. The introduction of a bulky secondary alkyl group at the α - or γ -position, however, significantly decreased the yields of **3** (see entries 8 and 9). Since the starting materials, propargyl carbonates **4**, are available by the addition of alkynyllithiums to aldehydes followed by esterification with ethyl chloroformate, the present method enjoys an advantage in that 1,3-butadienes having various substituents at the 1-, 2- and 4-positions are readily obtained with complete regio- and stereoselectivity.

Table 2 Reaction of propargyl carbonates 4 with alkylating agents 9



 a Isolated yield. b 1-Cyclohexyl-5-phenyl-1-pentyne was obtained in 31% yield.

In conclusion, we have developed a general and complete regioselective method for the generation of highly substituted titanacyclobutenes, which are difficult to generate regioselectively by conventional methods using titanium carbene complexes and alkynes. The present titanocene(π)-promoted reaction of propargyl carbonates and alkylating agents is useful for the complete regio- and stereoselective preparation of conjugated 1,3-dienes.

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Notes and references

‡ A representative experimental procedure is as follows: finely powdered molecular sieves 4 Å (120 mg), magnesium turning (35 mg, 1.44 mmol) and Cp₂TiCl₂ (299 mg, 1.2 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure. After cooling, THF (3 mL) and P(OEt)₃ (0.41 mL, 2.4 mmol) were successively added with stirring at 25 °C under argon. After 3 h, a THF (2 mL) solution of 3-(ethoxycarbonyloxy)-1,5-diphenyl-1-pentyne (**4b**) (123 mg, 0.40 mmol) was added to the reaction mixture at 25 °C. After 35 min, a THF (1 mL) solution of methallyl chloride (**9b**) (109 mg, 1.2 mmol) was added dropwise over 3 min and the mixture was further stirred for 2 h. The reaction was quenched by addition of 1 M NaOH, and the insoluble materials were filtered off through Celite and washed with diethyl ether and dried over Na₂SO₄. After

removal of the solvent, the residue was purified by PTLC (hexane) to give (5*E*)-2-methyl-7-phenyl-4-[(*E*)-phenylmethylidene]-1,5-heptadiene (**3a**) (91 mg, 83%). **3a**: found: C, 91.72; H, 8.20. C₂₁H₂₂ requires C, 91.92; H, 8.08%; $\delta_{\rm H}$ (300 MHz, CDCl₃, Me₄Si) 1.80 (s, 3 H), 3.07 (s, 2 H), 3.48 (d, *J* = 7.0 Hz, 2 H), 4.72–4.79 (m, 1 H), 4.83–4.89 (m, 1 H), 5.85 (dt, *J* = 15.6, 7.0 Hz, 1 H), 6.25 (d, *J* = 15.6 Hz, 1 H), 6.60 (s, 1 H) and 7.12–7.36 (m, 10 H); $\delta_{\rm C}$ (75 MHz, CDCl₃) 23.5, 36.2, 39.2, 111.0, 126.0, 126.7, 128.2, 128.4, 128.55, 128.59, 128.8, 131.4, 135.4, 137.2, 137.6, 140.5 and 143.0; $\nu_{\rm max}/{\rm cm}^{-1}$ 3081, 3025, 2968, 2910, 1651, 1599, 1495, 1451, 1030, 962, 891, 750 and 698.

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