

Science "Spring" Seminar

Carbonyl Olefination (2)

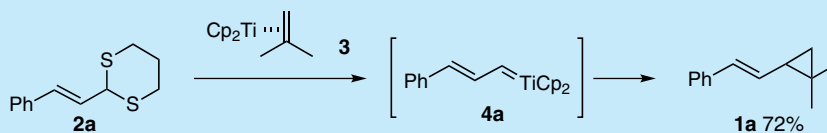
Takeshi Takeda

Department of Applied Chemistry, Tokyo University of Agriculture and Technology

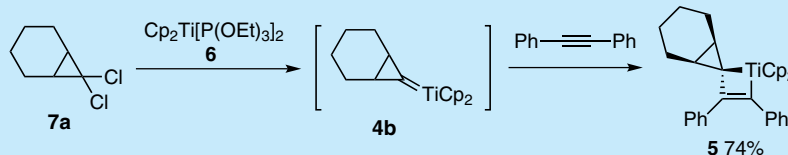
1. Titanium-carbene complexes

In 1995, we found that alkenylcyclopropanes **1** were produced by the reaction of β,γ -unsaturated thioacetals **2** with the titanocene(II)-olefin complexes **3** (Scheme 1).¹⁾ Since the active species generated by the desulfurizative titination of thioacetals were supposed to be the nucleophilic Schrock-type carbene complexes **4**, we have studied their reactions with a variety of unsaturated compounds. Although the

direct experimental evidence supporting the intermediary titanium carbene complexes has never been obtained so far, in 2008, we succeeded in the isolation and characterization of titanacyclobutene **5** bearing a spiro-bonded cyclopropane produced by the titanocene(II) **6**-promoted reaction of *gem*-dichloride **7a** with diphenylacetylene (Scheme 2)²⁾ and this experimental result indirectly but certainly supports the formation of carbene complex **4b**.



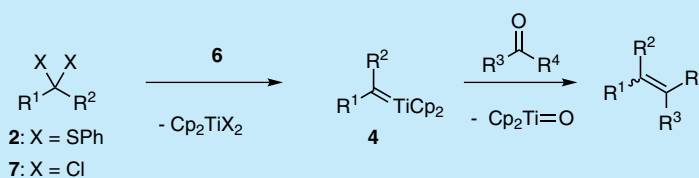
Scheme 1



Scheme 2

Similarly to methylidenetitanocene, generated from the Tebbe reagent, the titanium carbene complexes **4** produced by the reductive titination of thioacetals **2** or *gem*-dichlorides **7**

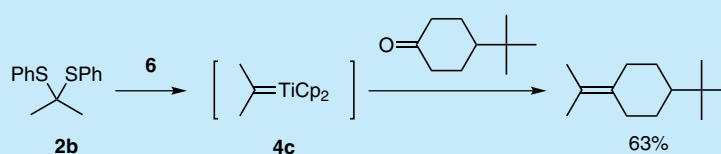
react with various carbonyl compounds (Scheme 3), and we have explored the distinctive advantages of this reaction over conventional carbonyl olefinations such as the Wittig reaction.³⁾



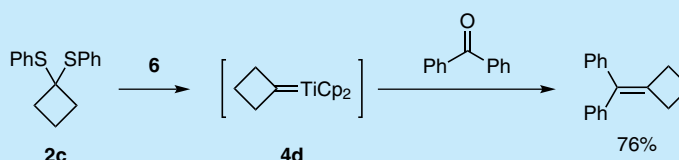
Scheme 3

As described in the previous article, the transformation of ketones into tetrasubstituted olefins is one of the most difficult problems remained in carbonyl olefination, and hence we challenged this problem by using titanium carbene complexes. For the synthesis of tetrasubstituted olefins, highly substituted alkylidene complexes are required. The desulfurative

titanation of certain sterically less crowded thioketals such as those derived from acetone **2b** and cyclobutanone **2c** affords the corresponding tetrasubstituted alkylidene complexes **4c** (Scheme 4)⁴ and **4d** (Scheme 5).⁵ In contrast, no carbene complexes are generated from more bulky thioketals.



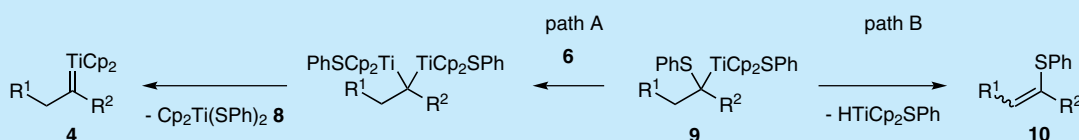
Scheme 4



Scheme 5

We assumed that the formation of carbene complexes proceeds through the stepwise reductive titration of two C-S bonds and following elimination of bis(phenylthio)titanocene **8** (Scheme 6, path A). In the case of thioketals bearing two bulky

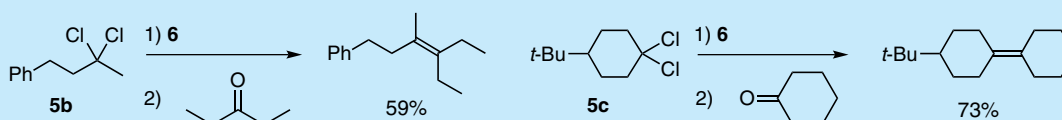
substituents, its steric hindrance interferes with the second reductive titration of C-S bond of the alkyltitanium species **9**, and, instead, the β -hydride elimination preferentially proceeds to produce alkenyl sulfides **10** (path B).



Scheme 6

In view of the fact that a C-Cl bond is more reactive than a C-S bond toward the titanocene(II) reagent, we assumed that the carbene complexes might be produced by using *gem*-dichlorides as starting materials. As we expected, tetrasubstituted olefins were obtained by the reaction of ketones with the organotitanium species generated by the reductive titration of

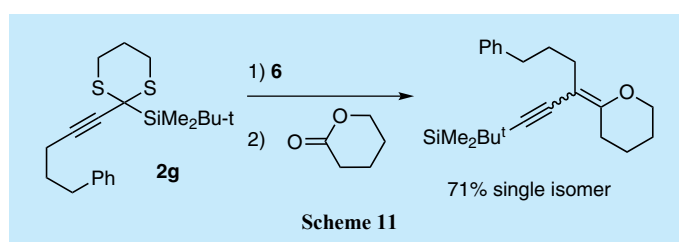
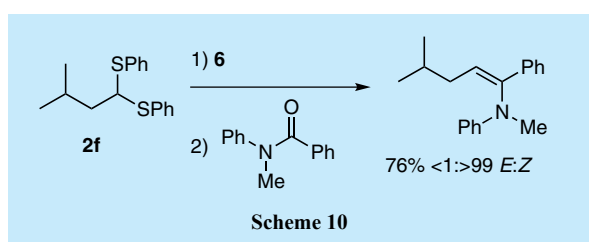
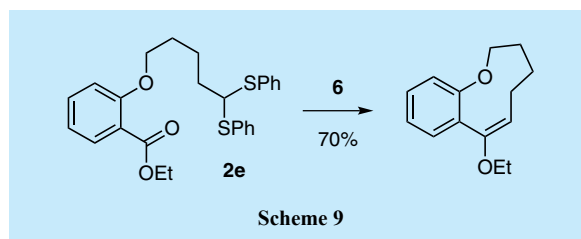
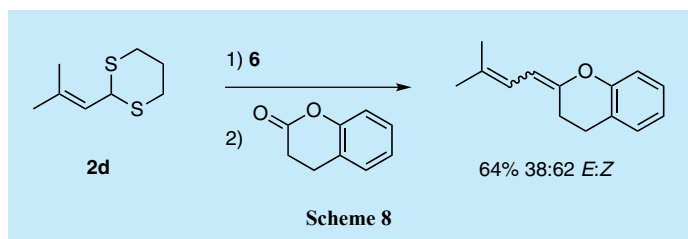
gem-dichlorides (Scheme 7).⁶ This olefination, however, still has a limitation in that it cannot be applied to the preparation of ethylenes having four ethyl or more sterically bulky alkyl groups and, to my regret, the conversion of ketones into highly substituted olefins is still a big challenge.



Scheme 7

Our carbonyl olefination using carbene complexes also found to be an answer to the several problems remained in the carbonyl olefination of carboxylic acid derivatives. As shown in Schemes 8,⁴⁾ 9,⁷⁾ 10,⁸⁾ and 11,⁹⁾ the treatment of esters, lactones, thioesters, and amides with a variety of carbene complexes generated from thioacetals and *gem*-dihalides affords the

corresponding heteroatom-substituted olefins. Since thioacetals are generally stable under various conditions, carboxylic acid derivatives bearing a thioacetal moiety are readily prepared and their intramolecular carbonyl olefination enables us to synthesize a range of carbo- and heterocycles as exemplified in Scheme 9

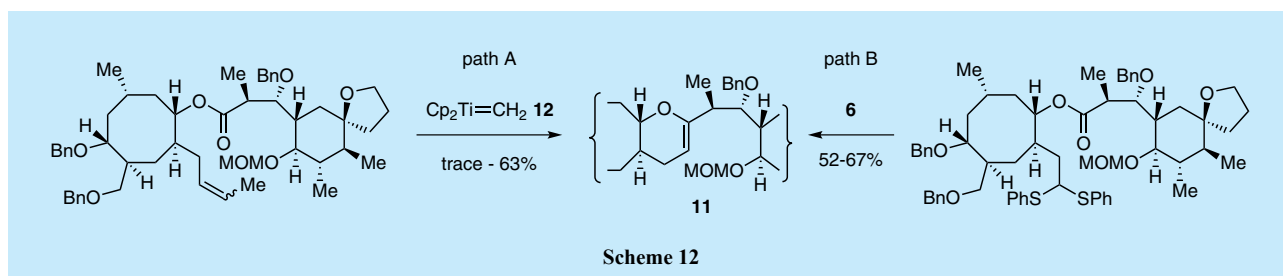


2. New reactions are rarely used as practical methods

One of my former students, who was involved in the study on the titanium carbene complexes in my group, had to synthesize highly substituted olefins during his post-doctoral work. He tried most of carbonyl olefination reactions including the Wittig reaction, but failed to get the desired product. Finally he decided to use the carbene complex generated from thioacetal and obtained the olefination product in a satisfactory yield. This episode tells us that we should accept the bitter reality that newly developed reactions are rarely used by other chemists as practical synthetic methods.

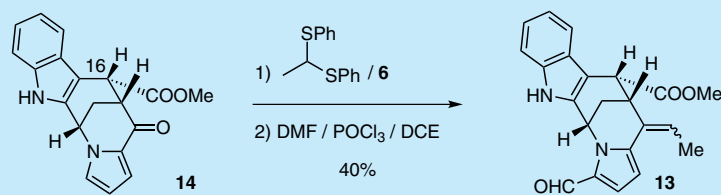
The carbonyl olefination using thioacetal-titanocene(II)

system was utilized for the construction of J-ring of ciguatoxin **11** (Scheme 12) by Prof. Hiram of Tohoku University.¹⁰⁾ To the best of my knowledge, this is the first application of our carbonyl olefination to the synthesis of natural products. Initially their strategy for the formation of J-ring was based on the method reported by Nicolaou et al., which consists of methylenation of the ester moiety in the J-ring precursor with methylenetitanocene **12** generated from the Tebbe reagent and the following ring-closing metathesis (Path A). This approach, however, was poorly reproducible and hence they needed an alternative method. They finally employed our intramolecular carbonyl olefination (Path B) which realized the gram-scale preparation of **11** with good reproducibility.



The thioacetal-based carbonyl olefination was also employed as “the last option” for the final ethylenation in the total synthesis of alstoscholarine **13** (Scheme 13).¹¹⁾ Since the ketone **14** was completely inactive toward the ylide generated from ethyltriphenylphosphonium salts, the addition of the ethyl Grignard reagent to the BOC-protected

14 and following dehydration was examined. Although such successive transformation gave the ethylenation product, the epimerization at the C-16 position also proceeded due to high basicity of the Grignard reagent. Then they tried the use of thioacetal-titanocene(II) system and obtained the desired olefination product as a mixture of stereoisomers (*E:Z* = ca. 3:1).

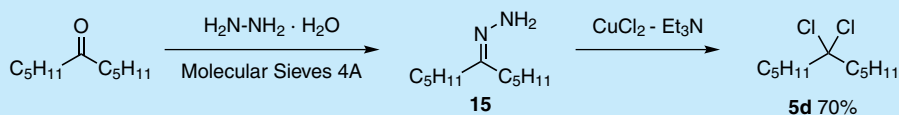


Scheme 13

3. We need to explore how to prepare novel starting materials

One of the major factors which determines the utility of synthetic reactions is the availability of starting materials. Even though the reaction itself is excellent, no one wants to use it if the preparation of starting material is troublesome or extremely difficult. As described above, the carbonyl olefination using *gem*-dichlorides is quite useful for the preparation of highly substituted olefins. However, there was no efficient method

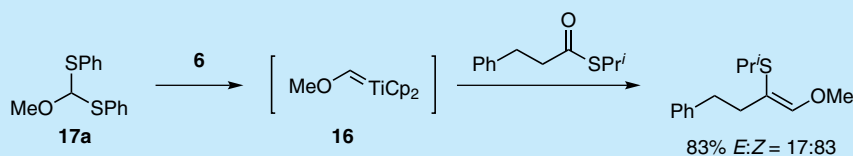
for the preparation of *gem*-dichlorides from ketones when we started this study. In general, *gem*-dichlorides are prepared by the reaction of ketones with phosphorous trichloride or thionyl chloride,¹²⁾ but it is quite difficult to suppress the concomitant formation of alkenyl chlorides due to the acidic reaction conditions. Then we explored an alternative way to obtain *gem*-dichlorides as pure forms and found a new method for their preparation from ketones via hydrazones **15** (Scheme 14).¹³⁾ Our new method enables us to prepare highly substituted carbene complexes and their use for carbonyl olefination.



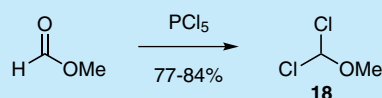
Scheme 14

Another reaction which we disclosed with the preparation of its starting materials is the alkoxy methylenation of carbonyl compounds. In 1998, we reported a new method for the preparation of enol ethers using methoxy group substituted carbene complexes **16** generated from methoxybis(phenylthio)methane (**17a**) (Scheme 15).¹⁴⁾ The starting material **17a** was prepared by the reaction of thiophenol with dichloromethyl methyl ether (**18**) obtained by the treatment of methyl formate with phosphorus pentachloride (Scheme 16).¹⁵⁾ If appropriate

dithioorthoformates **17** are available, a variety of enol ethers which are difficult to prepare by other methods are obtained because any dithioorthoformates **17** can be transformed into the corresponding carbene complexes. So a big question is how to obtain dithioorthoformates **17**. Preparation of functionalized dithioorthoformates from the corresponding formats is not feasible because the conversion of formats into dichloromethyl ethers must be carried out under strongly acidic conditions.



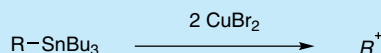
Scheme 15



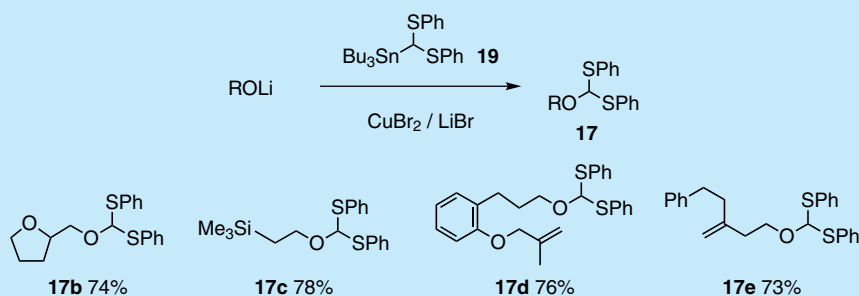
Scheme 16

In this context, after five years or so, we began to explore a new method for the preparation of functionalized dithioorthoformates **17**. Our basic idea for this problem is that *carbocation equivalents must be formed by the two electrons oxidation of organotin compounds* (Scheme 17). Indeed, the simple operation involving the treatment of tributyl[bis(phenylthio)methyl]stannane (**19**) with

lithium alkoxides and copper(II) bromide gave acid-labile dithioorthoformates bearing a terminal double bond or β -trimethylsilyl group (Scheme 18).¹⁶ The carbene complexes generated from these organosulfur compounds reacted with a variety of carbonyl compounds to produce enol ethers which are difficult to prepare by the conventional methods.



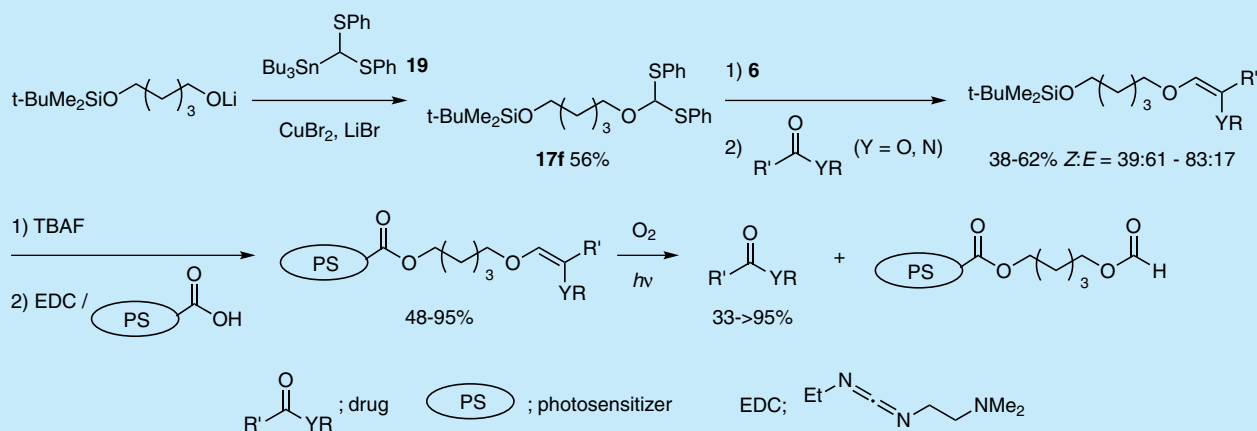
Scheme 17



Scheme 18

This sequence of reactions was employed for the construction of the site-specific prodrug release system (Scheme 19).¹⁷ Drugs are released through the scission of double bond bearing two heteroatoms by visible-light irradiation. The above carbonyl olefination using dithioorthoformates is probably only

a method of producing such double bonds, and the preparation of dithioorthoformate **17f** containing a TBDMS-protected hydroxyl group would be achieved only by the method using the organotin compound **19**.



Scheme 19

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Introduction of the author :

Takeshi Takeda

Professor, Department of Applied Chemistry, Tokyo University of Agriculture and Technology

Takeshi Takeda obtained his Ph.D. (1977) in chemistry from Tokyo Institute of Technology. He joined the University of Tokyo as an Assistant Professor in 1977. After a half year of postdoctoral work at University of California, Los Angeles, he moved to Tokyo University of Agriculture and Technology as an Associate Professor in 1981. He was appointed to a Professorship in 1994.

He received an Incentive Award in Synthetic Organic Chemistry, Japan (1987) and a Chemical Society of Japan Award for Creative Work (2003).

His current research interests include organic chemistry, organometallic chemistry, and organic synthesis.