Science "Winter" Seminar

Carbonyl Olefination (1)

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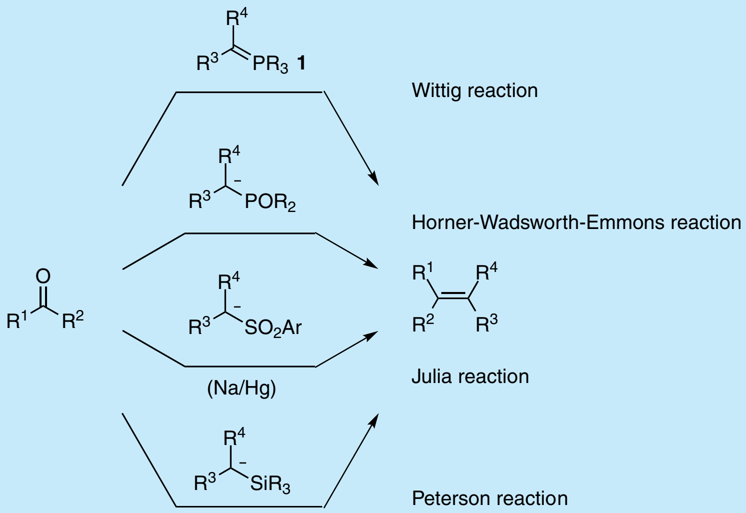
1. Introduction

In 1953, Wittig and Geissler reported that olefins were produced by the reaction of phosphonium ylides with carbonyl compounds.[1] This reaction, now known as the Wittig reaction,[2] enjoys a great advantage in that no ambiguity exists as to the location of the double bond in the product. Since the discovery of the Wittig reaction, the transformation of a C=O double bond of the carbonyl compound into a C=C double bond, often called as carbonyl olefination, has been extensively studied as one of the most important methods for the construction of carbon skeletons. Thus a variety of reactions, such as the Horner–Wadworth–Emmons reaction using organophosphorous compounds,[3] two Julia reactions (the Julia-Lythgoe and Julia-Kocienski reactions, see the column on the next page) using organosulfur compounds,[4] and the Peterson reaction using organosilicon compounds,[5] have been developed for this transformation (Scheme 1). Depending on their characteristic reactivity and selectivity, these reactions are employed for the synthesis of various organic molecules.

Despite these extensive studies, many problems still remain unsolved in carbonyl olefination. In this article, some of these problems are discussed along with our results of the study on this issue.

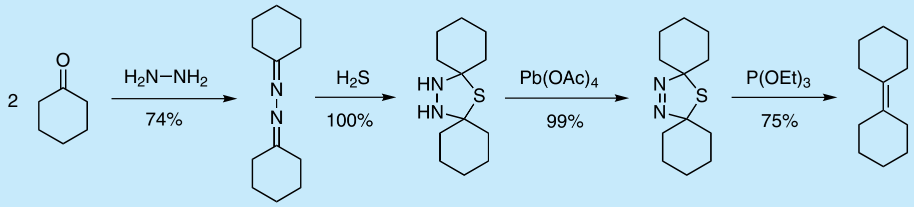


Scheme 1

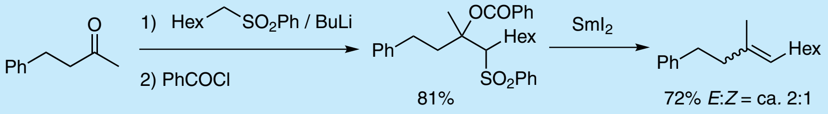
2. Tetrasubstituted Olefins

One of the serious drawbacks remaining in the Wittig and Horner–Wadsworth–Emmons reactions is that they cannot be employed for the transformation of ketones into tetrasubstituted olefins. In 1972, Barton reported the multistep synthesis of tetrasubstituted olefins via azines (Scheme 2),[6] in which he described that "the Wittig reaction has been widely used in the preparation of disubstituted olefins, but yields are lower in the case of trisubstituted olefins, and generally very low (often not reported) in case of tetrasubstituted olefins."

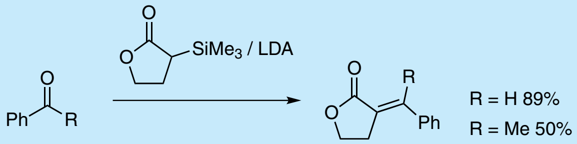
The transformation of ketones into trisubstituted olefins is also recognized to be difficult under the standard conditions of the Julia-Lythgoe reaction, and it can only be achieved by the modification using SmI_2 instead of Na(Hg) for the reduction of β-acyloxy sulfones (Scheme 3).[7] Furthermore, there seems to be no report on the preparation of tetrasubstituted olefins by the Julia reactions. As for the Peterson reaction, preparations of certain tetrasubstituted olefins containing a carbo- or heterocycle have been reported. However the yields are generally low as compared with the formation of corresponding trisubstituted olefins (Scheme 4).[8]



Scheme 2



Scheme 3

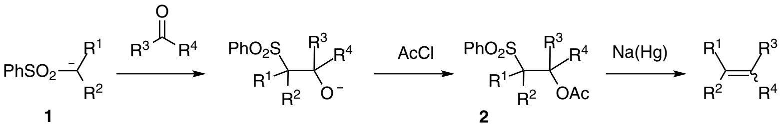


Scheme 4

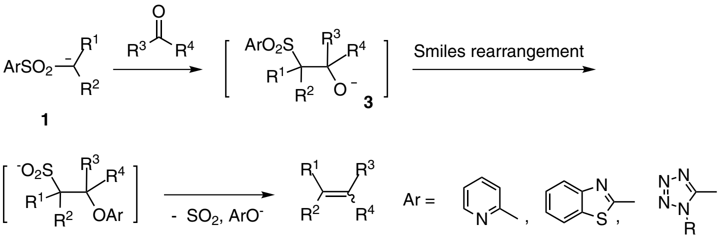
Two “Julia” Reactions

Although the names and reagents used are similar to each other, their reaction pathways are completely different. In 1973, Marc Julia and Jean-Marc Paris reported the carbonyl olefination using α-lithio sulfones **1**.[1] Later on, this “Julia” reaction was extensively studied by Lythgoe and Kocienski, and hence it is also called the Julia-Lythgoe reaction. The reaction was carried out in a same reaction vessel, but the reaction essentially consists of two steps, the addition of **1** to carbonyl compounds followed by acetylation and the reductive elimination of the resulting β-acetoxy sulfones **2**. Another “Julia” reaction named the Julia-Kocienski reaction was first reported by Sylvestre Julia in 1991[2] and extensively studied by Kocienski and co-workers. The reaction proceeds through the addition of α-lithio sulfones **1** to carbonyl compounds, the subsequent Smiles rearrangement, and elimination of sulfur dioxide and aryloxide.

Julia-Lythgoe reaction

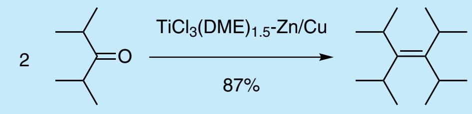


Julia-Kocienski reaction

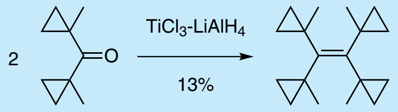


1) M. Julia, J.-M. Paris, *Tetrahedron Lett.* **1973**, 4833.
2) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Tetrahedron Lett.* **1991**, *32*, 1175.

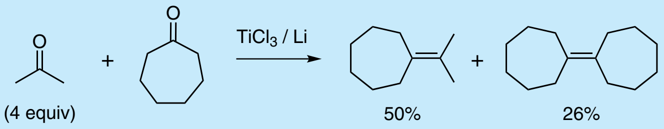
The most powerful tool to synthesize highly sterically-congested tetrasubstituted olefins would be the low-valent titanium mediated reductive coupling of ketones (the McMurry coupling).[9)] Although the preparation of ethylene bearing four *tert*-butyl groups has not appeared yet, highly sterically crowded olefins such as those shown in Schemes 5[10)] and 6[11)] were prepared by the McMurry coupling. The reaction, however, suffers several limitations. For example, the selective preparation of unsymmetrical olefins by the cross-coupling of two distinct ketones is generally difficult even though one of the coupling components is employed in large excess (Scheme 7). Therefore, a new efficient method for the transformation of ketones into highly substituted olefins is still required.



Scheme 5



Scheme 6

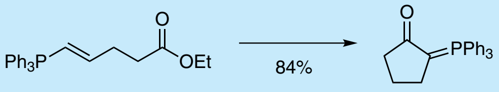


Scheme 7

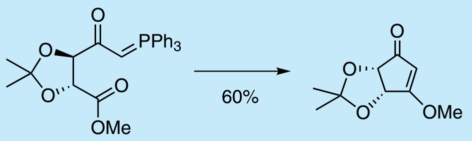
3. Olefination of Carboxylic Acid Derivatives

Although numerous efforts have been devoted to develop the methods for the transformation of carboxylic acid derivatives into heteroatom-substituted olefins, this transformation still remains problematic. Unlike the carbonyl olefination of aldehydes and ketones, it is recognized that the Wittig reaction cannot be employed for the olefination of carboxylic acid derivatives such as esters due to the preferential acylation of ylides. However, as shown in Schemes 8 and 9, whether the acylation (Scheme 8)[13)] or carbonyl olefination (Scheme 9)[14)] is preferred is largely dependent on the structure of substrates and, in certain cases, the process is synthetically useful for the preparation of heteroatom-substituted olefins in reasonable yields. The preferential carbonyl olefination shown in Scheme 9 is attributable to the conformation of starting material favorable to the formation of cyclic structure and a conjugated system stabilizing the olefination product.

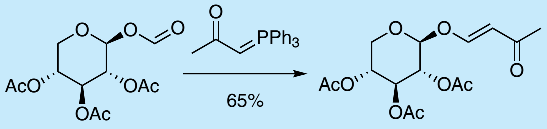
Some additional examples are depicted in Schemes 10,[15)] 11,[16)] 12,[17)] and 13.[18)] The carbonyl compounds employed in these reactions are restricted to formats and carboxylic acid derivatives bearing an electron withdrawing group such as perfluoroalkyl and acyl groups. These reactions are referred to as the non-classical Wittig reaction[19)] and often employed for the synthesis of heterocyclic compounds as indicated in the last example.



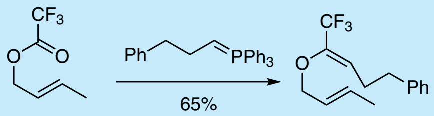
Scheme 8



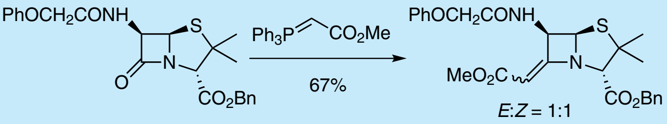
Scheme 9



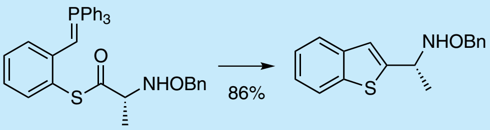
Scheme 10



Scheme 11



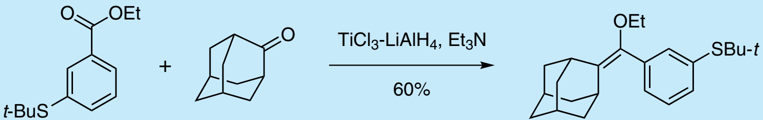
Scheme 12



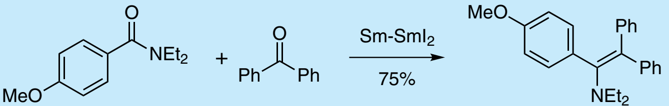
Scheme 13

The McMurry coupling is generally applied to the reductive coupling of aldehydes and ketones, but in certain cases, the reaction is also effective for the cross-coupling of esters and amides with ketones or aldehydes. Although the preparation of enol ethers and enamines by the intermolecular McMurry coupling were reported (Schemes 14[20)] and 15[21)]), these reactions should be considered as exceptional. In contrast, the intramolecular McMurry coupling is useful for the preparation of benzofurans (Scheme 16)[22)] and indoles (Scheme 17)[23)] and often employed for the synthesis of natural products such as alkaloids.

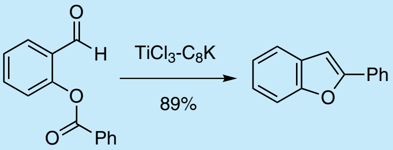
Several other reagents have also been developed for the olefination of carboxylic acid derivatives[24)] which include the organometallic species generated from the *gem*-dibromides-$TiCl_4$-Zn-TMEDA system (Scheme 18)[25)] and *gem*-dizinc compounds (Scheme 19).[26)]



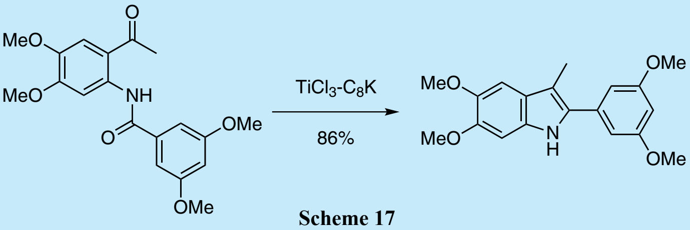
Scheme 14



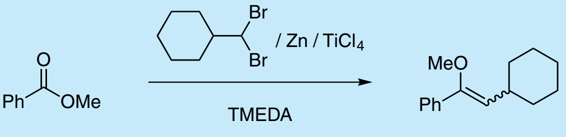
Scheme 15



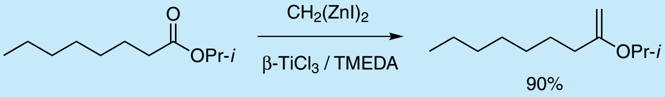
Scheme 16



Scheme 17



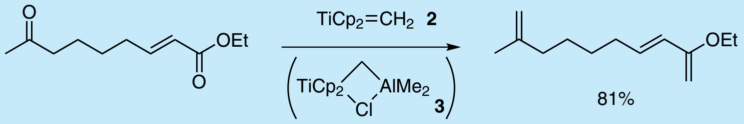
Scheme 18



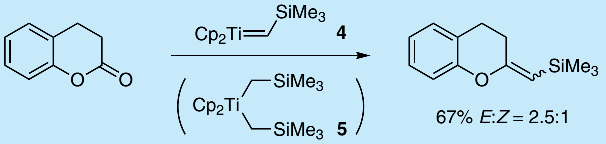
Scheme 19

As described above, various reagents can be employed to perform the carbonyl olefination of carboxylic acid derivatives, but the most promising reagent for this transformation would be titanium-carbene complexes. Since methylidenetitanocene **2** generated from the Tebbe reagent **3** was found to methylidenate carbonyl compounds in 1978,[27)] Pine, Grubbs, Petasis, and many other researchers studied the carbonyl olefination using titanium carbene complexes.[28)] The carbene complex **2** is the most frequently employed reagent for the methylidenation of carboxylic acid derivatives, and numerous applications have appeared as exemplified in Scheme 20.[29)] Titanium-alkylidene complexes such as **4** generated from bis(trimethylsilylmethyl) titanocene **5** (Scheme 21)[30)] are also powerful tools for the preparation of heteroatom substituted olefins from carboxylic acid derivatives. The formation of such alkylidene complexes by α-elimination of dialkyltitanocenes, however, still remains a serious problem in that it cannot be applied for the preparation of alkylidene complexes bearing a β-hydrogen.

In order to overcome all these drawbacks of conventional reactions, we have studied a new carbonyl olefination utilizing a wide variety of titanium carbene complexes generated by the desulfurizative titanation of thioacetals. The details of our results on this study will be discussed next.



Scheme 20



Scheme 21

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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.