Dithioacetals as an Entry to Titanium–Alkylidene Chemistry: A New and Efficient Carbonyl Olefination

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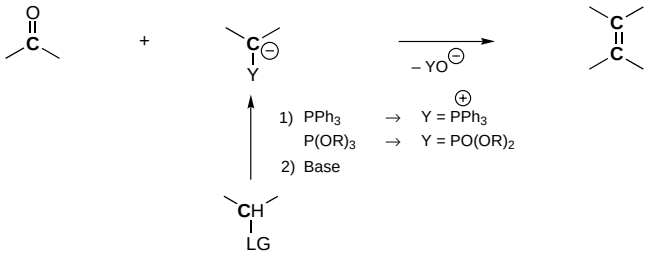
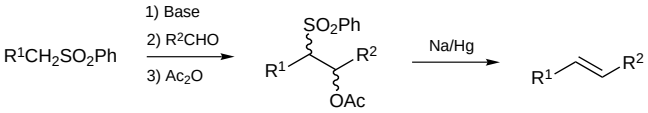
Reactions in which two halves of a complex molecule are linked by means of a convergent synthetic strategy belong to the most valuable framework-building reactions in organic synthesis. Especially successful are those reactions in which C–C double bonds are formed, such as the Wittig reaction and its variants according to Horner, Wadsworth, and Emmons (referred to here as Wittig-type reactions).[1] Decisive for the effectiveness of these methods is the simple preparative access to both individual components—a carbonyl compound as well as a Wittig-type reagent, which can be obtained, for instance, by the reaction of an alkyl halide with phosphanes or phosphites followed by deprotonation (Scheme 1). Only such



Scheme 1. Schematic representation of the Wittig and Horner–Wadsworth–Emmons reactions. LG = leaving group.

a simple and general approach enables the synthetic chemist to convert any two complex building blocks into carbonyl and Wittig-reagent components in a late step of the synthetic sequence. The components can be subsequently coupled by either an inter- or intramolecular olefination reaction.

However, Wittig-type reactions are also subject to certain limitations. One example is the *cis* selectivity upon use of nonstabilized ylides under salt-free reaction conditions. Fortunately, the Wittig-type reactions can be supplemented by the Julia–Lythgoe olefination (Scheme 2), which is a general method for preparing *trans*-disubstituted olefins.[2, 3] The components required for the Julia–Lythgoe olefination—the carbonyl and sulfone components—also meet the



Scheme 2. Stereoselective synthesis of disubstituted *trans*-olefins according to Julia and Lythgoe.

criterion of being readily available and allow the corresponding functionalization in a late synthetic step.

Another disadvantage of Wittig-type reactions is their limitation to aldehydes and ketones as the carbonyl component; carboxylic acid derivates are generally inert in this respect. Furthermore, Wittig-type reactions and Julia–Lythgoe olefinations both require a more or less basic reaction medium. Especially in the case of easily enolizable carbonyl compounds, this can lead to undesired side reactions such as elimination and racemization of adjacent stereocenters. The olefination of sterically demanding carbonyl substrates also clearly demonstrates the limitations of the Wittig reaction.

For this reason, considerable efforts have been devoted to finding improved olefination reagents that can overcome these shortcomings of both the Wittig-type reactions and Julia–Lythgoe olefinations. A milestone was already reached in 1978 by Tebbe, who recognized the usefulness of the titanium–aluminum complex **1** for carbonyl methylenations.[4] In addition to the Tebbe reagent **1**, the titanacyclobutane **2** reported by Grubbs[5] and the Petasis reagent **3**[6] are available for efficient methylenation of carbonyl compounds (Scheme 3). These reagents are reactive under neutral to slightly Lewis acidic conditions, which allows easily enolizable carbonyl compounds to be used in methylenation reactions without competing side reactions. Another advantage is the clean methylenation of carboxylic acid derivatives with formation of, for example, preparatively valuable enol ethers and enamines.[7]

A plausible intermediate of this olefination is the titanium–methylene species **4**, which is formed from **1** by removal of $AlMe_2Cl$ with a Lewis base, from **2** by fragmentation with elimination of isobutene, and from **3** by α-elimination and release of methane. However, none of these three routes to titanium–carbene complexes of type **4** proved to be generally applicable. Consequently, the use of these reagents in synthesis is essentially limited to the transfer of a methylene unit.[8] From a synthetic viewpoint, a general and easy route to

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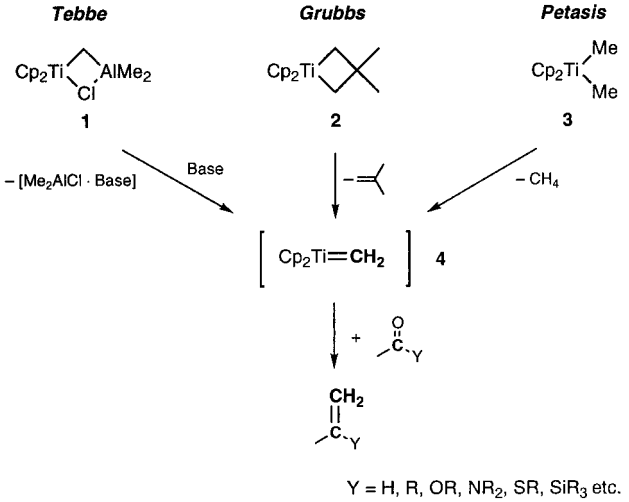
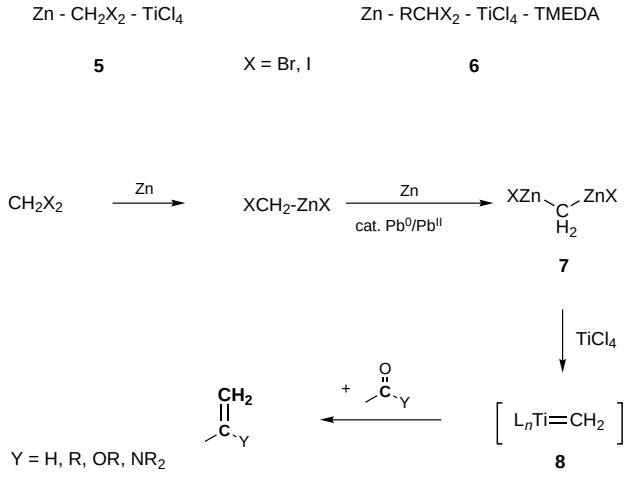


Scheme 3. Carbonyl methylenation with the titanium–methylene species **4** prepared from the Tebbe, Grubbs, or Petasis reagents (**1**–**3**).

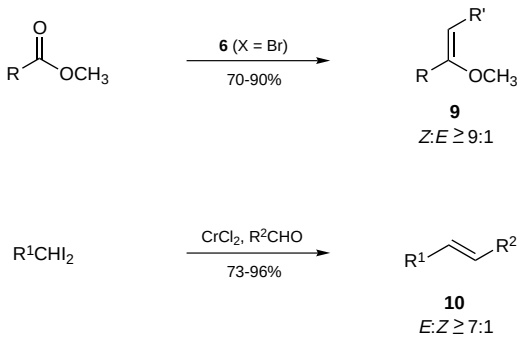
substituted titanium–alkylidene species and their use in carbonyl olefinations would be more desirable.

The first progress was made by Takai and Lombardo, who developed an in situ entry to titanium–alkylidene chemistry starting from the reagent combinations **5** and **6** (Scheme 4).[9] These reactions proceed via a *gem*-dizinc compound **7** (its formation is catalyzed by traces of lead or lead(II) salts), which is subsequently transmetalated with $TiCl_4$ to the titanium–alkylidene species **8**, the actual olefination reagent. To date, **8** has not been characterized in detail.[10] These in situ reagents exhibit chemoselectivities similar to those of the structurally defined methylenation reagents **1**–**3**.



Scheme 4. Takai–Lombardo reagents; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

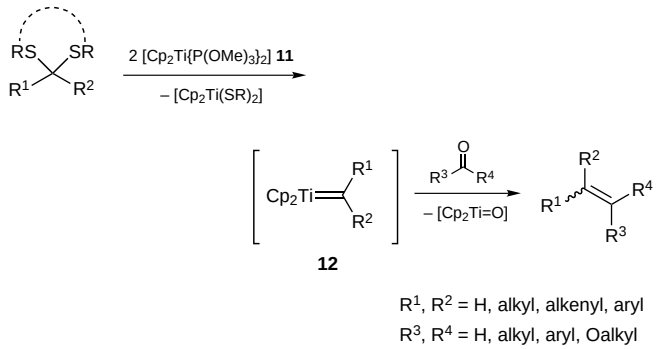
The advantage of the Takai–Lombardo reagents is the possibility of transferring substituted alkylidene units in addition to methylene units. The use of the olefination reagent **6** allows the general alkylidenation of carboxylic esters.[11] In this transformation, the (*Z*)-enol ethers **9** are obtained with high stereoselectivity (Scheme 5). A variation



Scheme 5. General alkylidenation of esters **9** and the synthesis of the disubstituted (*E*)-alkenes **10** starting from aldehydes and chromium(II) reagents according to Takai and Utimoto.

of this reaction was developed in 1986 by Takai and Utimoto, in which geminal dihaloalkanes were added to aldehydes in a reaction mediated by chromium dichloride. This led to the stereoselective formation of the corresponding *trans*-olefins **10**.[12] The major drawback of this method is the rather cumbersome access to the respective substituted dihalomethane compounds, which prevents a broad application of this reaction for synthesis.

The solution to the above problem was recently found by Takeda et al., who reported on the desulfurization of dithioacetals as a general and easy entry to titanium–alkylidene chemistry.[13] Dithioacetals, which are easily accessible from carbonyl compounds, are treated with the titanocene source $[Cp_2Ti\{P(OEt)_3\}_2]$(**11**), which was specifically developed for this purpose; the respective titanium–alkylidene species **12** is formed, presumably by desulfurization (Scheme 6). The most important subsequent reaction of this



Scheme 6. Carbonyl olefination with titanium–alkylidene species **12** prepared from dithioacetals according to Takeda et al.

species is carbonyl olefination, which proceeds smoothly with aldehydes, ketones, and esters. The intermediates formed in these reactions exhibit a chemoselectivity spectrum similar to that of the titanium reagents **1**–**3**, **5**, and **6**. No limitations have yet been observed with respect to the structure of the dithioacetals; that is, even 1-substituted dithioacetals with β-hydrogen atoms can be converted. It is still unclear as to which functional groups can be tolerated in this reaction.

A clear disadvantage is the unsatisfactory stereoselectivity observed for the olefination of aldehydes so far. However, one

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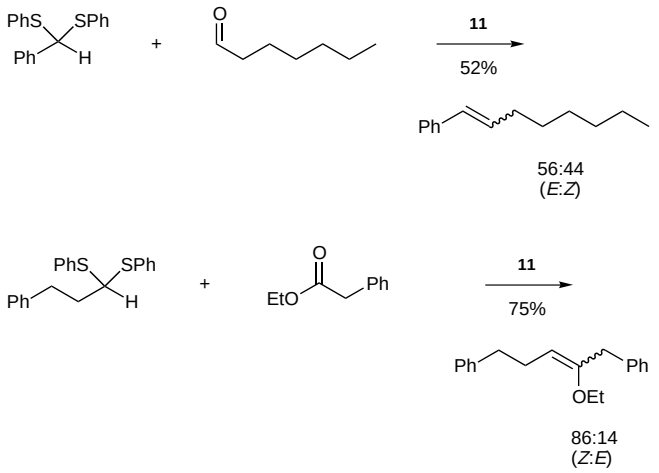
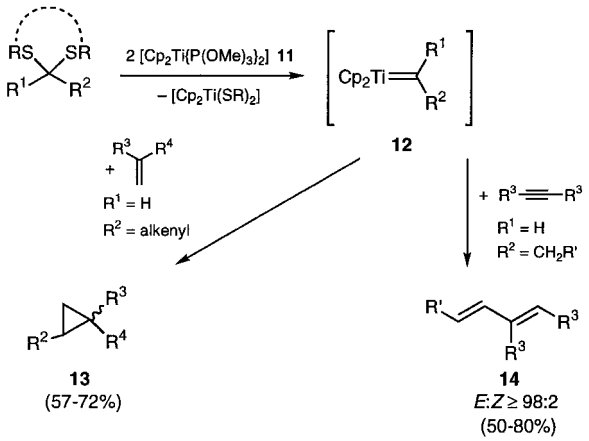
can easily envision that modifying the microenvironment of the reactive titanium center will bring about improvements. Better selectivities have been obtained in the olefination of carboxylic esters (Scheme 7).



Scheme 7. Stereoselectivity of the Takeda olefination.

The good accessibility of dithioacetals offers the possibility, as with Wittig-type reactions, to convert any two complex fragments into an olefin with the titanium reagent **11** in a late step of the synthetic sequence. This olefination is therefore as valuable as the Wittig-type reactions. Moreover, this reaction offers all the advantages of the titanium-mediated reactions that proceed in Lewis acidic media.

Interestingly, the subsequent reactions of the titanium–alkylidene species **12** obtained from dithioacetals are not limited to carbonyl olefinations. When the carbene complex is prepared in the presence of olefins, the latter are smoothly cyclopropanated (Scheme 8; →**13**).[14] Furthermore, the reaction of symmetrically disubstituted acetylenes with dithioacetals containing an α methylene unit provides the corresponding trisubstituted 1,3-diene **14** in a stereoselective fashion.[15]



Scheme 8. Reactions of the titanium–alkylidene species **12**, prepared from dithioacetals, with olefins and acetylenes.

Dithioacetals have already proven to be very useful in organic synthesis. For instance, they function as carbonyl protecting groups that can be used orthogonal to *O*,*O*-acetals.[16] The introduction of a dithioacetal leads to an umpolung of the carbonyl group (dithiane method according to Seebach).[17] As a result, any complex dithioacetal can be obtained by a deprotonation–alkylation sequence. This remarkable multifunctionality of the dithioacetal unit has now been expanded by the work of Takeda et al. with respect to the specific formation of titanium–alkylidene species. Although the subsequent chemistry of this species needs to be established in detail, the intermolecular carbonyl olefination has given a glimpse of the synthetic possibilities of this reaction strategy. In addition to the Wittig-type reaction and the Julia–Lythgoe olefination, this olefination variant has the potential of becoming another general olefination reaction which proceeds under Lewis acidic conditions.

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Direct Measurement of Dihedral Angles with High-Resolution NMR Spectroscopy

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Since the discovery of the nuclear Overhauser effect (NOE)[1] and scalar coupling constants[2] decades ago, NMR-derived structure calculations of biomolecules largely depended on measurement of these two parameters.[3] Therefore, few scientists in this field expected that a new parameter for structure determination could be developed. The group of Griesinger at the University of Frankfurt recently changed this paradigm with the invention of an NMR method which directly measures angles between bond vectors.[4] The new parameter is widely applicable for isotopically labeled molecules and will certainly set a new direction in future design of experiments to determine the structure of biomolecules by NMR spectroscopy. The information extracted from these experiments will significantly improve the resolution of NMR structures and may provide new ways to obtain information on molecular dynamics.

The new parameter, cross-correlated dipolar relaxation (CCDR), can easily be explained in a simplified form. All coherences between nuclear spins that finally give rise to NMR signals relax (decay) with a certain rate and eventually disappear. In dipolar relaxation the relaxation of a spin is mediated by the fluctuating magnetic field caused by adjacent spins. Cross-correlated dipolar relaxation indicates that the dipolar coupled spin pair is not isolated, but experiences fluctuating magnetic fields from other spin pairs, which influence its relaxation rate. The dipolar interaction between these magnetic moments depends on the angle between them [Eq. (1) in which k is defined according to Eq. (2)].[5] θ is the

$$\mathrm{CCDR}_{ijkl} = k(3\cos^2\theta - 1) \quad (1)$$

$$k = \frac{2}{5}\frac{\gamma_i\gamma_j}{r_{ij}^3}\frac{\gamma_k\gamma_l}{r_{kl}^3}\left[\frac{\hbar\mu_0}{4\pi}\right]^2\tau_c \quad (2)$$

angle between the internuclear vectors that link nuclei i and j, and k and l (Figure 1). The internuclear distances r are well-known, and the rotational correlation time τ_c can be measured

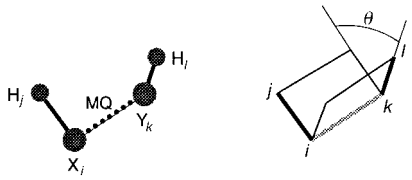

Figure 1. Schematic representation of a pair of bond vectors. The relaxation rate of the multiple quantum coherence (MQ) is dependent on the angle θ between the bond vectors.

independently. All other factors are constants. The angle θ between bond vectors is then the sole unknown in Equation (1) and can be readily and precisely determined by measurement of the cross-correlated dipolar relaxation rate. It should be emphasized that θ is measured *directly*, without the need of experimental calibration as, for example, the Karplus curve for J coupling constants.

Cross-correlated dipolar relaxation can conveniently be measured in novel triple-resonance experiments, that is, experiments that utilize the ^{1}H, ^{13}C, and ^{15}N nuclei in isotopically enriched biomolecules. In triple-resonance NMR experiments designed for that purpose, for example a nondecoupled heteronuclear multiple quantum experiment, each signal has a double doublet fine structure. The splitting of the signal is caused by the large one-bond couplings $^1J_{\mathrm{H,N}}$ and $^1J_{\mathrm{H,C}}$ (Figure 2). The individual lines of this double doublet relax with different rates due to the phenomenon of cross-correlated dipolar relaxation. Thus, the relaxation rate can be directly extracted from the intensity of individual lines [Eq. (3)]. CCDR is the relaxation rate, t is the time the

$$\mathrm{CCDR}_{ijkl} = \frac{1}{4t}\ln\left[\frac{I(\alpha\beta)I(\beta\alpha)}{I(\alpha\alpha)I(\beta\beta)}\right] \quad (3)$$

selected coherences experience relaxation, and I the signal intensities of the spin states $\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, and $\beta\beta$. The relative

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