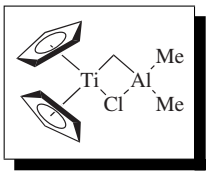
μ-Chlorobis(cyclopentadienyl) (dimethylaluminum)-μ-methylenetitanium[1]



[67719-69-1] $C_{13}H_{18}AlClTi$ (MW 284.60)

InChI = 1/2C5H5.2CH3.CH2.Al.ClH.Ti/c2*1-2-4-5-3-1;;;;;;/h2*1-5H;2*1H3;1H2;;1H;/q;;;;;;;+1/p-1/f2C5H5.2CH3.CH2.Al.Cl.Ti/h;;;;;;1h;/q;;;;;;-1;m/r2C5H5.C3H8AlClTi/c2*1-2-4-5-3-1;1-4(2)3-6-5/h2*1-5H;3H2,1-2H3

InChIKey = QEJAQNUJXFLWSP-HAKBBFDRCS

(methylenating agent for alkenation of carbonyl compounds,[2–4] particularly esters, ketones, and aldehydes; of low basicity and functions without epimerization at α-chiral centers)

Alternate Name: Tebbe reagent.

Physical Data: red solid.

Solubility: highly sol toluene, benzene, or dichloromethane; will dissolve in THF at low temperature (but not stable for prolonged periods in ethereal solvents). Nearly insol saturated hydrocarbons.

Form Supplied in: may be purchased as the pure solid or prepared from titanocene dichloride and trimethylaluminum.

Handling, Storage, and Precautions: the dry solid is air-sensitive and may be pyrophoric in air, especially when impure; it must be handled under an atmosphere of nitrogen or argon. The reagent is most conveniently stored and handled as a toluene solution; in this form the reagent is somewhat pyrophoric in air and must be handled using syringe and cannula techniques as practiced when using Grignard or alkyllithium solutions.

Original Commentary

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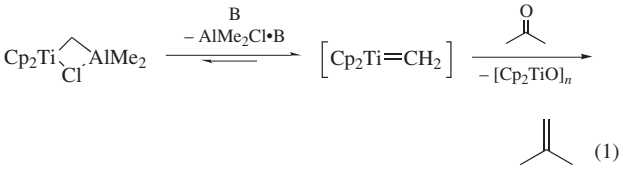
Tebbe Reagent as a Source of '$Cp_2Ti{=}CH_2$'. The complex $Cp_2TiCH_2{\cdot}AlMe_2Cl$, commonly referred to as the Tebbe reagent,.[5] is a source of the reactive titanium methylene species '$Cp_2Ti{=}CH_2$' as shown in eq 1. The methylene intermediate, formation of which is greatly accelerated by bases such as THF or pyridine, is useful for the methylenation of carbonyl compounds in a process similar to Wittig alkenation; the driving force is the high oxophilicity of titanium. The scope of reactivity is greater than with the corresponding phosphoranes;[6] thus esters and amides are converted to vinyl ethers and enamines by the Tebbe reagent.[2,7] The lower basicity of the Tebbe reagent offers further advantages over the Wittig procedure (see below). Although many examples of methylenation of unsaturated substrates are known, and carbon–carbon double bonds usually do not interfere, it should be noted that the Tebbe reagent will react with certain alkenes to form titanacyclobutanes.[8] These titanacycles, of importance as intermediates in degenerate metathesis of terminal alkenes and ring-opening metathesis polymerization of strained cyclic alkenes,[9] and as synthetic reagents themselves,[1b] have been studied in some detail. The most stable titanacyclobutanes are those derived from monosubstituted alkenes; even these will revert to free alkene and active methylene when heated to about 60 °C.[10] Therefore mild heating may be used to improve yields of irreversibly formed methylenation products for certain substrates.[3] Furthermore, use of excess Tebbe reagent will in certain cases lower the yield of alkene product.[3,11]



(1)

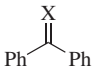
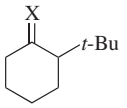
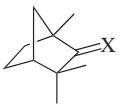
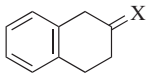
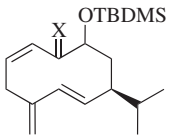
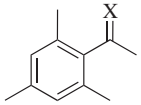
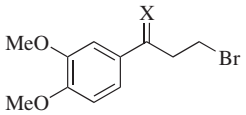
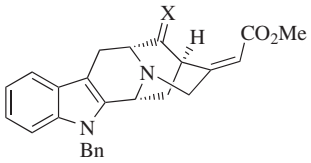
The reagent may be purchased as a pure solid, or synthesized as such using Schlenk line and glovebox techniques.[5a,12] Since isolation of the Tebbe reagent is time-consuming, in situ preparations of the complex have been developed.[3,13] It should be noted that in situ preparation produces a solution with one equiv of excess $AlMe_2Cl$ and often affords somewhat lower yields than the isolated reagent.[1a,13a] Typical conditions[2,13a] for use involve combining the reagent in toluene solution at low temperature with the substrate and a Lewis base such as THF and/or pyridine. After warming to room temperature, the solution is chilled and quenched with aqueous sodium hydroxide, diluted with ether, dried, filtered through Celite, and the product further purified, often by chromatography on neutral or basic alumina.

Tebbe methodology is specific for methylene transfer. However, approaches to analogous Group 4 metal reagents having substituted alkylidene units have been developed and show considerable promise.[1a,14] Several other titanium-based reagents for methylene transfer have been developed.[1a,15,16] A widely used system for methylenation of ketones[15a] is the still undefined mixture formed from $Zn/CH_2X_2/TiCl_4$. Also, thermolysis of Cp_2TiMe_2 provides a clean aluminum-free source of $Cp_2Ti{=}CH_2$ and shows considerable synthetic promise.[16] These various methylenation and alkylidenation processes have been comprehensively reviewed.[1a]

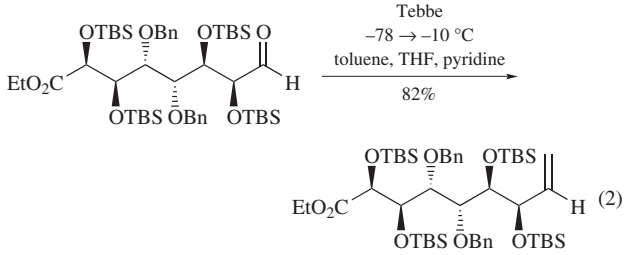
Methylenation of Aldehydes and Ketones. The Tebbe reagent accomplishes methylenation of aldehydes and ketones.[4,5a,11,17–23] Table 1 shows some representative conversions with yields for the Wittig reagent included where available; the titanium reagent affords consistently higher yields and is less sensitive to steric crowding than ***Methylenetriphenylphosphorane***.[4] It is particularly useful in preparation of exocyclic alkenes (e.g. entries 2, 4, 5 and 8); only in extremely hindered substrates such as fenchone (entry 3) is the reagent ineffective. Also, the titanium complex efficiently methylenates such readily enolizable ketones as β-tetralone (entry 4).

The Tebbe reagent will methylenate aldehydes and ketones without epimerization at α-chiral centers, as illustrated in eq 2.[22] The relatively low basicity of this reagent also permits conversions such as eq 3, which gives almost exclusively β-elimination across

Table 1 Methylenation of ketones with $Cp_2TiCH_2{\cdot}AlMe_2Cl$

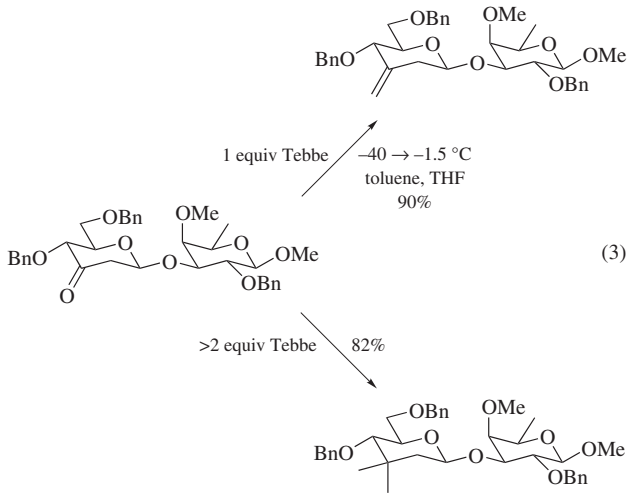
Entry	Yield (%)	Substrate (X=O) and Product (X=CH_2)
1[4]	97; Wittig 46	
2[4]	96; Wittig 80	
3[4,23]	16; Wittig 5	
4[23]	84	
5[19]	55	
6[4]	77; Wittig 4	
7[18]	93	
8[21]	63	

the C(1′)–C(2′) bond when attempted by the Wittig method.[11] When a 'large excess' of Tebbe reagent is used in eq 3, *gem*-dimethylation occurs via a titanacyclobutane. Ketones with α,α-disubstitution (e.g. eq 4) will enolize rather than methylenate;[23] these titanium enolates are not active in the aldol reaction. The Tebbe reagent shows synthetically useful selectivity for ketones in preference to esters, as in the conversion of entry 8 (where 15% methyl ketone byproduct was observed), which was unsuccessful using $Zn/CH_2X_2/TiCl_4$ due to cyclopropanation. However, the $Zn/CH_2X_2/TiCl_4$ mixture is much more widely used for ketone methylenation since in certain preparations it will not react with esters.[1a]

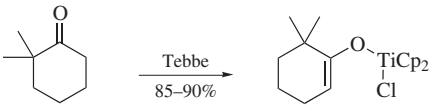


(2)

Methylenation of Esters and Lactones. The greatest advantage of the Tebbe reagent is that, unlike phosphorous ylides, it may be used to convert esters and lactones to versatile enol ethers.[2] The reaction is quite general and typically proceeds in good to excellent yield.[3,7,24–50] Several representative conversions are presented in Table 2.



(3)

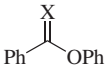
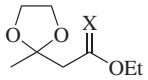
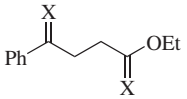
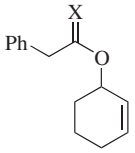
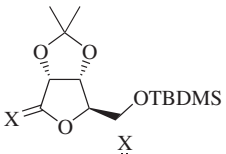
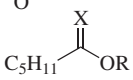
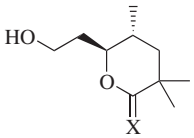
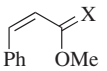
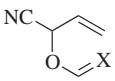
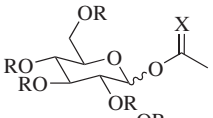
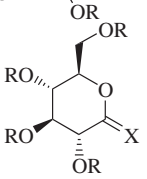
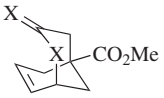
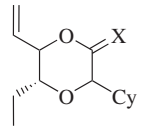
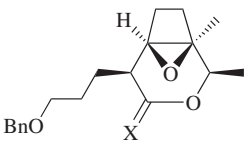


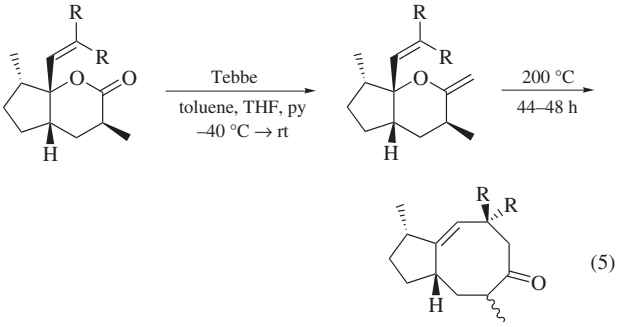
(4)

The procedure is tolerant of the acetal (entries 2 and 5) and cyano (entry 9) groups. Double bonds typically retain their stereochemistry (entry 8) and position. In a few instances, double bond migration has been reported upon workup;[30,47] precautions to minimize such rearrangement are described.[13a] Other compatible functionalities include various siloxy groups,[36,46] halide,[44,48] and thioacetal.[24] Ketone and ester groups may be simultaneously methylenated (entry 3), or a keto group may be preferentially methylenated with 1 equiv of reagent.[7,21] Literature estimates of ketone versus ester selectivity are given as 4:1 in general[2] and 25–30:1 for acetophenone against methyl benzoate.[23] It has been observed that yields may differ depending on whether isolated Tebbe reagent is used or if the complex is generated in situ; for example, 94% in entry 1 compared with 68–70% by in situ methods.[13a] Nonetheless, yields are often excellent using the in situ reagent (e.g. entry 11 and others[3,35]), which is considerably less expensive than the isolated complex. Since enol ethers are not known to form titanacyclobutanes on reaction with the Tebbe complex, *gem*-dimethylation does not occur when excess reagent is employed.[3]

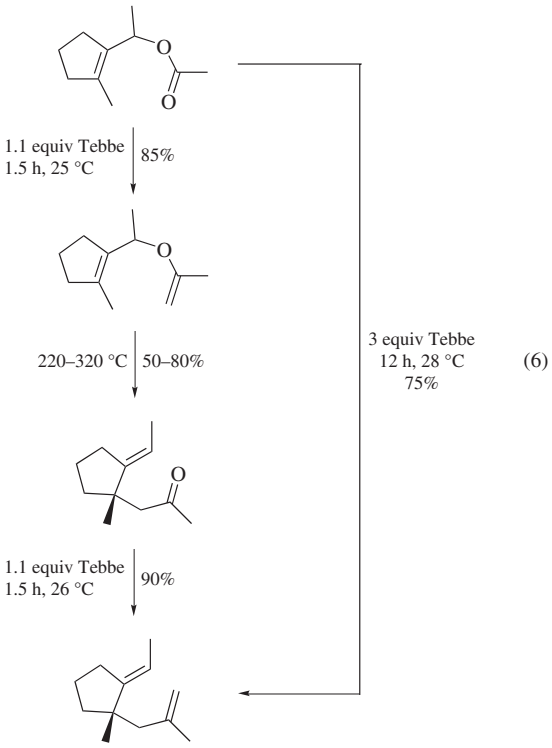
Methylenation of allyl esters (Table 2, entries 4, 9, 12, and 13) affords allyl vinyl ethers[2,24,25,27,32,42–45,49] which are useful substrates for the Claisen rearrangement (e.g. eqs 5[25] and 6[24a]). Although the methylene group of the Ti complex is mildly basic, solutions of the reagent are Lewis acidic, particularly when an extra equivalent of $AlMe_2Cl$ is present from in situ reagent preparation. The acidic character of the reagent has been used to advantage in a mild one-pot synthesis of 1,5-dienes from allyl esters in which a Claisen rearrangement occurs under Lewis acid catalysis (eq 6 and entry 12).[24a]

Table 2 Methylenation of esters with $Cp_2TiCH_2{\cdot}AlMe_2Cl$

Entry	Yield (%)	Substrate (X=O) and Product (X=CH_2)
1[7]	94	
2[2]	87	
3[2]	97	
4[2]	96	
5[26]	85	
6[29]	R=Bn, 47 R=$CHPh_2$, 76 R=trityl, trace	
7[46]	76	
8[2]	79	
9[45]	–	
10[33]	R=Bn, 87–90	
11[35]	R=Me, 95 R=Bn, 88	
12[41]	ca. 50	
13[43]	65	
14[50]	94	

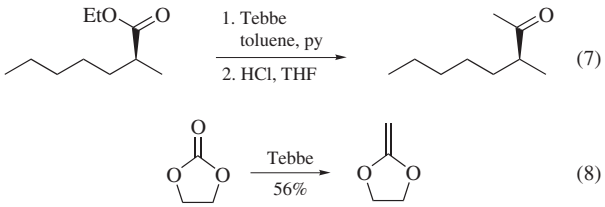


R = H, 91%; R = Me, 87%



The Tebbe complex has found frequent application in carbohydrate chemistry.[26,31b,33,35,36]

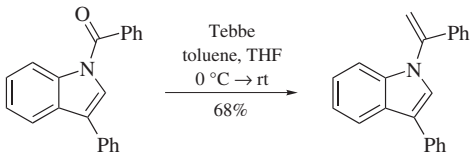
The titanium reagent allows transformations of esters without epimerization at α-chiral centers, as is illustrated in the methyl ketone preparation of eq 7.[28b] Cyclic carbonates may be methylenated as well (eq 8).[1b]



In at least one case where the Tebbe procedure is ineffective, presumably for steric reasons, an ester has been efficiently methylenated with $Zn/CH_2X_2/TiCl_4$.[38] However, hindered esters may be methylenated with the Tebbe reagent (e.g. entry 7).

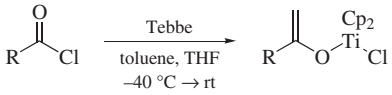
Methylenation of Amides. Amides have been converted to enamines of methyl ketones by the Tebbe reagent (eq 9).[1a,b,7,51]

No added base is required. Isolation of enamines is possible, or in situ alkylation may be performed.[7] The reaction has been little developed.



(9)

Titanium Enolates from Acid Chlorides. Acid chlorides have been reported to react with the Tebbe reagent to afford titanium enolate complexes (eq 10),[52] although yields are much lower than those obtained using titanacyclobutane precursors.[53] These enolate complexes of methyl ketones are known to participate in aldol reactions.[53]



(10)

Other Reactions of the Tebbe Reagent. Silyl esters and thioesters are methylenated by the Tebbe reagent.[1a] The complex is known to react with alkynes to give stable titanacyclobutenes.[54] Reaction with anhydrides gives enolate complexes which are not active in the aldol reaction.[55] By contrast, unhindered imides may be methylenated in good yield with excellent selectivity in unsymmetrical cases.[55] Nitriles react to afford vinylimidotitanium complexes, which have been studied in some detail.[56] The reagent has found application in the preparation of various organometallic complexes.[57]

First Update

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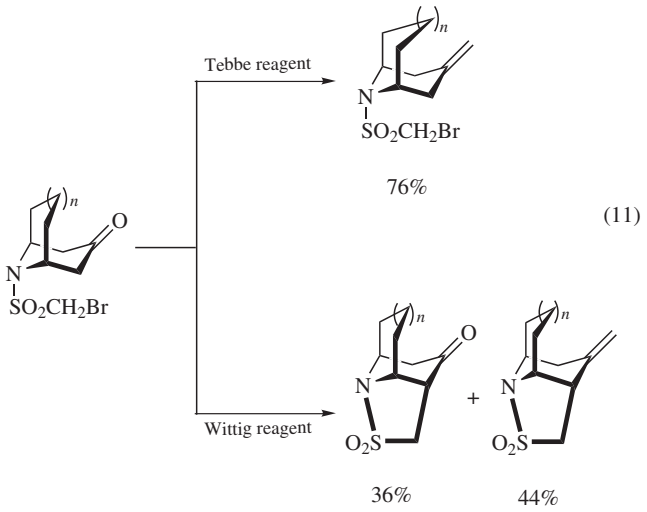
Introduction. The Tebbe reagent has been reviewed comprehensively.[58] This nonbasic methylenation reagent offers some advantages over other methylenation processes, e.g., the Wittig reaction, especially in the cases of base-sensitive substrates and sterically hindered carbonyl groups. At the same time, its special feature of methylenation on carboxylic acids and their derivatives makes it a very powerful tool for synthetic organic chemists. In addition, tandem Tebbe-Claisen reactions, sulfoxide reductions, and carbometallation reactions are some of the more promising new features of this reagent.

Methylation of Aldehydes and Ketones. This reagent works very well with sterically hindered molecules where other methylenation reagents are less successful.[59] Furthermore, olefination with the Tebbe reagent proceeds without scrambling of adjacent stereogenic centers (Table 3, entries 1 and 2).[60–62]

Stereochemistry aside, the Tebbe reagent can also be used to selectively perform methylenation reactions while preserving a host of other functionalities such as alkenes and esters.[64] In such cases, the Tebbe reagent works better for olefinations than the Wittig reagent, which may interfere with protecting groups present during methylenation (eq 11).[69]

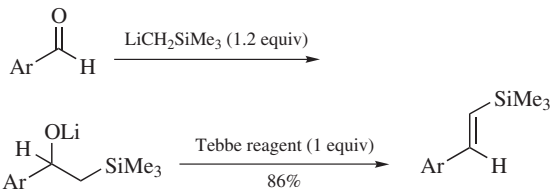


(11)

Methylenation of aldehydes is an important reaction class, as demonstrated in the total synthesis of (±)-gelsemine (Entry 1, Table 4).[70]

Aldehydes can be transformed to alkenes, for use in copolymerization reactions: in addition, the titanium complex also promotes the copolymerization processes after methylenation (Entry 4, Table 4).[73]

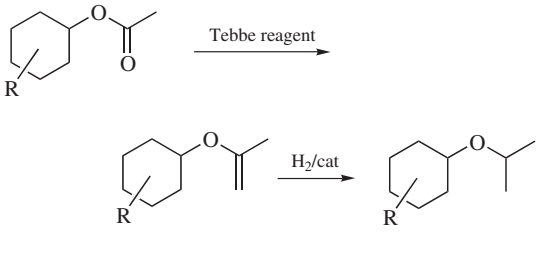
When stereoselective synthesis of vinylsilanes, important vinyl anion equivalents,[74] is a challenge by conventional methods, the Tebbe reagent is often successful, with exclusive formation of the *E*-isomer (eq 12).[75]



(12)

Methylenation of Esters and Lactones. Methylenation of esters and lactones by the Tebbe reagent is well known in synthetic organic chemistry. Several examples are provided in Table 5.

Methylenation of acetates followed by hydrogenation forms isopropyl ethers in high yield (eq 13).[86]



(13)

Table 3 Methylenation of ketones

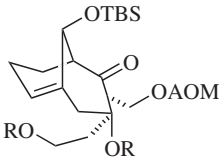
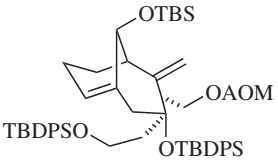
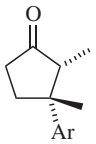
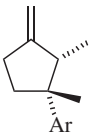
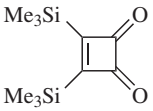
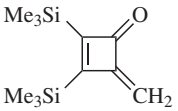
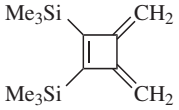
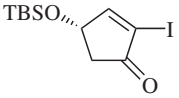
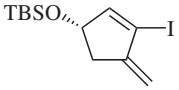
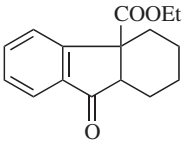
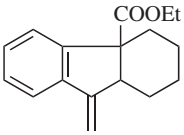
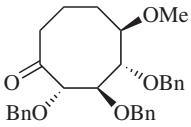
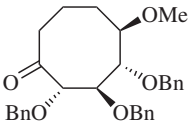
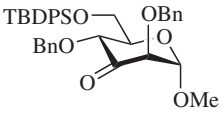
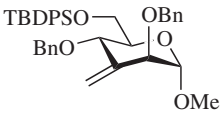
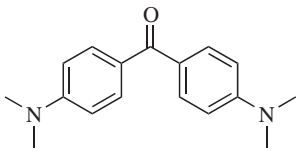
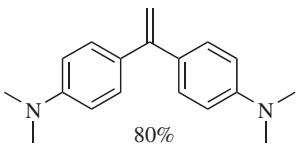
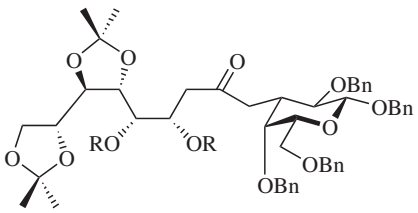
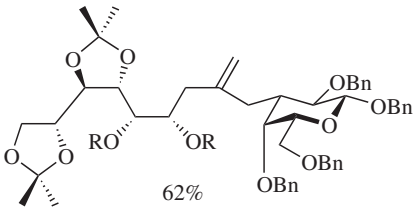
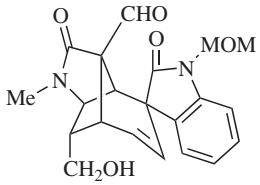
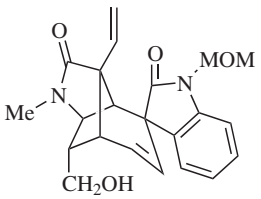
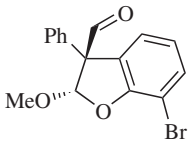
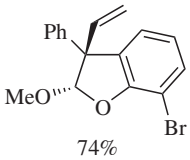
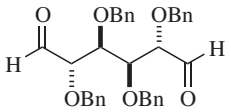
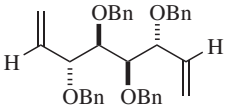
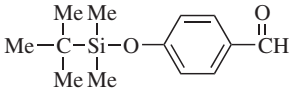
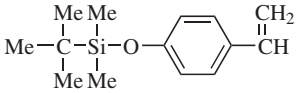
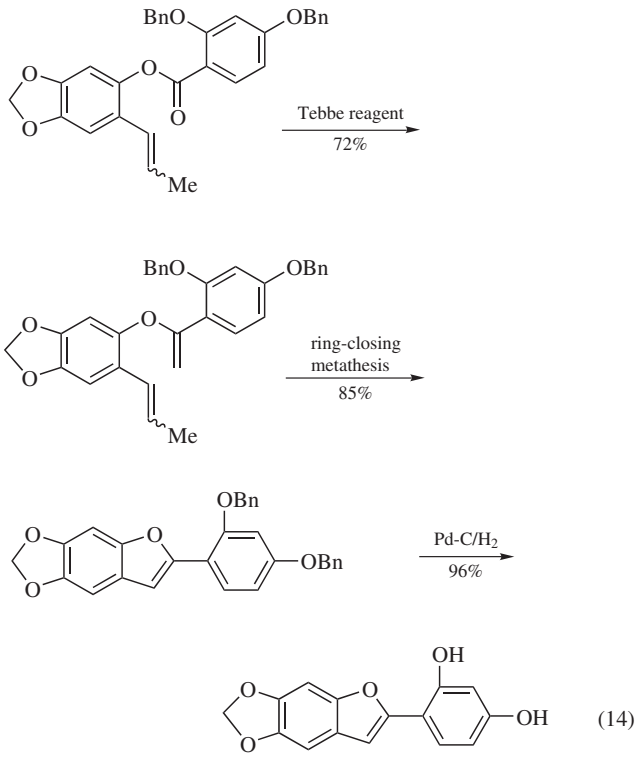
Entry	Ketone	Product	Ref.
1	 R = $SiPh_2Bu^t$ AOM = *p*-Anisyloxymethyl	 AOM = *p*-Anisyloxymethyl 77%	60
2		 56%	61
3		 54%  34%	62
4		 79%	63
5		 75%	64
6		 82%	65
7		 95%	66
8		 80%	67
9	 R = TBS	 62%	68

Table 4 Methylenation of aldehydes

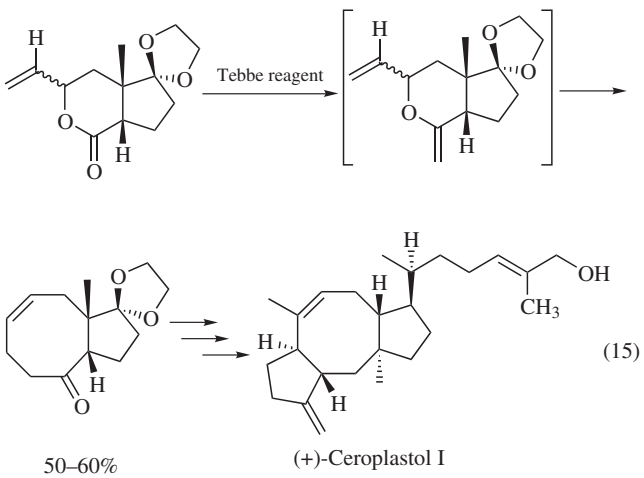
Entry	Aldehyde	Product	Ref.
1		 65%	70
2		 74%	71
3		 47%	72
4		 82%	73

Improving significantly on the earlier synthesis.[87] of 2-(2′,4′-dihydroxyphenyl)-5,6-(methylenedioxy)benzofuran, the antifungal phytoalexine isolated from aerial part of *Sophora tomentosa* L, Grubbs demonstrated a concise route combining a Tebbe reaction with ring-closing metathesis (eq 14).[88]



(14)

Tandem Tebbe-Claisen Sequences. Paquette et al. successfully used a tandem Tebbe-Claisen approach for the synthesis of (+)-ceroplastol I (eq 15).[89] The versatility of this general methodology was further demonstrated by the Nicoloau group.[90] This innovative chemistry was then used as an important tool in the synthesis of maitotoxin (eq 16).[91] Godage et al. used this same method in the synthesis of various *C*-glycosides (eq 17).[92] The method was further extended toward the synthesis of *C*-glycosyl amino acids[93] and ciguatoxin CTX3C.[94,95]



50–60% (+)-Ceroplastol I (15)

Reduction of Sulfoxides. In the Nicolaou approach to diazonamide A the Tebbe reagent was useful in reducing a sulfoxide group (eq 18), to the corresponding sulfide.[71,96] The Tebbe reagent was subsequently to reduce sulfoxides effectively in a wide range of structures (Table 6). A reasonable mechanism for sulfoxide reduction has been proposed (eq 19).[71,96]

Table 5 Methylenation of esters and lactones

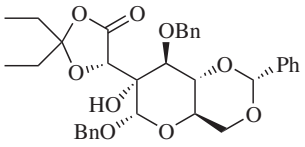
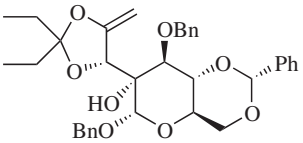
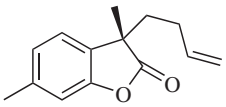
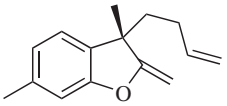
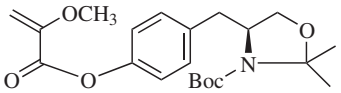
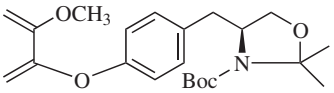
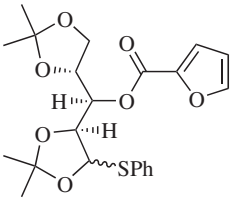
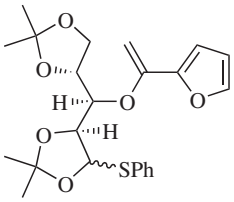
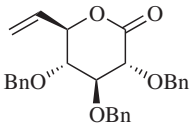
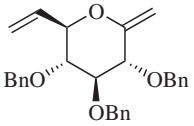
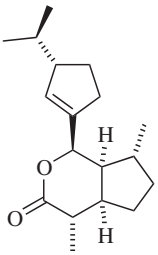
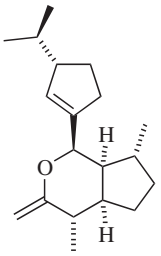
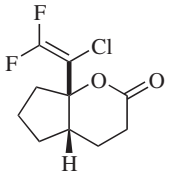
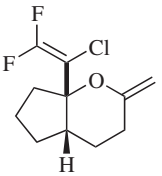
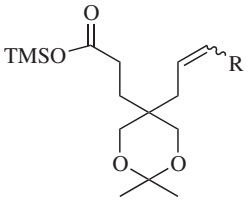
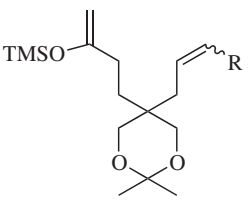
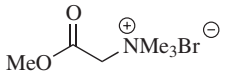
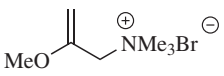
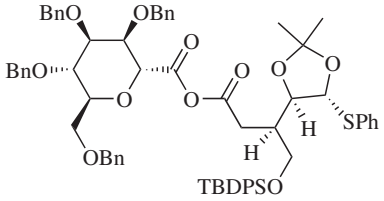
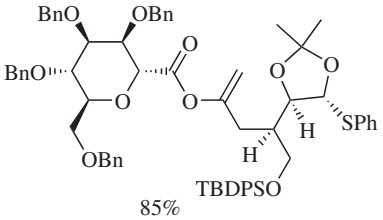
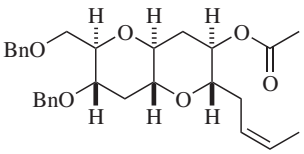
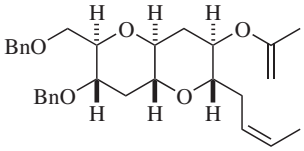
Entry	Ester	Product	Ref.
1		 84%	76
2		 60%	77
3		 64%	78
4		 90%	79
5		 84%	65
6		 98%	80
7		 89%	81
8		 >90%	82

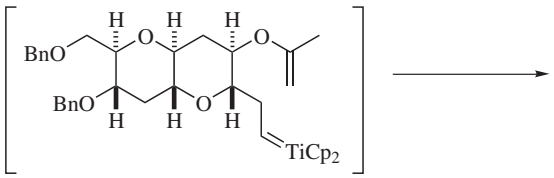
Table 5 Continued

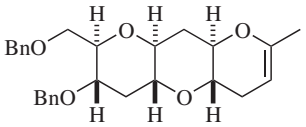
Entry	Ester	Product	Ref.
9		 36%	83
10		 85%	84, 85



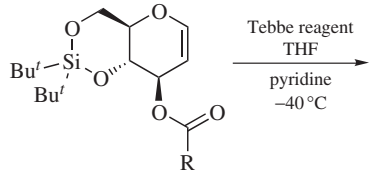


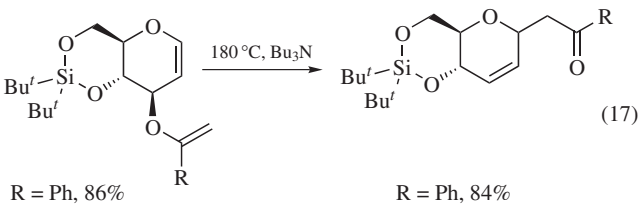
77%





65% (16)

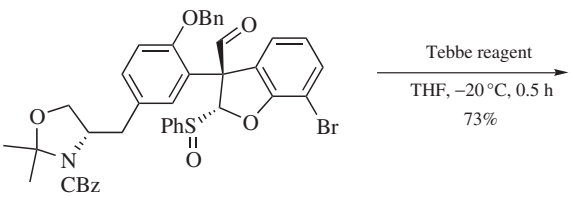


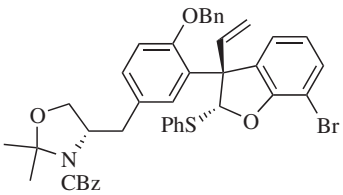


(17)

R = Ph, 86%
R = *n*-octyl, 91%
R = -$(CH_2)_3$NHBoc, 94%
R = -$(CH_2)_{14}CH_3$, 95%

R = Ph, 84%
R = *n*-octyl, 89%
R = -$(CH_2)_3$NHBoc, 69%
R = -$(CH_2)_{14}CH_3$, 88%

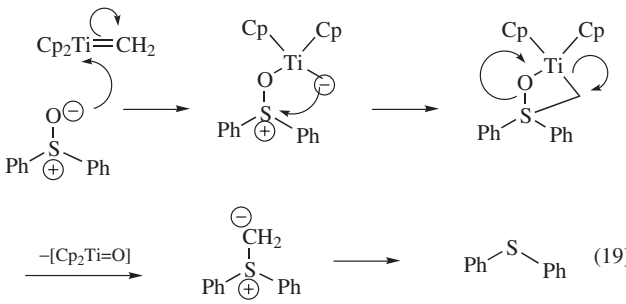




(18)

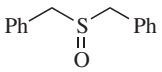
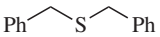
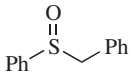
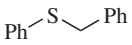
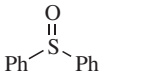
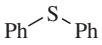
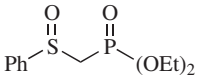
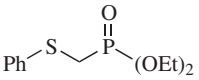
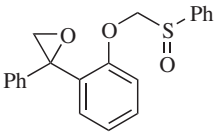
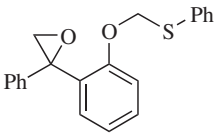
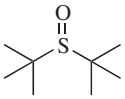
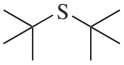
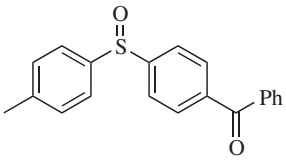
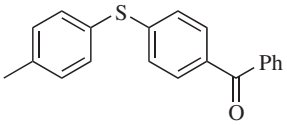
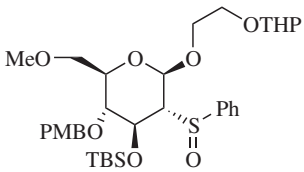
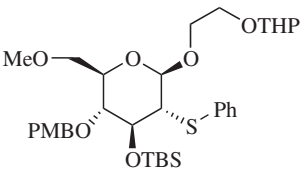
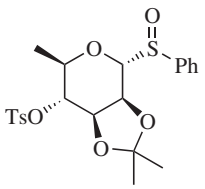
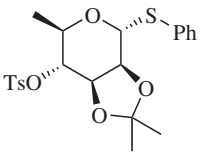
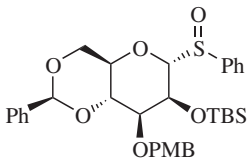
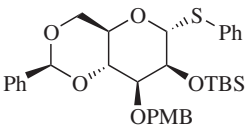
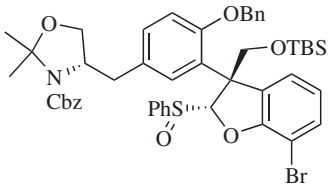
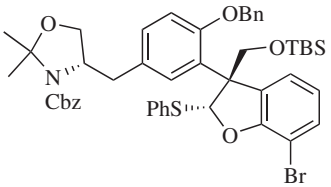
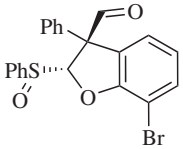
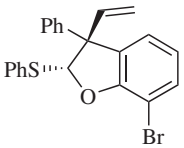
Reaction with Thiol Esters. On reaction with the Tebbe reagent thiol esters produce vinyl sulfides (eq 20).[97] An exception occurs in the case of eq 21, whereby a thiolactone generates a methanoanthracene and the sulfur is removed simultaneously during the methylenation process.[98]

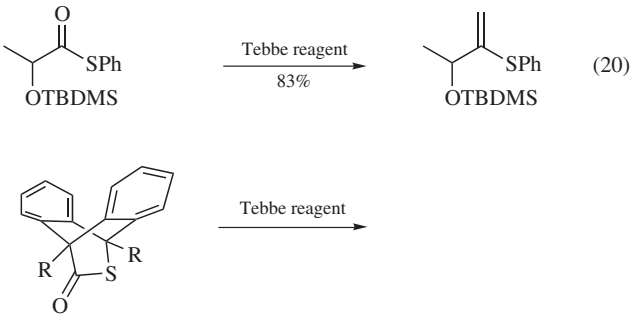
Carbometallation Reactions. The Tebbe reagent forms a titanocyclobutene very fast in the presence of a base and diphenyl acetylene.[99] On the other hand, in the absence of a base, the titanocyclobutene system is not formed, and instead a methyltitanation reaction takes place very slowly over 24 th (eq 22). In either case, on treatment with acid followed by hydroysis, alkenes form stereoselectively.

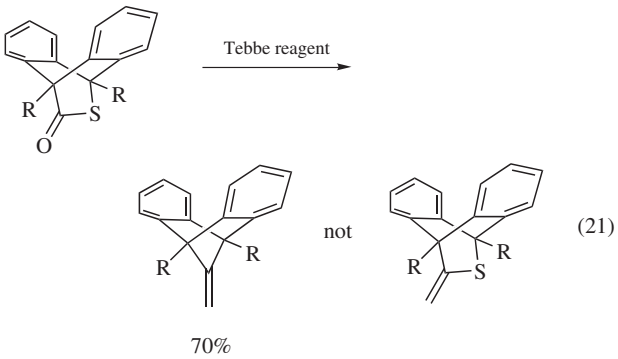


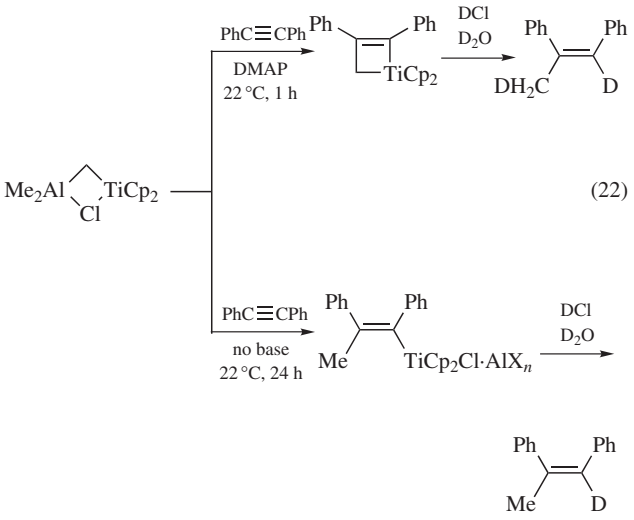
(19)

Table 6 Reduction of sulfoxides to sulfides

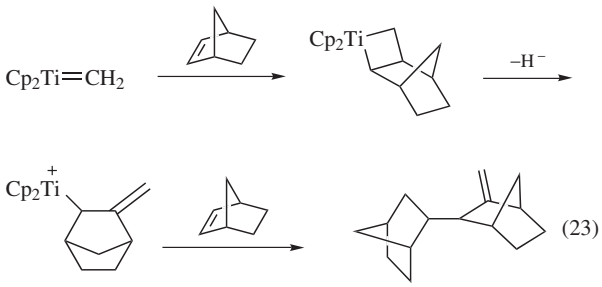
Entry	Sulfoxide	Product	Time (h)	Yield (%)	Ref.
1			2	80	96
2			3	81	96
3			0.5	94	96
4			4	77	96
5			2	50	96
6			18	25	96
7			1	85	96
8			3	79	96
9			1	76	96
10			0.5	84	96
11			1	83	96
12			1	78	71



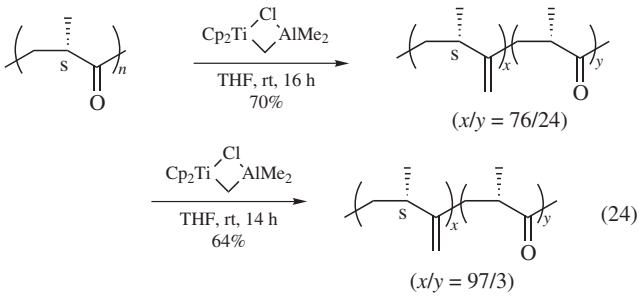




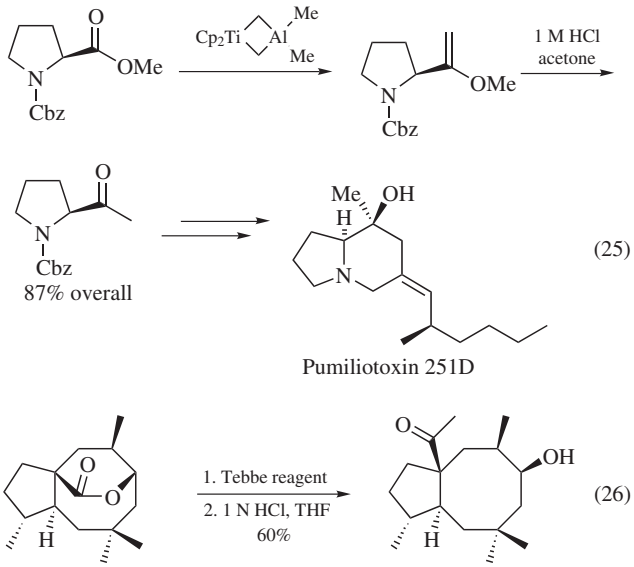
Olefin Polymerization. Ethylene polymerization and norbornane oligomerizations using the Tebbe reagent have been performed under varying conditions (eq 23): mechanistic studies were also conducted on this process.[100]



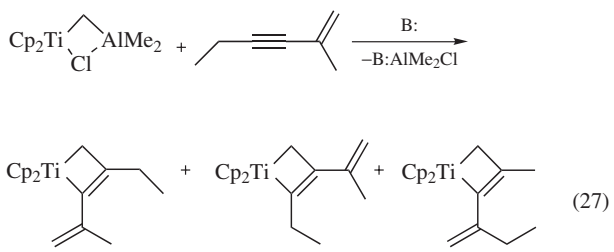
Nozaki et al. first introduced the concept of polymerization using a chiral monomer that adds an additional methylene to the repeating polymer unit (eq 24).[101] As noted above, this approach uses the Tebbe reagent itself for both the methylenation and subsequent polymerization steps.



Formation of Enol Ethers from Esters and Subsequent Transformation to Ketones. Formation of a ketone from an ester group without changing stereochemistry is a challenge for the synthetic chemist. In this situation, the Tebbe reagent helps to pursue these difficult transformations in a convenient way. One such example, in the synthesis of pumiliotoxin 251D, as represented in eq 25.[102] A further application of this reaction with a more complex substrate is given in eq 26.[103]



Metathesis. The Tebbe reagent can be used to form titanacyclobutenes bearing vinyl substituents on the α-position of the metallocyclobutene (eq 27).[104]



Related Reagents. Bis(η5-cyclopentadienyl)(diiodozinc)-(μ-methylene)titanium; Bis(cyclopentadienyl)dimethyltitanium; Bis(cyclopentadienyl)-3,3-dimethyltitanacyclobutane; Dibromomethane–Zinc–Titanium(IV) Chloride; Diiodomethane.

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