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Carbonyl-Coupling Reactions Using Low-Valent Titanium

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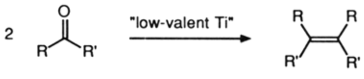
Contents

I. Introduction

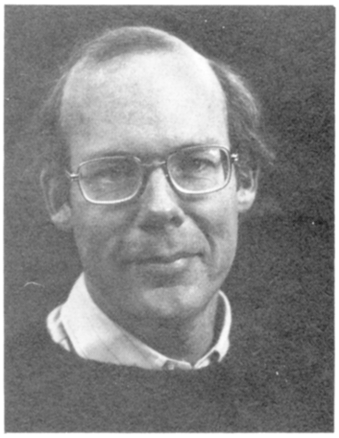
Some years ago, we[1] and two other groups[2,3] made the independent and simultaneous discovery that ketones and aldehydes undergo reductive dimerization to yield olefins on treatment with low-valent titanium reagents. Our own reagent system was prepared by reduction of $TiCl_3$ with $LiAlH_4$ in tetrahydrofuran, while that of Mukaiyama was prepared from $TiCl_4$/Zn and that of Tyrlik from $TiCl_3$/Mg.



R, R' = H, alkyl, or aryl

It was clear from the outset that the reactivity of the low-valent titanium reagent depended strongly on its method of preparation. Although our $TiCl_3/LiAlH_4$ system was capable of coupling both aromatic and aliphatic substrates, the Mukaiyama and Tyrlik systems appeared limited to aromatic cases. Subsequent work[4] showed that the most reactive and reproducible reagent could be prepared from $TiCl_3$/Zn–Cu, and it is with this material that most couplings are now done.

Three reviews[5–7] and over 100 papers have appeared in the past decade reporting an extraordinary variety of synthetic uses of the titanium-induced carbonyl-coupling reaction. A number of highly strained olefins, many unusual aromatic molecules, and a varied selection of complex natural products have all been synthesized by using carbonyl coupling as the key synthetic step. The present review surveys the status of the reaction 15 years after its discovery and draws some general lessons to help guide future work.



John McMurry did his undergraduate work at Harvard and his graduate work at Columbia with Gilbert Stork, receiving his Ph.D. in 1967. After 13 years on the faculty of the University of California at Santa Cruz, he returned east in 1980 as Professor of Chemistry at Cornell University. His research interests center on organic synthesis, including the development of new synthetic methods and the synthesis of unusual molecules, both natural and unnatural.

II. Reagents Used for Carbonyl Coupling

The ability to couple all manner of ketones and aldehydes to give olefins in high yield is unique to titanium.[8] We ourselves in early unpublished work[9] examined the possibility of using other transition metals (Al, Si, Sc, V, Cr, Mn, Fe, Co, Ni, Cu, Zr, Nb, Mo, Sn, W) to effect the reaction, and Geise has reported[10] attempts at using Mo, Zr, Nb, V, Co, Ni, Cu, Fe, Cr, Zn, Mn, Sn, Al, Hf, and Ta. Only with tungsten is more than a small amount of deoxygenation observed, and then only when diaryl ketones are used as substrates. More recently, Rieke has shown that active uranium prepared by reduction of UCl_4 with lithium naphthalenide is also effective for the coupling of aryl ketones.[11]

The original low-valent titanium reagent system that appeared best for the widest variety of substrates was prepared[1] by reaction of $TiCl_3$ with $LiAlH_4$ in the ratio 2:1. Assuming that the full reducing power of $LiAlH_4$ is used, 4 equiv of hydride should be able to reduce 2 equiv of $TiCl_3$ to the formal Ti(I) oxidation state or to a mixture of Ti(0) and Ti(II) oxidation states. In fact, the latter mix is probably closer to the truth, and the active coupling species is almost certainly Ti(0) as Geise has shown.[12,13] Owing to problems with reagent reproducibility, other preparations of low-valent titanium soon supplanted the original $TiCl_3/LiAlH_4$ procedure. We reported[14] in 1976 that a highly active Ti(0) reagent could be prepared by reduction of $TiCl_3$ with 3 equiv of potassium in THF, and soon thereafter[15] we introduced the use of $TiCl_3$/Li and then $TiCl_3$/Zn–Cu as

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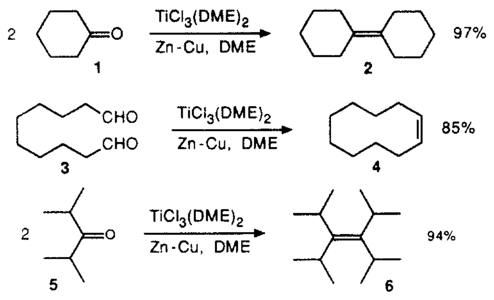
safer alternatives. That Ti(0) is the active species in these reagent preparations is clear both from the stoichiometry of the reduction and from the studies of Geise.

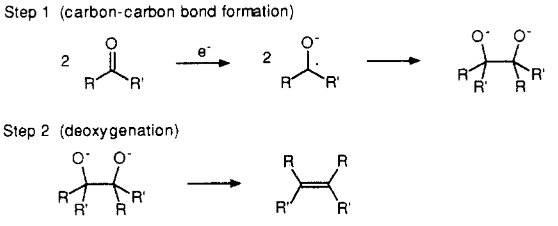
Numerous attempts have been made to improve the ease and reproducibility of low-valent titanium preparation, and the reagent systems $TiCl_4/Zn/pyridine$[16] and $TiCl_3/K/graphite$[17-19] have been suggested. Our own choice, however, is a modification of the $TiCl_3/Zn-Cu$ system introduced in 1978. We have recently found that treatment of $TiCl_3$ with refluxing dimethoxyethane (DME) for several days results in precipitation of a crystalline blue $TiCl_3(DME)_{1.5}$ solvate that can be reduced with zinc–copper couple to yield an extraordinarily active Ti(0) reagent.[20] Even aging and partially oxidized batches of $TiCl_3$ that give poor yields of coupled product by other methods give excellent results with this new preparation. Tetraisopropylethylene, for example, was originally reported by Morton[21] to be formed in 12% by reaction of diisopropyl ketone with $TiCl_3/LiAlH_4$, but the new $TiCl_3(DME)_{1.5}/Zn-Cu$ procedure gives the product in 94% yield.[22]



III. Mechanism of the Carbonyl-Coupling Reaction

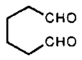
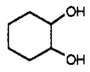
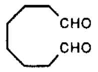
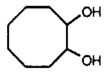
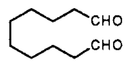
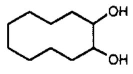
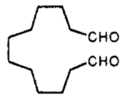
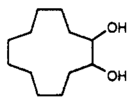
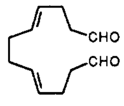
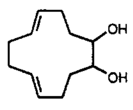
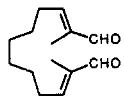
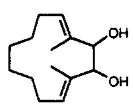
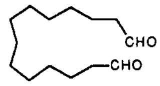
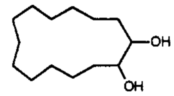
A. The Organic Part

The carbonyl-coupling reaction takes place in two steps: (1) reductive dimerization of the starting ketone or aldehyde to form the carbon–carbon bond, and (2) deoxygenation of the 1,2-diolate intermediate to yield the alkene.



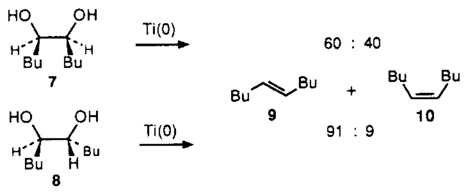
The first step is simply a pinacol reaction and is not unique to low-valent titanium. It has been known since 1859[23] that reducing metals are capable of adding an electron to a ketone or aldehyde carbonyl group, yielding an anion radical that dimerizes. The evidence for this first step in the titanium-induced coupling reaction is straightforward, because the intermediate pinacols can be isolated in high yield if the carbonyl-coupling reaction is carried out at 0 °C rather than at solvent reflux temperature. If the isolated pinacols are then subjected to treatment with low-valent titanium at 60 °C, deoxygenation occurs to yield the product alkene.

TABLE I. Titanium-Induced Intramolecular Pinacol Couplings

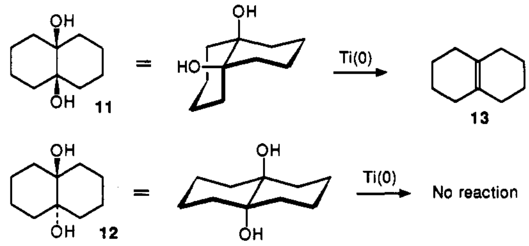
Entry	Dialdehyde	Pinacol	cis/trans Ratio	Yield (%)
1			100 : 0	85
2			70 : 30	82
3			25 : 75	80
4			25 : 75	75
5			5 : 95	83
6			5 : 95	84
7			30 : 70	89

In view of the remarkable yields often obtained in titanium-induced carbonyl couplings, it appears that low-valent titanium at 0 °C is actually the reagent of choice for carrying out pinacol reactions. Unfortunately, threo,erythro mixtures of diols are usually obtained from intermolecular reactions, and the factors that control product stereochemistry are not well understood. In fact, it has even been shown by Mundy that the stereochemistry of a pinacol reaction product can differ depending on the nature of the reducing metal.[24] With *intra*molecular reactions of dicarbonyl compounds, however, we have recently found[25] that predictable results are obtained and that high product yields are formed (Table I).

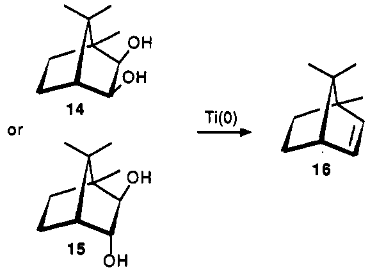
The second step of the carbonyl-coupling reaction to yield alkenes is the more interesting one because it was mechanistically unprecedented at the time of its discovery and is uniquely carried out by low-valent titanium. Although the details of the pinacol deoxygenation process are difficult to study owing to the heterogeneous nature of the reaction mixture, the broad outlines are clear. It has been shown, for example, that the two C–O bonds do not break at the same time and that a mixture of *cis*- and *trans*-alkenes is produced starting from a diol of known stereochemistry. The mixture is not the same starting from the *meso*- and *d,l*-5,6-decanediols, however, indicating that the reaction is very close to being concerted.[4]



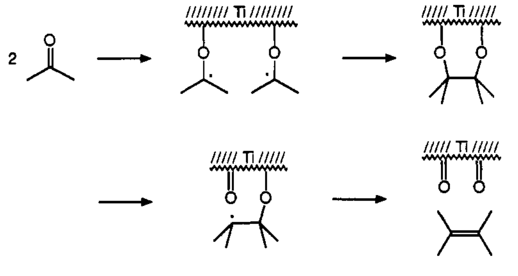
A further piece of mechanistic information is that the two oxygen atoms of the pinacolate intermediate must be able to approach and bond to a common surface. Thus, the cis isomer of 9,10-decalindiol reacts smoothly with low-valent titanium to yield the expected olefin, but the trans isomer is recovered unchanged after prolonged treatment.[4] The two oxygens of the cis diolate are in close proximity, but the two oxygens of the trans diolate are prevented by the steric bulk of the two rings from touching a common surface.



Yet a third piece of evidence is the demonstration that the two oxygen atoms of the pinacolate intermediate, although they must have a certain proximity, need not be able to bond to a common titanium atom in a five-membered ring. Thus, deoxygenations of the *cis*- and *trans*-camphanediols occur at approximately the same rate even though the oxygen atoms of the trans isomer are too far apart to bond to a common titanium atom.[4] By contrast, $Pb(OAc)_4$ cleavage of the two diols, a reaction known to require a five-membered intermediate, occurs approximately 10^6 faster on the cis isomer than on the trans isomer.[26]



Taken together, the above evidence leads us to conclude that titanium-induced deoxygenation of pinacolates takes place by coordination of the pinacolate to the surface of a small, zero-valent titanium particle, followed by stepwise cleavage of the C–O bonds with formation of a π-bonded olefin and an oxide-coated titanium surface.[4] The two oxygens must be able sterically to reach the same surface, but not the same titanium atom. This conclusion has been confirmed by extensive ESR spectroscopic work in which signals attributable to the titanium-bound pinacolate intermediate and to the π-bonded olefin product were observed.[13]



B. The Inorganic Part

Investigations using ESR have shown that, regardless of how it is prepared, the active low-valent coupling species is almost certainly Ti(0) particles in finely divided form.[13] When Mg, K, or Li is used as the reductant, ESR signals from Ti(III) and Ti(II) oxidation states gradually disappear as Ti(0) is formed. When $LiAlH_4$ is used, some Ti(II) remains because of incomplete reduction, but Ti(0) is still presumed to be the active form. The reagent prepared by Zn/Cu reduction of $TiCl_3$ has not been studied, but there is no reason to believe that it differs from the other four.

TABLE II. Functional-Group Compatibility of Titanium-Induced Carbonyl Coupling

compatible	semicompatible	incompatible
acetal	alkyne	allylic alcohol
alcohol	amide	1,2-diol
alkene	carboxylic acid (?)	epoxide
alkyl silane	ester	enedione, quinone
amine	ketone	halohydrin
ether	nitrile (?)	α-halo ketone
halide	toluenesulfonate	nitro
sulfide		oxime
vinyl silane		sulfoxide

The difference in behavior of different low-valent titanium preparations is probably due to the particle size, surface area, physical nature of the surface (edges, corners, holes), and solvent. The solvent is important during the preparation of the reagent because it appears to stabilize the zero-valent particles during their formation. A titanium mirror is formed from $TiCl_3/LiAlH_4$ if a weakly coordinating solvent like ether is used, but a fine suspension of black particles is formed in the presence of a more strongly coordinating solvent like THF or DME. Use of still more strongly coordinating solvents like pure pyridine prevents the $TiCl_3/LiAlH_4$ reagent from working.[13]

IV. Scope of the Carbonyl-Coupling Reaction

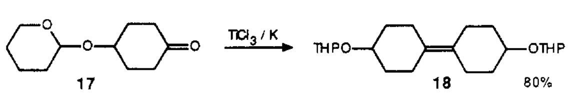
A. Functional-Group Compatibility

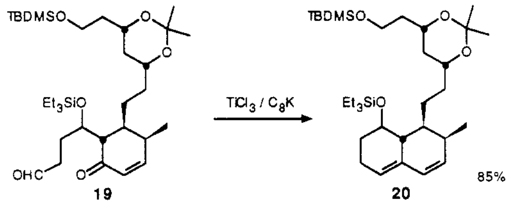
The presence in a substrate of certain easily reducible functional groups is not compatible with the carbonyl-coupling reaction because of the strong reducing power of Ti(0). Although no full study of functional-group compatibility has been published,[27] scattered literature results, together with some of our own unpublished work, suggest that functional groups fall into three categories (Table II).

1. Compatible Functional Groups

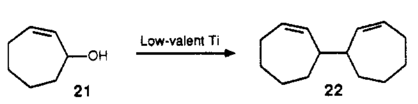
All of the groups in this category survive the carbonyl-coupling reaction, although some of the more hydrolytically sensitive groups like acetals and silyl ethers may undergo deprotection during workup if precautions are not taken to keep the solution basic. If this causes difficulty, it is sometimes best to carry out the coupling in the presence of a small amount of a tertiary amine (pyridine or triethylamine) and to quench the reaction with aqueous carbonate to assure basicity.

Acetal. There are few reported carbonyl-coupling reactions in the presence of acetal groups, but we have found in unpublished work[28] that THP ether **17** couples in high yield, and Clive has reported[19] coupling of acetal **19** in the course of a compactin synthesis. To prevent acid-catalyzed hydrolysis of an acetal group during workup, it is best to quench the coupling reaction with aqueous sodium carbonate or aqueous ammonia.

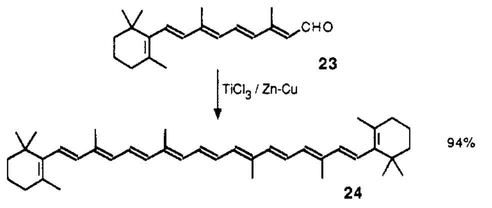




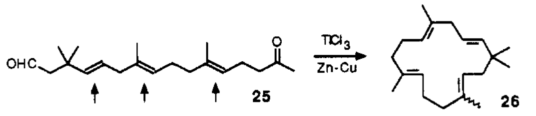
Alcohol. As was the case with acetals, there have been few carbonyl-coupling reactions carried out in the presence of free alcohol groups, although there is no reason to expect difficulty. We have found that saturated alcohols such as cholesterol are completely unaffected by low-valent titanium, even on prolonged exposure at THF reflux. Allylic alcohols, however, undergo a coupling reaction to yield 1,5-dienes.[29]



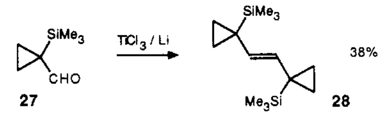
Alkene. Alkenes are inert to low-valent titanium, and a large number of successful coupling reactions have been carried out in the presence of carbon–carbon double bonds. β-Carotene, for example, can be prepared in high yield from retinal.[1]



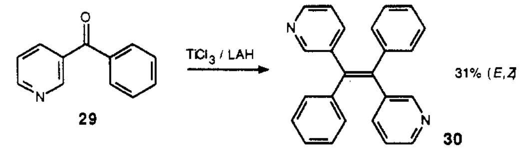
It is also important to note that no double-bond isomerization, either positional or geometric, occurs during the coupling reaction. In our synthesis of flexibilene,[30] for example, the three double bonds present in the starting material maintained complete stereochemical integrity during the coupling.

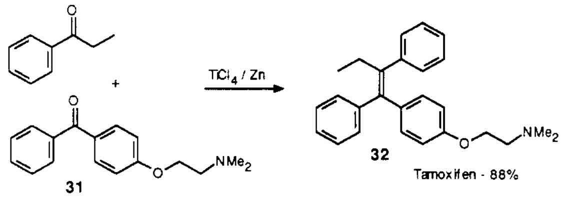


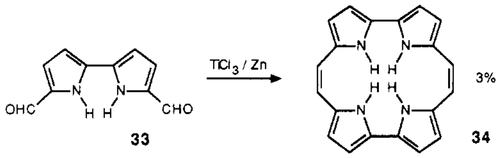
Alkyl silane. Tetraalkylsilanes appear to be inert to the carbonyl-coupling reaction conditions, as indicated by Paquette's successful coupling of formyl(trimethylsilyl)cyclopropane.[31]



Amine. Amines are inert to low-valent titanium, and their addition has even been recommended to improve yields in coupling reactions and to maintain basicity.[32] The amine is usually tertiary,[33] but use of pyrrole **33** with a free N–H group has also been reported.[34] Note that in the second of the following examples, the product obtained in a single step by a *mixed* coupling reaction of propiophenone with the substituted benzophenone **31** is the antitumor agent tamoxifen (**32**).[36]

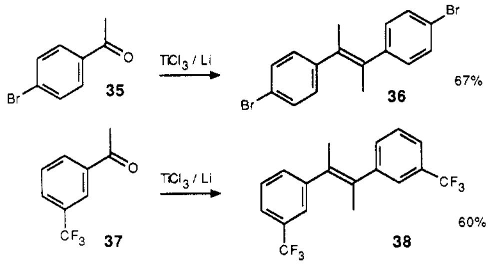




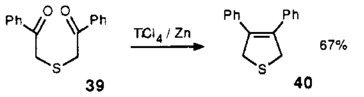


Ether. All manner of ethers appear to be compatible with the carbonyl-coupling reaction, and THF and dimethoxyethane are even used as reaction solvents. Other ethers that have proven unaffected by low-valent titanium include benzyl ethers[36] and silyl ethers.[37]

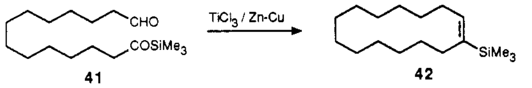
Halide. With the exception of 1,2-dihalides, organohalides are not reduced by low-valent titanium reagents, as demonstrated in the following two cases.[38]



Sulfide. At least one report has appeared in which carbonyl coupling was carried out in the presence of a sulfide.[39] The generality of the process has not been established, but there is no reason to expect problems with other sulfides.



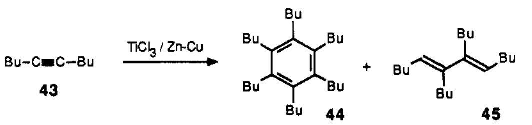
Vinyl silane. We have discovered in unpublished work that keto acyl silanes undergo intramolecular coupling to yield vinyl silanes.[40] The products appear to be stable to reaction conditions, indicating that a coupling reaction in the presence of this functional group should occur without difficulty.



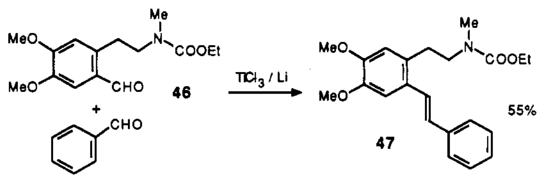
2. Semicompatible Functional Groups

All of the groups in this category react slowly with low-valent titanium, and their survival during a coupling reaction depends on experimental conditions. Coupling reactions that take place in a few hours can often be accomplished without damage to these semicompatible functional groups, but more difficult couplings that require extended periods of time can usually not be done. In practice, this means that most intermolecular reactions as well as those intramolecular reactions that form a five- or six-membered ring are feasible. Intramolecular reactions that form eight- or higher-membered-ring sizes need high-dilution conditions, however, and the semicompatible functional groups are sometimes unable to survive the lengthy addition times necessary to achieve this dilution.

Alkyne. We are unaware of any attempted coupling reaction in the presence of a carbon–carbon triple bond. In unpublished work,[41] however, we have found that slow reaction of alkynes occurs to yield trimers (substituted benzenes) and dimers on treatment with Ti(0) for extended periods. 5-Decyne, for example, gives hexabutylbenzene (50%) and 6,7-dibutyl-5,7-dodecadiene on treatment with Ti(0) for 20 h at THF reflux.

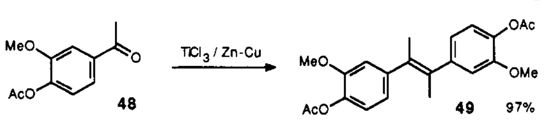


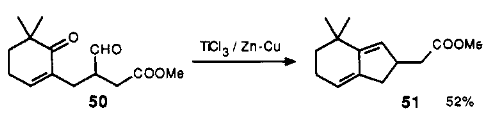
Amide. Amides react slowly with low-valent titanium but are compatible with carbonyl coupling unless extended reaction periods are used. The only example we are aware of where this has been carried out is the mixed coupling of aldehydo urethane **46** reported by Castedo.[42]



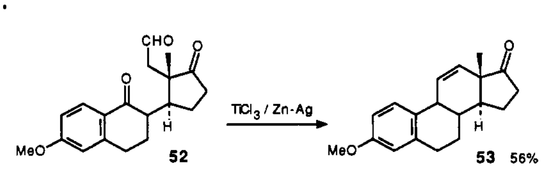
Carboxylic Acid. We are unaware of any attempts at carbonyl coupling in the presence of a carboxylic acid group. Geise has shown[27] that carboxylic acids and their salts react slowly with low-valent titanium ($TiCl_3$/$LiAlH_4$), but we would expect them to survive all but extended reaction periods.

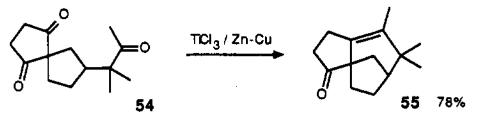
Ester. Numerous successful dicarbonyl-coupling reactions have been carried out in the presence of an ester group. As indicated previously, however, the reaction is successful only when it is intermolecular[43,44] or when it involves formation of a five- or six-membered ring.[45–47]





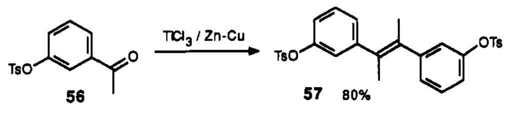
Ketone. It seems paradoxical to say that a ketone can survive the ketone-coupling reaction, yet this is exactly what can happen if intramolecular cyclization leading to a five- or six-membered ring occurs rapidly enough so that the reaction can be quenched before competing intermolecular dimerization takes place. Two such instances have been reported, one by Ziegler in the context of an estrone total synthesis (**52** → **53**),[48] and the other by Burnell in the context of a khusimone synthesis (**54** → **55**).[49] The khusimone synthesis is particularly interesting because it implies that a six-membered ring forms more easily than a three-membered ring.





Nitrile. As with carboxylic acids, we are unaware of any attempted carbonyl couplings in the presence of nitrile groups. Nitriles react slowly with low-valent titanium[27] but should survive exposures of moderate length.

Toluenesulfonate. One example has been reported in which an intermolecular carbonyl coupling was achieved in the presence of a tosylate group (**56** → **57**).[43] We would expect the reaction to be general in light of our own experience on the difficulty of reducing sulfones with low-valent titanium.

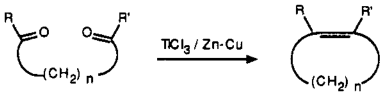


3. Incompatible Functional Groups

All of the groups in this category undergo rapid reduction on treatment with low-valent titanium—so rapid that they cannot survive carbonyl coupling. Indeed, low-valent titanium may well be the reagent of choice for reducing some of these groups in a preparative sense.[50] Thus, allylic and benzylic alcohols are rapidly coupled to yield 1,5-hexadienes and bibenzyls,[29] 1,2-diols (pinacols) are reduced to yield alkenes,[4] epoxides are deoxygenated to yield alkenes,[51] enediones and quinones are reduced to yield saturated diketones and hydroquinones,[52] halohydrins are reduced to yield alkenes,[53] α-halo ketones are dehalogenated to yield ketones,[54] aromatic nitro compounds are reduced to yield anilines,[55] aliphatic nitro compounds are reduced to yield imines,[56] oximes are reduced to yield imines,[57] and sulfoxides are reduced to yield sulfides.[58]

B. Intramolecular Carbonyl Couplings

The real value of the carbonyl-coupling reaction for organic synthesis lies in the fact that intramolecular couplings of dicarbonyl compounds take place in good yield to give cycloalkenes.[4,59] Rings of all sizes from 3 through 20 have been formed, and there is no reason to suspect that still larger rings would not form smoothly. Numerous specific examples are shown later in Tables IV and V.

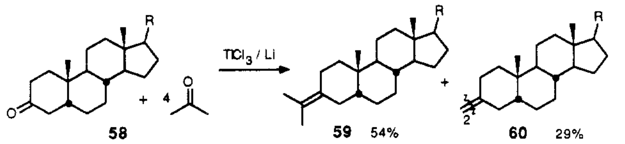


A comparison of cyclization yields for the titanium-induced carbonyl-coupling reaction versus several other well-known methods is shown in Figure 1. Although the exact yields shown in the figure do not necessarily represent optimized conditions, the trends in the data are probably real (the numbers for titanium-induced cyclizations represent work done 10 years ago[4] and could be substantially improved today with the $TiCl_3(DME)_{1.5}$/Zn–Cu procedure;[20] the numbers for acyloin, Dieckmann, and Thorpe–Ziegler reactions are taken from Bloomfield's literature review[60]). We have found on many occasions that titanium-induced dicarbonyl-coupling reactions give uniformly good results regardless of the size of the ring being formed. The Thorpe–Ziegler and Dieckmann reactions, by contrast, show a large decline in yield for medium-size rings, and the acyloin condensation shows a somewhat smaller decline, even when carried out in the presence of chlorotrimethylsilane.[61]

It should be noted that titanium-induced dicarbonyl couplings, like other cyclization reactions to form medium and large rings, require high dilution in order to achieve intramolecular cyclization rather than intermolecular polymerization. In practice, this is achieved by first preparing a slurry of the Ti(0) reagent and then adding a solution of the dicarbonyl compound over a 30–40-h period via a syringe pump. Full experimental details of an optimized procedure have been published.[20]

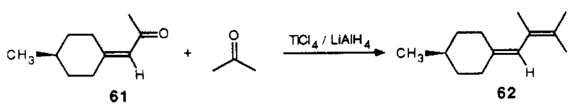
C. Mixed Coupling Reactions

The intermolecular carbonyl-coupling reaction is usually limited to the preparation of symmetrical olefins by dimerization of a ketone or aldehyde. When a mixture of two different carbonyl compounds is allowed to react with Ti(0), a roughly statistical mixture of the possible alkene coupling products is normally obtained.[62] For synthetic purposes, such mixed couplings are generally useful only if one component is used in excess and if the products are easily separable. For example, reaction of 3-cholestanone with a fourfold excess of acetone gives the mixed product, isopropylidenecholestane (59), in 54% yield and the symmetrical product, cholestanylidenecholestane (60), in 29% yield.[62] 2,3-Dimethyl-2-butene is also formed, presumably, but is lost during workup.



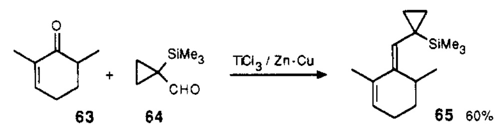
58 59 54% 60 29%

Although the yields are moderate, the simplicity of the mixed coupling procedure recommends itself when only small quantities of the mixed product are needed. For example, mixed coupling of acetone with chiral α,β-unsaturated ketones like (*R*)-(−)-(4-methylcyclohexylidene)acetone (61) has been used by Walborsky to prepare diene 62, necessary for a chiroptical study.[63]



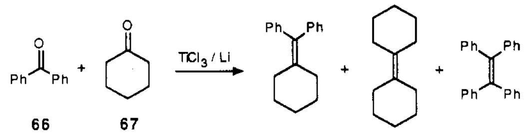
61 62

Another example of a mixed carbonyl-coupling reaction was used recently by Paquette in a synthesis of the sesquiterpene vetispirene.[64] Reaction of *equimolar* amounts of 2,6-dimethyl-2-cyclohexenone and formyl(trimethylsilyl)cyclopropane with Ti(0) gave the mixed coupled product (65) in 60% yield. It is not obvious why the mixed product should be favored so strongly over the symmetrical products in this case.



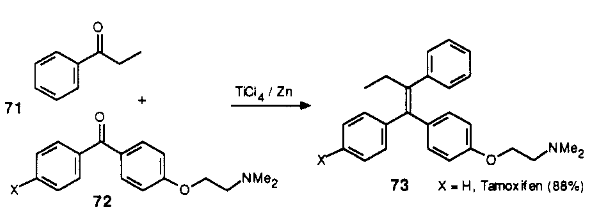
63 64 65 60%

The one general exception to the rule that mixed coupling reactions give mixtures of products occurs when one of the carbonyl partners is a diaryl ketone.[62] Coupling of a diaryl ketone with an equimolar amount of any ketone or aldehyde yields predominantly the mixed coupled product.



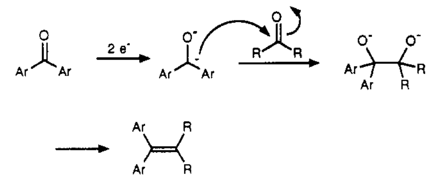
66 67 68 78% 69 19% 70 6%

This mixed coupling reaction has been used as the key step in the synthesis of the antitumor agent tamoxifen (73) and several of its analogues.[35,65]



71 72 73 X = H, Tamoxifen (88%)

The selective mixed coupling reaction of diaryl ketones can best be accounted for by a change in mechanism of the carbon–carbon bond-forming step from radical to polar. It is known that the *second* reduction potential of diaryl ketones is less negative than the first reduction potential of normal saturated ketones.[66] In other words, a diaryl ketone accepts two electrons to yield a dianion more easily than a normal saturated ketone accepts a single electron to yield an anion radical. If dianion formation is rapid and quantitative and if the dianion then adds to the saturated ketone by a nucleophilic addition mechanism, the mixed pinacol product will be produced selectively.



V. Uses of the Carbonyl-Coupling Reaction

A. Synthesis of Strained Olefins

One of the earliest uses of the carbonyl-coupling reaction in synthesis was for the preparation of strained olefins (Table III). The large thermodynamic driving force provided by the formation of titanium–oxygen bonds makes it possible to build a large amount of strain into the product during a carbonyl-coupling reaction, thereby allowing the synthesis of sterically hindered tetrasubstituted double bonds.

The examples in Table III show that the carbonyl-coupling reaction provides a remarkably easy synthesis of some highly strained molecules. Lenoir's coupling

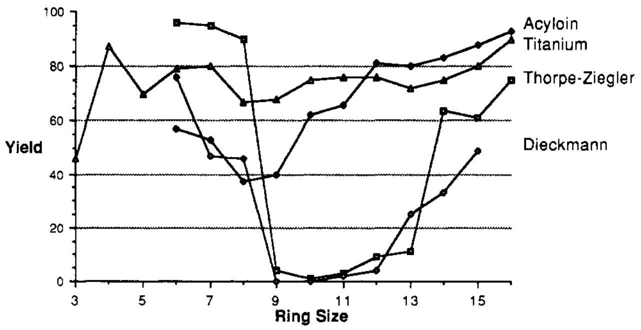


Figure 1. A yield comparison of several common methods of cyclization.

TABLE III. Synthesis of Strained Olefins

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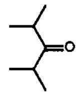
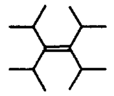
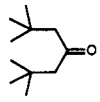
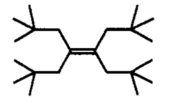
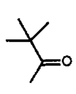
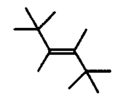
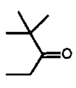
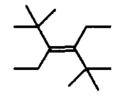
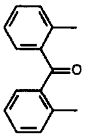
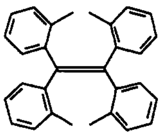
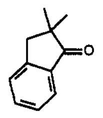
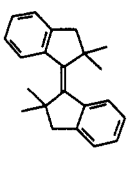
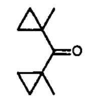
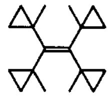
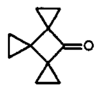
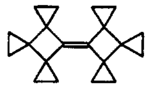
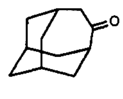
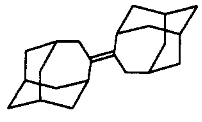
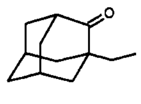
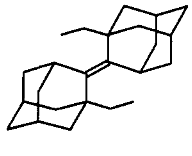
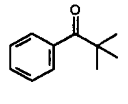
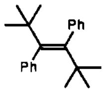
1			21, 67
2			68
3			69
4			70
5			71
6			72
7			73
8			74
9			75
10			76
11			76

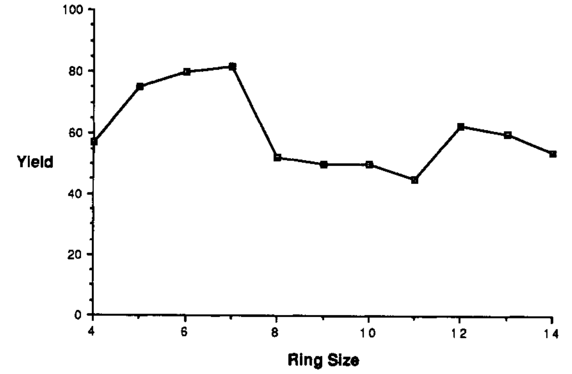
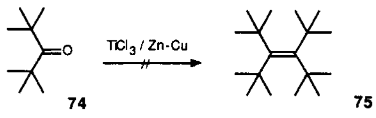


Figure 2. Synthesis of cycloalkanones by keto ester coupling.[122]

of ethyladamantanone (entry 10) represents the synthesis of a "tied-back" diisopropyl-di-*tert*-butylethylene, and entries 7 and 8 represent syntheses of tied-back tetra-*tert*-butylethylenes. Unfortunately, the synthesis of tetra-*tert*-butylethylene itself has been unsuccessful thus far. Attempted coupling of di-*tert*-butyl ketone with Ti(0), both in our own laboratories and in that of others, has provided tantalizing glimpses of an impure dimeric hydrocarbon but has not yielded pure isolable product.



B. Synthesis of Unusual Molecules

A second general use of the carbonyl-coupling reaction has been for the synthesis of molecules with unusual structures. The ability of the coupling reaction to form medium and large rings in high yield, while building in considerable strain at the same time, has led to the use of the reaction in a wide variety of circumstances (Table IV). Noteworthy among the many remarkable achievements recorded are Marshall's synthesis of the betweenanenes (entry 1), Yamamoto's synthesis of [7]circulene (entry 11), Vogel's synthesis of cyclic tetrapyrroles (entry 20), and Shimizu's synthesis of the ferrocene cyclophanes (entries 22–24).

The Vogel syntheses shown in entries 20 and 21 are particularly interesting because they involve *two* coupling reactions, the first intermolecular and the second intramolecular. Since steric constraints prevent the two carbonyl groups in the dipyrrole or difuran substrates from reacting with each other, it is only after an initial dimerization that cyclization can occur. The ferrocene syntheses in entries 22–24 are also of particular interest because they demonstrate that unusual organometallic functionality is compatible with low-valent titanium reactions. Finally, the remarkable reaction reported in entry 25 evidently involves coupling at the ortho position of an aromatic ring, rather than direct carbonyl coupling. The direct coupling is strongly hindered for steric reasons.

We ourselves have made use of the carbonyl-coupling reaction in the synthesis of an unusual series of cyclic polyenes (entries 26–27), in the synthesis of *in*-bicyclo[4.4.4]tetradecene (entry 28), and in the synthesis of a crossed diene (entry 29). The triene shown in entry 26 was prepared in the hope that the three double bonds might be close enough to show a hyperconjugative interaction via p-orbital overlap in the center of the molecule. Although photoelectron spectroscopy revealed little interaction among orbitals, a more thorough

TABLE IV. Synthesis of Some Unusual Molecules

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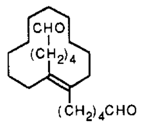
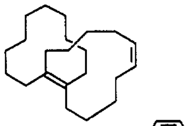
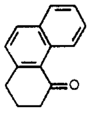
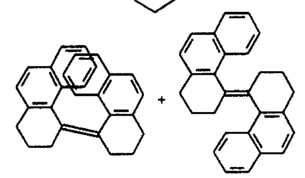
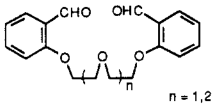
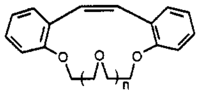
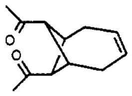
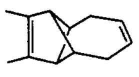
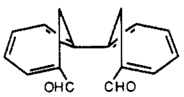
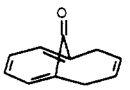
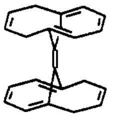
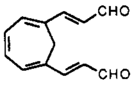
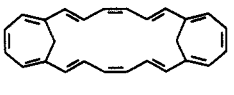
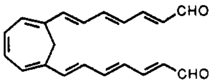
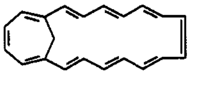
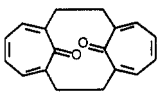
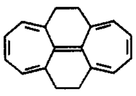
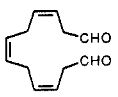
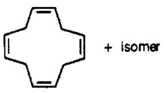
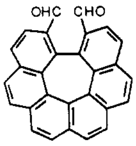
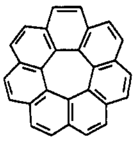
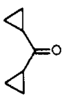
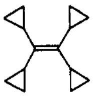
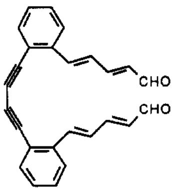
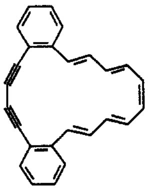
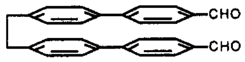
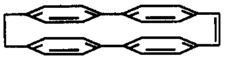
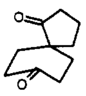
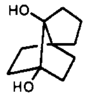
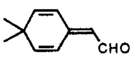
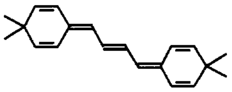
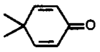
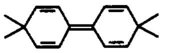
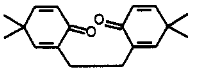
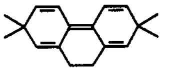
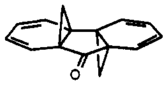
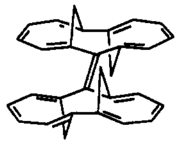
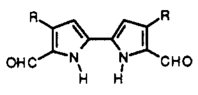
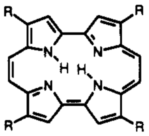
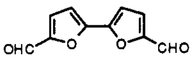
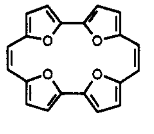
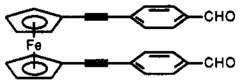
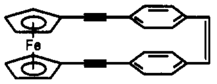
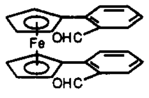
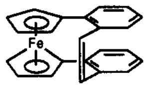
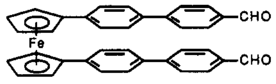
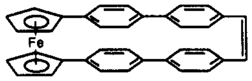
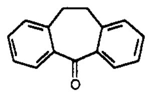
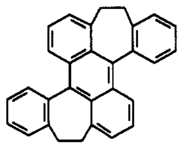
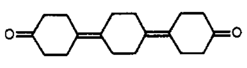
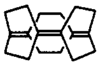
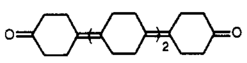
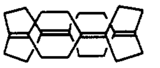
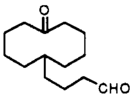
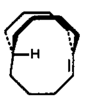
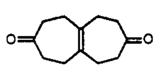
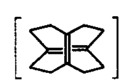
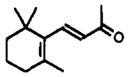
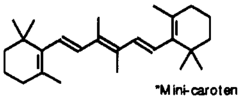
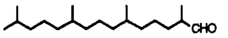
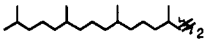
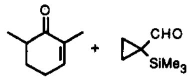
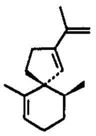
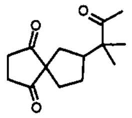
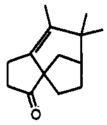
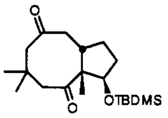
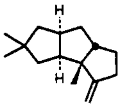
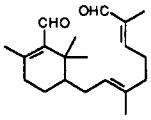
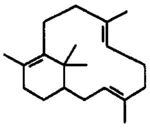
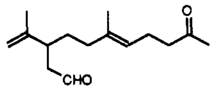
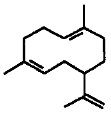
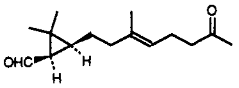
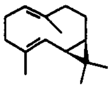
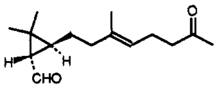
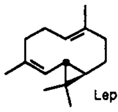
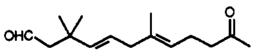
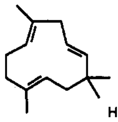
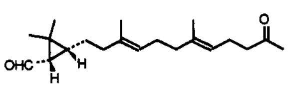
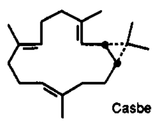
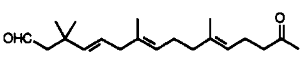
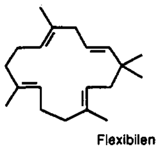
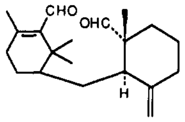
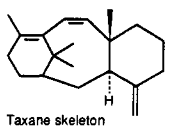
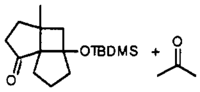
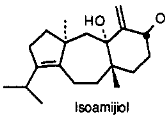
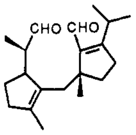
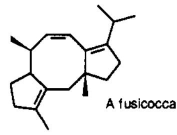
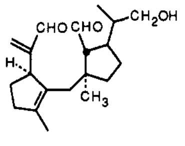
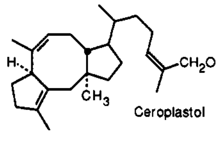
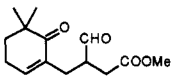
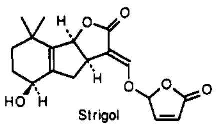
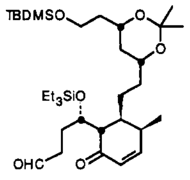
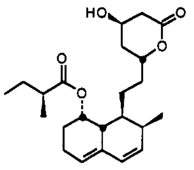
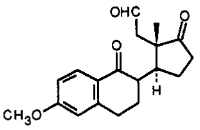
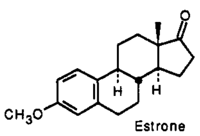
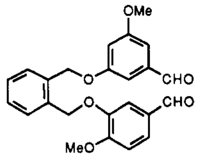
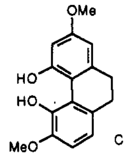
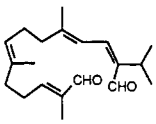
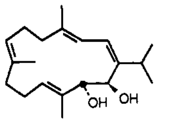
1			77
2			78
3	 n = 1,2		79
4			80
5			81
6			82
7			83
8			83
9			84
10			85
11			86
12			87
13			88
14			89
15			90
16			91
17			92
18			92
19			93
20	 R = Me, Et, Pr		94
21			95
22			97
23			98
24			98
25			99
26			100
27			101
28			102
29			103

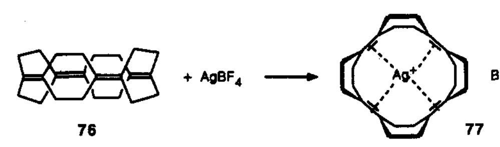
analysis of the situation using ab initio calculations has indicated that both through-bond and through-space interactions are in fact sizable, but that the two effects oppose one another.[104]

The corresponding tetraene shown in entry 27 was prepared as a potential tetradentate ligand with the idea that it might be able to complex and sequester a metal atom or ion in its cavity. In fact, reaction of the tetraene with $AgBF_4$ yields stable silver/olefin complex 77, shown by X-ray crystallography to have the Ag^+ ion in the center. This substance, the first square-planar d^{10} organometallic complex known, is stable to heat,

TABLE V. Synthesis of Natural Products

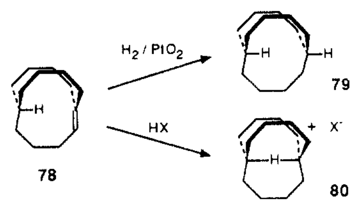
Entry	Substrate	Natural Product	Ref.
1		 "Mini-carotene"	106, 107
2		 Crude-oil marker	108, 109
3		 Vetispirene	64
4		 Isokhusimone	49
5		 Hirsutene	110
6		 Verticillene	111
7		 Helminthogermacrene	112
8		 Bicyclogermacrene	113, 114
9		 Lepidozene	113
10		 Humulene	30, 115
11		 Casbene	114
12		 Flexibilene	30
13		 Taxane skeleton	116
14		 Isoamijiol	37, 117
15		 A fusicoccane	118
16		 Ceroplastol	119
17		 Strigol	45
18		 Compactin	19
19		 Estrone	48
20		 Cannithrene II	120
21		 Sarcophytol B	25

light, and hydroxylic solvents that would instantly decompose any normal silver/olefin complex. It is, however, decomposed by reducing agents to yield silver metal and recovered tetraene.[105]

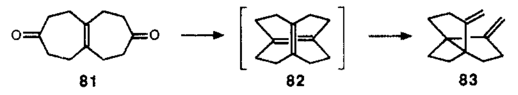


76 → 77

in-Bicyclo[4.4.4]tetradecene (**78**), prepared by the keto aldehyde carbonyl-coupling reaction shown in entry 28, was synthesized as a precursor to *in,out*-bicyclo[4.4.4]tetradecane (**79**) and to the *in*-bicyclo[4.4.4]-1-tetradecyl cation (**80**). This extraordinary cation, the first stable organic substance to contain a three-center, two-electron C–H–C bond, has yielded some fascinating chemistry. Its preparation by any method other than carbonyl coupling would probably be most difficult.



The final entry in Table IV records an attempted synthesis of a bicyclododecadiene (82) whose two double bonds are rigidly held close (2.32 Å calculated), yet perpendicular. Even though the molecule is highly strained (calculated ΔH_f = 67.6 kcal/mol) carbonyl coupling of the appropriate diketone 81 takes place in good yield to provide a cyclized diene product. Unfortunately, the desired product 82 undergoes rapid Cope rearrangement so that only rearranged diene 83 can be isolated.

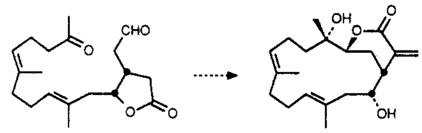


C. Synthesis of Natural Products

The carbonyl-coupling reaction is proving increasingly valuable in natural-product synthesis, as shown by the more than 20 exaples collected in Table V. The first two entries in the table make use of the intermolecular coupling of a monocarbonyl precursor, but most of couplings are intramolecular. Weedon's hirsutene synthesis (entry 5) is even "doubly intramolecular" since two rings are formed at the same time from a cyclooctanedione. Both oxygenated and nonoxygenated products are represented in the table.

A variety of different ring sizes are obtained by the coupling procedure, illustrating the power and generality of the method. Five-membered rings are formed in the hirsutene (entry 5) and strigol (entry 17) syntheses; six-membered rings are formed in the isokhusimone (entry 4), compactin (entry 18), and estrone (entry 19) syntheses; eight-membered rings are formed in the taxane (entry 13), fusicoccane (entry 15), and ceroplastol (entry 16) syntheses; ten-membered rings are formed in the helminthogermacrene (entry 7), bicyclogermacrene (entry 8), and lepidozene (entry 9) syntheses; an eleven-membered ring is formed in the humulene synthesis (entry 10); a twelve-membered ring is formed in the verticillene (entry 6) synthesis; fourteen-membered rings are formed in the casbene (entry 11), cannithrene II (entry 20), and sarcophytol B (entry 21) syntheses; and a fifteen-membered ring is formed in the flexibilene (entry 12) synthesis.

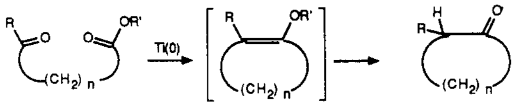
Our own efforts are presently concentrated on using the carbonyl-coupling reaction in the synthesis of complex macrocyclic natural products such as the cembranoid diterpenes.[121] Both their biological activity—many members of this large class of natural products have been found to be antitumor agents—and their macrocyclic structure make cembranoids natural targets for synthesis by a carbonyl-coupling route. Our recent synthesis of sarcophytol B (Table V, entry 21) is a simple example, but we are currently pursuing the synthesis of more complex oxygenated cembranoids such as crassin (85). One possibility is to use a low-temperature carbonyl coupling of a lactone keto aldehyde such as 84 to form a macrocyclic ring, followed by further manipulations as necessary. The pinacol that results either can be used as such (in a crassin synthesis) or can be deoxygenated by any of several mild methods to yield an alkene that can be converted into other cembranoids.



The notion of using a two-step procedure that proceeds through an isolable pinacol, rather than a one-step procedure that gives an alkene directly, is one that should greatly extend the utility of the carbonyl-coupling reaction. Compounds like lactone keto aldehyde 84 that have a "semicompatible" functional group are stable and can be cyclized with a low-temperature, titanium-induced pinacol coupling but are unstable and would be destroyed at higher temperatures.

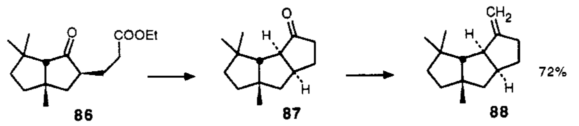
VI. Keto Ester Couplings

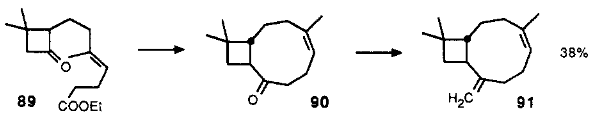
Although most intramolecular carbonyl-coupling reactions involve diketone, dialdehyde, or keto aldehyde substrates, we showed several years ago that the reaction could be extended to keto *esters*.[122] The result is a method of cycloalkanone synthesis.



As shown by the results plotted in Figure 2, the reaction works particularly well for the formation of five-, six-, and seven-membered rings, but other ring sizes are formed in lower yields. We have also found that a significant amount of work is often needed to optimize each individual case for medium and large rings, further decreasing the synthetic potential of the method. Our best results, however, are usually obtained with a low-valent titanium reagent prepared by reduction of $TiCl_3$ with $LiAlH_4$ in the presence of triethylamine. For reasons not presently understood, neither the $TiCl_3$/Zn–Cu reagent nor the $TiCl_3(DME)_{1.5}$/Zn–Cu reagent works as well.

Thus far, the keto ester coupling reaction has been used in syntheses of capnellene (88)[123] and isocaryophyllene (91).[124] The capnellene synthesis used the reaction to form a cyclopentanone ring, and the isocaryophyllene synthesis formed a cyclononenone ring.





The isocaryophyllene synthesis represents the only case noted to date in which olefin isomerization occurs during a carbonyl-coupling reaction. Since a control experiment showed that the *E* isomer of ketone **90** is stable to low-valent titanium, the double-bond isomerization must be occurring while the substrate is still bonded to the titanium reagent and before the coupling reaction is complete. It should also be noted that the isocaryophyllene synthesis required extensive optimization to achieve the 38% yield figure, demonstrating again the difficulties encountered when other than five-, six-, and seven-membered rings are prepared by keto ester coupling.

VII. Conclusions

The carbonyl-coupling reaction has evolved over the past 15 years into a general and powerful method of carbon–carbon bond formation. Although plagued in its early years by quality-control difficulties with the available $TiCl_3$ reagent, this problem has been overcome, and high product yields are now routinely obtained. That the reaction is of great value in synthetic ventures of many kinds, from strained olefins to unusual molecules to natural products, has been amply demonstrated by the many examples presented in this review. The reaction can be used in both an inter- and an intramolecular manner, but it is clear that its major importance is for the formation of medium- and large-ring cycloalkenes.

The largest current drawback of the reaction is its intolerance of other easily reduced functional groups. Even this problem is now being overcome with the recent development of low-temperature coupling methods, and we look forward to increasing use of the titanium-induced, carbonyl-coupling reaction in synthesis.

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