olefinic group. In ion III the same arguments are valid for interaction with the $C_{7,8}$ double bond. However, the bent-bond orbitals of cyclobutene in III turn out to be more suitable to overlap with C_7 in an unbridged configuration.

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A New Method for the Reductive Coupling of Carbonyls to Olefins. Synthesis of β-Carotene[1]

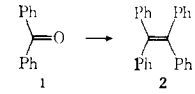
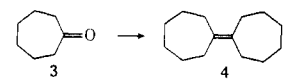
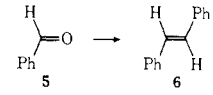
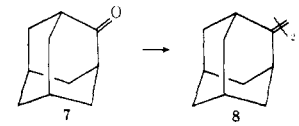
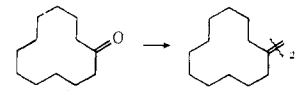
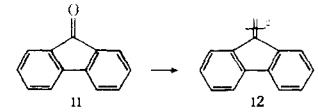
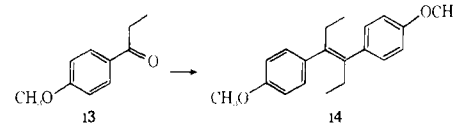
Sir:

The reactivity of $LiAlH_4$ as a reducing agent can be greatly modified by addition of metal salts. It is well known, for example, that a reagent prepared from $LiAlH_4$ and $AlCl_3$ is capable of reducing α,β-unsaturated ketones to olefins.[2] We have recently been involved in a study of $TiCl_3$ as a reducing agent in organic synthesis,[3-5] and we therefore thought it would be of interest to examine the reactivity of a $LiAlH_4$–$TiCl_3$ reagent.

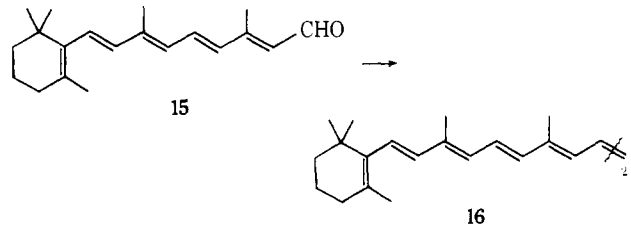
One equivalent of powdered $LiAlH_4$ was added to a stirred slurry of 2 equiv of $TiCl_3$ under nitrogen in dry THF. Instantaneous reaction occurred accompanied by the evolution of heat and gas and by a rapid color change to deep black. After addition of a THF solution of 1 equiv of benzophenone, followed by 4 hr of reflux, we isolated a 95% yield of tetraphenylethylene (mp 220–221°; lit.[6] 220°). This remarkable result is precedented only by the recent report of Sharpless[7] on the reductive coupling of aromatic ketones using low-valency tungsten complexes.[8] Our reaction, however, appears to work equally well for both saturated and unsaturated ketones. Some results are given in Table I.

One result in particular requires comment. Adamantylideneadamantane (**8**) was produced in 85% yield from 2-adamantanone. This olefin is of current interest,[9-11] and our synthesis is an improvement over the multistep methods which now exist for its preparation.[12,13]

Table I. Some Reactions of Carbonyl Compounds with $LiAlH_4$–$TiCl_3$

	% yield
	95
	95
	85
	85
	80
	95
	85

The coupling reaction is probably limited to the synthesis of symmetrical olefins but even so should prove valuable. β-Carotene (**16**) for example is a symmetrical

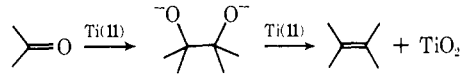


polyolefin of commercial importance as a food coloring agent and is generally prepared by a multistep route from vitamin A.[14] We therefore subjected retinal (**15**) to treatment with the $LiAlH_4$–$TiCl_3$ reagent and isolated β-carotene in 85% yield (mp 180–182°; lit.[15] 183°). Multiple unsaturation in the substrate is clearly compatible with the reaction.

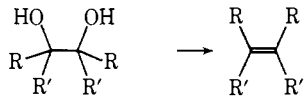
A detailed understanding of the reaction mechanism must await knowledge of the nature of the reagent. The course of the reaction can be readily accounted for, however, if one assumes that Ti(II) species are involved.[16] Ti(II) is a strong reducing agent [$Ti^{2+} = Ti^{3+} + e^-$; 0.37 V] and should be capable of effecting a pinacol reduction to an intermediate diol. Further reduction, either through formation of a cyclic Ti(II)

(1) The material covered in this communication is the subject of a U. S. Patent Application filed by the Regents of the University of California.
(2) J. H. Brewster and H. O. Bayer, *J. Org. Chem.*, **29**, 105, 116 (1964).
(3) L. C. Blaszczak and J. E. Mc Murry, *J. Org. Chem.*, **39**, 258 (1974).
(4) J. E. Mc Murry and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971).
(5) J. E. Mc Murry and J. Melton, *J. Org. Chem.*, **38**, 4367 (1973).
(6) A. Orekhoff, *Bull. Soc. Chim. Fr.*, **25**, 86 (1919).
(7) K. B. Sharpless, M. A. Umbreit, M. T. Nieh, and T. C. Flood, *J. Amer. Chem. Soc.*, **94**, 6538 (1972).
(8) Two alternate procedures for reductively coupling aromatic ketones to olefins with titanium-based reagents have recently appeared: S. Tyrlik and I. Wolochowicz, *Bull. Soc. Chim. Fr.*, 2147 (1973); T. Mukaiyama, T. Sato, and J. Hanna, *Chem. Lett.*, 1041 (1973). Neither of these procedures appears capable of coupling aliphatic ketones, however.
(9) A. P. Schaap and G. R. Faler, *J. Amer. Chem. Soc.*, **95**, 3381 (1973).
(10) J. H. Wieringa, J. Strating, H. Wynberg, and W. Adam, *Tetrahedron Lett.*, 169 (1972).
(11) J. Strating, J. H. Wieringa, and H. Wynberg, *Chem. Commun.*, 907 (1969).
(12) A. P. Schaap and G. R. Faler, *J. Org. Chem.*, **38**, 3061 (1973).
(13) H. W. Geluk, *Synthesis*, 652 (1970).
(14) For a listing of β-carotene syntheses, see O. Isler, Ed., "Carotenoids," Birkhauser Verlag, Basel, 1971, Chapter 6.
(15) "The Merck Index," 8th ed, Merck and Co., Rahway, N. J., 1968, p 213.
(16) $TiCl_3$ alone is not responsible for the reaction as we determined in a control reaction on cycloheptanone.

complex followed by concerted loss of TiO_2 or by stepwise loss of the oxygens then gives the product olefin.



Evidence in support of this hypothesis comes from observation of a black color characteristic of Ti(II) species[17] and from the fact that, when the reaction is allowed to proceed only to partial completion, pinacols can be isolated as by-products in many cases. van Tamelen has already shown that the 1,2-diol, *meso*-hydrobenzoin, is reduced to *trans*-stilbene by a $TiCl_3$–CH_3Li reagent [presumably *via* Ti(II)],[18] and we have further demonstrated that treatment of either benzpinacol (**17**) or the dilithium salt of cyclododecanone pinacol (**18**) with the $LiAlH_4$–$TiCl_3$ reagent also yields



17, R = R′ = Ph
18, R, R′ = $-(CH_2)_{10}-$

the corresponding olefins. Thus the reagent affords a method for the reduction of 1,2-diols to olefins and competes favorably with other methods of doing the transformation.[19]

One further observation which should be made is that if $LiAlH_4$ is serving merely to reduce Ti(III) to Ti(II), then other reagent systems producing Ti(II) might also effect the coupling reaction. There have in fact been two quite recent reports on the use of Zn–$TiCl_4$ and Mg–$TiCl_4$ reagents to couple aromatic ketones.[8] We ourselves have also shown that a variety of reducing agents including $LiBH_4$, CaH_2, and LiH will reduce either $TiCl_3$ or $TiCl_4$ to a reagent which will couple aromatic ketones. In our experience, however, the $LiAlH_4$–$TiCl_3$ system has given superior yields, particularly in the case of aliphatic ketones.

Our study is continuing, but it seems clear already that low-valent titanium reagents have considerable potential in organic synthesis.

(17) E. E. van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, **87**, 3277 (1965).
(18) K. B. Sharpless, R. P. Hanzlik, and E. E. van Tamelen, *J. Amer. Chem. Soc.*, **90**, 209 (1968).
(19) See K. B. Sharpless and T. C. Flood, *J. Chem. Soc., Chem. Commun.*, 370 (1972), and references therein.

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Electron Spin Resonance Studies on Diol Dehydrase.[1] III. Rapid Kinetic Studies on the Rate of Formation of Radicals in the Reaction with Propanediol

Sir:

Recent electron spin resonance studies with diol dehydrase,[2,3] ethanolamine ammonia-lyase,[4,5] and glycerol dehydrase[6] have provided evidence that the coenzyme B_{12} dependent rearrangements catalyzed by these enzymes proceed through radical intermediates. Mechanisms which have been proposed to account for these observations have postulated that the carbon–cobalt bond of the coenzyme is cleaved homolytically in the presence of substrates to give $B_{12}(r)$ (a paramagnetic low-spin cobalt(II) species) and organic radicals. Substrates and substrate analogs, when incubated with holo-diol dehydrase, convert 40–100% of the available coenzyme to these intermediates.[2] Although the substantial conversion of coenzyme B_{12} to $B_{12}(r)$ strongly implicates $B_{12}(r)$ in the catalytic process, it has so far not been demonstrated that this rate of formation is rapid enough to function as an intermediate. We have now employed rapid freeze–quench electron spin resonance techniques to determine the rate of formation of $B_{12}(r)$ and the organic radical in the reaction catalyzed by diol dehydrase with its normal substrate.

Rapid freeze quenching of reactions for esr studies was accomplished with the use of an apparatus designed according to Ballou.[7,8] The total dead time including mixing and freezing was 5–7 msec; other pertinent technical information and the procedures employed have been described.[8] All operations were carried out in the dark to avoid photolysis of the coenzyme. Diol dehydrase (free of propanediol) and a fivefold excess of coenzyme B_{12} were deoxygenated by three cycles of evacuation and flushing with O_2-free nitrogen in a vessel which served as a reservoir for the holoenzyme during a series of rapid freeze experiments. Anaerobic conditions were necessitated since oxygen inactivation of the holoenzyme in the absence of substrate would normally occur during the course of one series of experiments (3–4 hr). In the rapid freeze experiments reported here, 0.2–0.4 ml of the holoenzyme was rapidly mixed, at 5–7°, with an equal volume of 0.2 *M* propanediol. The samples were frozen after reaction times of 3–200 msec in isopentane at −140° and esr spectra of the packed samples were obtained in a Varian E-9 spectrometer with the sample temperature maintained in a stream of nitrogen at −130° to −140°. Manual mixing experiments were conducted by incubating 55 units of dioldehydrase and a fivefold excess of coenzyme B_{12} aerobically, at room temperature for 4 min to form the holoenzyme followed by the addition of propanediol to a concentration of 0.1 *M* in a final volume of 0.27 ml. After 15 sec of incubation at 5°, the samples were frozen in isopentane at −140°.

Figure 1A shows that after 3 msec of reaction time, the esr spectrum obtained from the reaction of 1,2-propanediol with the holoenzyme was qualitatively the same as that produced in a manual mixing experiment (15 sec) (Figure 1B), with the exception of an addi-

(1) This work was supported by research grants from the National Institutes of Health (GM-12633 [R.H.A.] and Training Grant GM-212 [J.E.V.]) and the Public Health Service (GM-1869 [J.A.F.]). This is publication No. 957 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Mass.

(2) T. H. Finlay, J. Valinsky, A. S. Mildvan, and R. H. Abeles, *J. Biol. Chem.*, 248, 1285 (1973).
(3) J. E. Valinsky, R. H. Abeles, and A. S. Mildvan, *J. Biol. Chem.*, 249, 2751 (1974).
(4) B. Babior and D. Gould, *Biochem. Biophys. Res. Commun.*, 34, 441 (1969).
(5) B. Babior, T. H. Moss, and D. C. Gould, *J. Biol. Chem.*, 247, 4389 (1972).
(6) S. A. Cockle, H. A. O. Hill, R. J. P. Williams, S. P. Davies, and M. A. Foster, *J. Amer. Chem. Soc.*, 94, 275 (1972).
(7) We gratefully acknowledge the advice and assistance of Dr. Graham Palmer and Dr. David Ballou in the initial rapid freeze experiments and the assistance of Robert A. Hannula in performing the experiments.
(8) D. P. Ballou, Ph.D. Thesi , University of Michigan, 1968.