Nickel-Catalyzed Conjugate Addition of Alkenylzirconium Species to α,β-Unsaturated Ketones

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Abstract: Alkenylzirconium(IV) complexes, prepared by hydrozirconation of the corresponding acetylenes with $Cp_2Zr(H)Cl$ ($Cp = \eta^5$-C_5H_5), can be utilized in conjugate addition to α,β-enones, catalyzed by $Ni(AcAc)_2$ (AcAc = 2,4-pentanedionate). No 1,2 addition of the alkenyl group is observed, and no trans-cis isomerization occurs. Conjugate addition of terminal alkenyls proceeds faster than that of internal alkenyls. The product of conjugate addition to α-substituted cyclic enones is the trans-1,2-disubstituted cyclic ketone. Attempts to catalyze conjugate addition of *alkyl*zirconium species to α,β-enones using nickel complexes have not been successful. The active form of the catalyst is postulated to be a reduced nickel species, generated by transfer of alkenyl groups from Zr to Ni(II), followed by reductive elimination of diene. It is found that reduction of $Ni(AcAc)_2$ with 1 equiv of DiBAH, prior to reaction, gives an efficient catalyst for improved yields in the case of conjugate addition. $Co(AcAc)_2$ and $Pd(AcAc)_2$/DiBAH were found comparable to $Ni(AcAc)_2$ as effective conjugate addition catalysts. Applications of this conjugate addition reaction to synthesis of prostaglandin analogues are described.

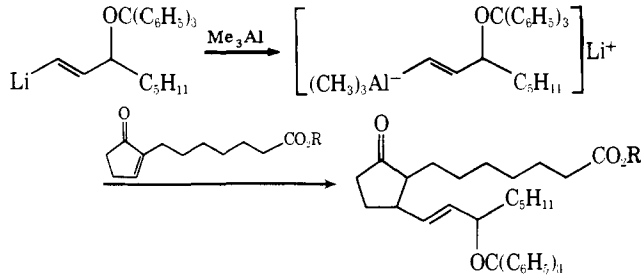
I. Introduction

Conjugate addition of organic groups to α,β-unsaturated carbonyl compounds through the intermediacy of organometallic reagents is now a commonly employed method in organic synthesis.[1,2] Of crucial significance to the development of this general type of reaction was the observation by Kharasch and Tawney[3] that transition-metal salts could divert the course of addition of Grignard reagents to α,β-enones from 1,2 to 1,4. The implication of organocopper species as the reactive intermediates in these copper-catalyzed Grignard reactions[4] led to the extensive development of a new area of organometallic chemistry, that of stoichiometric organocopper reagents. These were found to be useful species for conjugate addition of organic side chains to a variety of α,β-unsaturated carbonyl substrates, for coupling with organic halides,[5] and for other types of carbon–carbon bond formation processes.[6-8]

Organocopper reagents are commonly formed by reacting an organolithium reagent with a copper salt or complex. Therefore, the versatility of organocuprates as reagents notwithstanding, extensive research has been done aimed at developing species which could duplicate beneficial aspects of cuprate chemistry while not relying on lithium reagent precursors; implementation of lithium-based cuprate processes is often hampered by the tedious preparation of these organolithium precursors. Another facet of organocopper chemistry is that these species must be activated toward carbon–carbon bond forming processes. Cuprate species ("R_2CuLi") are reactive, but their use involves sacrifice of one "R" group since only one of them is usually transferred in the conjugate addition. Mixed cuprates, which were developed to overcome this inefficiency, are generally of reduced reactivity compared with cuprates.[9] In the special case of alkenylcuprates, important to the synthesis of various natural products, it is necessary to generate and maintain stereochemically pure alkenyl species. Alkenyllithium reagents used to prepare the corresponding cuprates are obtained by metal–halogen exchange with the corresponding alkenyl halide or by reaction of these organic halides with lithium metal.[10] Although the conversion of alkenyl halides to alkenyllithium reagents occurs predominantly with retention of configuration, some loss of double-bond stereochemistry can occur.[11] Lastly, alkenylcuprate species are generally utilized at low temperature since they are thermally unstable.

Organoaluminum compounds have been considered as replacements for cuprates in conjugate addition procedures. For example, alkenylalanes can be obtained directly from acetylenes by hydroalumination, thus bypassing the need to prepare an alkenyllithium reagent stereospecifically by an indirect route. Once activated as alanates, these aluminum species partake in conjugate addition reactions to unsaturated ketones. For example, Bernady and Weiss have used the "ate" complex shown in Scheme I in reaction with 2-(6-carboethoxyhexyl)-2-cyclopentenone to obtain ethyl 9-oxo-13-*trans*-prostenoate in 76% yield.[12] The preparation of alkenylalanate species is, however, not without complications. For example, hydroalumination of acetylenes, although yielding primarily the alkenylalanane, is accompanied to some extent by substitution to form alkynylalanes.[13] As well, hydroalumination of substituted acetylenes can prove difficult: Reaction of DiBAH with propargylic ethers does not always result in cis hydroalumination, and reductive cleavage of the carbon–oxygen bond may occur. Indeed, from a practical standpoint, it is often best to prepare an (allylically) oxygen-substitued alkenylalanate by reaction between trimethylaluminum and a substituted lithium alkenyl. Thus, regarding ease of precursor synthesis, the use of these aluminum species for conjugate addition offers no advantage over the alkenylcuprate-based routes since both routes rely on the availability of the corresponding alkenyllithium reagent. Work involving cuprates and alanates indicates, therefore, that an alternative route to organometallic species activated toward conjugate addition would be desirable if this route combined stereospecificity of product formation with high yields and ease of implementation.

Scheme I



II. Nickel-Catalyzed Conjugate Addition of Organozirconium Compounds to α,β-Enones

A. Attempts at Direct Transfer. As discussed above, organocopper and organoaluminum species are valuable reagents for extending the carbon framework of a molecule via conjugate addition; these routes are, however, not without drawbacks associated with ease of preparation of starting materials, stability of reagents, and specificity of reaction. Hydrozirconation of olefins and acetylenes using Cp_2ZrHCl had been studied

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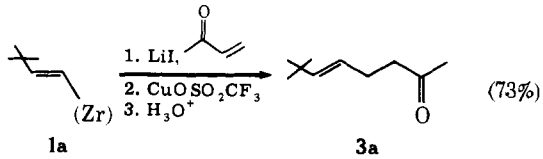
Scheme II



1a 3a

and found to proceed in high yield, and in the latter case, by stereospecific cis addition of the metal hydride to an acetylene, with good regioselectivity in cases where unsymmetrically substituted acetylenes were employed[14] (see Table I). If the organic group could be transferred directly from zirconium to an enone in 1,4 fashion, a considerable improvement in conjugate addition methodology could be realized since the reactive organometallic intermediate could be prepared directly from an acetylene with high stereo- and regiospecificity. As well, Cp_2ZrHCl has never been observed to deprotonate terminal acetylenes or to reductively cleave propargylic ethers.

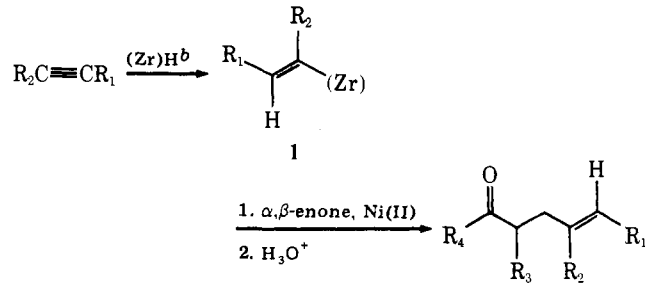
Unfortunately, direct transfer of alkenyl or alkyl groups from Cp_2ZrCl- to α,β-unsaturated carbonyl substrates proceeds only sluggishly and in low yield. For example, 1,4 addition of alkyl groups to methyl vinyl ketone or to 2-cyclohexen-1-one proceeded in less than 10% yield after 2 days at room temperature.[15]

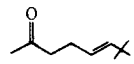
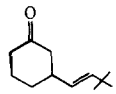
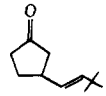
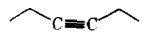
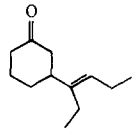
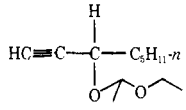
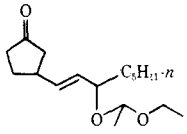
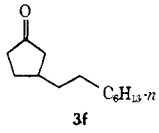
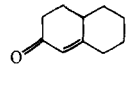
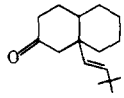
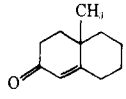
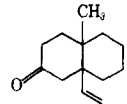
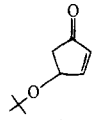
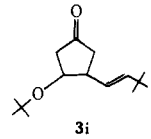
B. Stoichiometric Transmetalation. It had been found possible to use an organozirconium compound in tandem with a second metal for the purpose of carbon–carbon bond formation. For example, hydrozirconation of alkenes or alkynes followed by transmetalation of the organic group to $AlCl_3$ yields $RAlCl_2$ species; these, in turn, can be acylated with various acyl halides to form ketones.[16,17] Alkenyl groups were found to transmetalate far more rapidly than did alkyl ones. Finding a transmetalation sequence for conjugate addition would enable one to utilize the advantages of hydrozirconation mentioned above in conjunction with the conjugate addition propensity of the second metallic species. Because Cu(I) was known to be effective in promoting conjugate addition of a variety of organic groups to unsaturated carbonyl compounds, transmetalation of organic groups from zirconium to Cu(I) was attempted as a means to facilitate the otherwise tedious preparation of alkenylcuprates. Alkyl groups do not transmetalate from zirconium to Cu(I) at a synthetically useful rate. However, alkenyl groups may be transferred from Zr to Cu(I), giving alkenylcopper complexes in which the regio- and stereochemistries of the hydrozirconation reaction are preserved. Alkenyl Cu(I) species prepared by transmetalation behave analogously to those prepared from alkenyllithium reagents and cuprous halides. Reaction between **1a** and a slight excess of CuCl in THF gave a homogeneous solution which slowly decomposed (at 0 °C) to give a copper mirror and a colorless solution from which the diene, 2,2,7,7-tetramethyl-3,5(*E*,*E*)-octadiene, was obtained in 90% yield by extraction and removal of solvent.[18] Similar results can be obtained using copper(I) triflate.

Alkenyl Cu(I) complexes prepared by transmetalation can be captured as "cuprates" by LiI and used subsequently in conjugate addition reactions involving α,β-unsaturated ketones (Scheme II). This transmetalation route to alkenyl Cu(I) species is an improvement over hydroalumination routes by virtue of its efficiency. However, alkenylcopper compounds generated by transmetalation are no more stable thermally than are those obtained in conventional manner from organolithium or aluminum reagents. Most importantly, in this process copper can be employed only as a *stoichiometric* reagent.

C. Use of $Ni(AcAc)_2$ for Catalysis of Conjugate Addition of Alkenylzirconium Compounds to α,β-Enones. The possibility of activating organozirconium species toward conjugate addition using a second metallic species *catalytically* was examined. Both Mole[19] and Ashby[20] had observed that $Ni(AcAc)_2$ (AcAc = 2,4-pentanedionate) would catalyze the 1,4 addition of trimethylaluminum to various α,β-unsaturated ketones. When a mixture of zirconium alkenyl and α,β-enone was added to a solution containing a catalytic amount of $Ni(AcAc)_2$ in THF at 0 °C, high yields of conjugate adduct

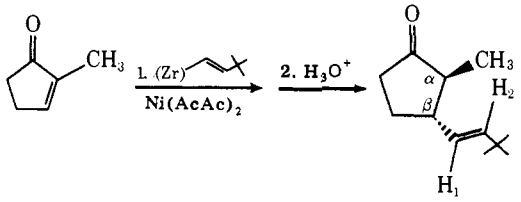
Scheme III[a]



acetylene	α,β-enone, 2	product	yield, %[c,d]
HC≡C–		 3a	>95
HC≡C–		 3b	77 (73), 59 (57)[e]
HC≡C–		 3c	78
		 3d	low (6–10)
		 3e	(59)[f]
HC≡CC6H13-n		 3f	(49), (46)[f]
HC≡C–	 2a	 3g	32.3
HC≡C–	 2b	 3h	<10
HC≡C–	 2f	 3i	76.9[e,f]

[a] All reactions were performed using **2** as the limiting reagent unless otherwise noted. [b] (Zr) = $(\eta^5\text{-}C_5H_5)_2Zr(Cl)$–. [c] VPC yield. [d] Isolated yield (chromatographed on silica gel). [e] **2** used in excess. [f] Yield not optimized.

Scheme IV



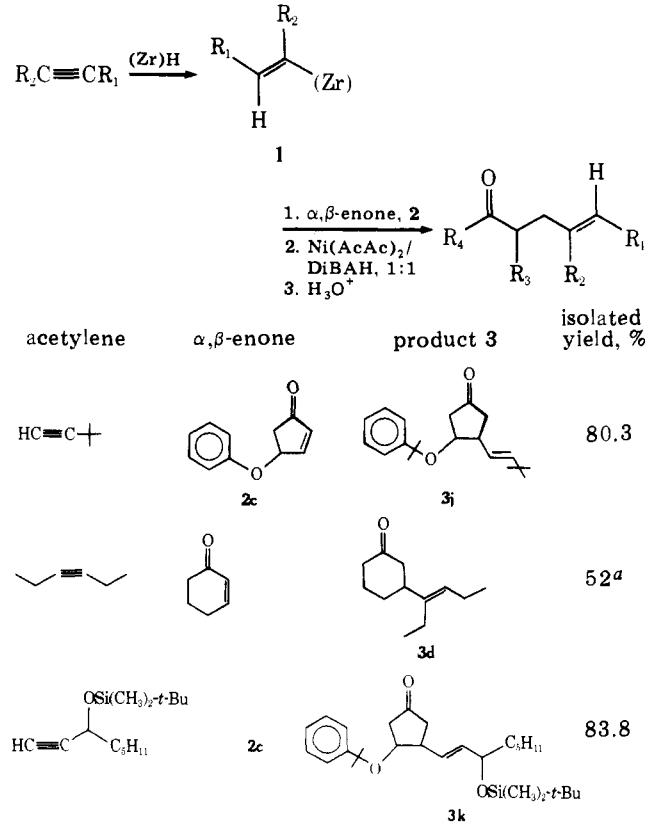
products could be obtained in 4–6 h (see Scheme III).[21] No 1,2 addition of the alkenyl group to the carbonyl unit was observed in any of these reactions and no isomerization of the alkenyl unit from trans to cis was observed. Attempts to catalyze conjugate addition of *alkyl*zirconium species to α,β-enones using nickel complexes have not yet been successful. This may be due to relative inefficiency of transmetalation of alkyl groups between zirconium and another transition metal.[16,17]

The structure of the α,β-enone substrate plays a major role in determining the degree of these conjugate addition reactions. Conjugate addition proceeds in very good yield when the substrate is a cyclic or acyclic species, but the yield of conjugate adduct to $\Delta^{1(9)}$-octalone-2 (**2a**)[22] is lower (33%) and only a small amount of product is obtained in attempts at conjugate addition to 10-methyl-$\Delta^{1(9)}$-octalone-2 (**2b**).[23] These results have been attributed to steric factors.

Nickel-catalyzed conjugate addition of alkylzirconium species to β-substituted cyclic enones proceeds to give, after aqueous workup, the trans disubstituted cyclic ketone as shown in Scheme IV. This same stereochemical course is observed for organocuprate conjugate addition reactions involving similar enones and side chains.[24]

D. Improvements in Nickel Catalysts. In original studies $Ni(AcAc)_2$, alone, was used to promote conjugate addition of alkenylzirconium species to α,β-enones. It was observed that in all $Ni(AcAc)_2$-based procedures some symmetrical diene resulted from coupling of two alkenyl units of the alkylzirconium starting material. It was postulated that the active form of the catalyst was a reduced nickel species, generated by transfer of alkenyl groups from zirconium to Ni(II), followed by reductive elimination of diene. Indeed, when the reaction between cyclohexenone, $Ni(AcAc)_2$, and **1a** was monitored as a function of time, it was found that diene formation, although relatively slow, was always observed prior to the onset of conjugate addition. In a parallel experiment it was noted that the solution formed by allowing $Ni(AcAc)_2$ to react with 0.5 equiv of **1a** (to give 0.5 equiv of symmetrical diene) contained a highly active catalyst for conjugate addition of alkenylzirconium species to an enone. Activation of Ni(II) in catalysis experiments is therefore believed to occur through reduction of a fraction of total Ni(II) added (by reductive elimination of diene derived from the alkenylzirconium starting material). To avoid the consumption of valuable alkenylzirconium starting material in the activation step for $Ni(AcAc)_2$, the added nickel compound was reduced *prior* to reaction with the enone and zirconium alkenyl by addition of 1 equiv of DiBAH.[25] This provided us with an efficient conjugate addition catalyst system whose utilization resulted in formation of essentially no dienic byproduct. Because $Ni(AcAc)_2$ (in the absence of DiBAH) was believed to be activated as a catalyst through transmetalation from a zirconium alkenyl, it was postulated that the low yield observed for *internal* alkenyl group transfer (Scheme II) was due to steric hindrance of the initial transmetalation step from zirconium to nickel. The use of *prereduced* nickel catalyst species, which obviates the transmetalation activation route, resulted in an acceptable yield of desired product **3d** (Scheme V). It is interesting to note that Negishi's work[26,27] has revealed that transmetalation of internal alkenyl units from zirconium to Ni(II) or Pd(II) proceeds very slowly compared with that for transmetalation of terminal alkenyl units.

Scheme V



[a] Yield not optimized.

The catalyst system, $Ni(AcAc)_2$/DiBAH (1:1), remained active for conjugate addition reactions for 5–6 h at 0 °C.[28] Low product yields have been noted in several cases where steric hindrance to conjugate addition is significant. This was attributed to slow rates for conjugate addition relative to catalyst deactivation, since in these cases the presence of additional alkenylzirconium species or increased reaction times did not improve the yield of the desired product. $Ni(mesal)_2$/DiBAH (1:1) (mesal = methylsalicyldimino)[29] was found to be a slightly longer lived catalyst system.

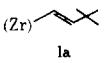
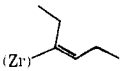
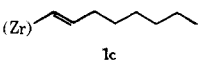
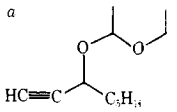
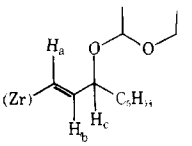
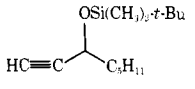
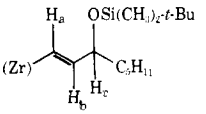
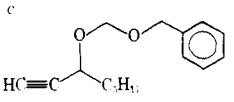
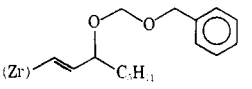
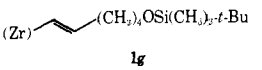
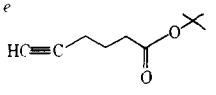
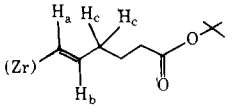
Other metal AcAc complexes were examined empirically to determine their effectiveness as catalysts for conjugate addition. Of these only $Co(AcAc)_2$ and $Pd(AcAc)_2$/DiBAH were found comparable to $Ni(AcAc)_2$ in this capacity.

III. Synthetic Applications

A. Conjugate Addition. We chose to study the application of nickel-catalyzed conjugate addition of zirconium alkenyls to prostaglandin synthesis, a field which has made extensive use of conjugate addition reactions involving alkenyl derivatives of other metals such as copper and aluminum.[30,31] The β side chain of many prostaglandins, 3-hydroxy-*trans*-1-octen-1-yl, can be prepared by hydrozirconation of the corresponding protected octynol to give the trans-alkenylzirconium compound **1e** (Table I). This zirconium alkenyl is then reacted with 4-cumyloxy-2-cyclopenten-1-one (**2c**) in the presence of $Ni(AcAc)_2$/DiBAH to give **3k** (84%) (Scheme V).

B. Alkylation of the Zirconium Enolate Product of Conjugate Addition. The initial product of nickel-catalyzed conjugate addition of an alkenylzirconium complex to an α,β-enone is the zirconium *O*-enolate.[21] Two such zirconium enolates, **4a** and **4b**, have been isolated from reaction mixtures by extraction and removal of solvent and characterized by NMR spectroscopy (Figure 1). Aldol condensation of formaldehyde with

Table I. ^{1}H NMR Spectra (C_6D_6) of Zirconium Alkenyls

acetylene	Zr-alkenyl	δ (C_6D_6), ppm
3,3-dimethyl-1-butyne	 **1a**	1.20 (s, 9 H) 5.90 (s, 10 H) 6.15 and 5.85 (d, J = 18 Hz) 6.90 and 6.65 (d, J = 18 Hz)
3-hexyne	 **1b**	0.88 (t, 3 H, J = 7 Hz) 1.05 (t, 3 H, J = 7 Hz) 1.99 (br q, 2 H, J_{obsd} = 7 Hz) 2.56 (br q, 2 H, J_{obsd} = 7 Hz) 5.83 (br t, 1 H, J_{obsd} = 6 Hz) 6.18 (s, 10 H)
1-octyne	 **1c**	1.15–1.82 (m, 11 H) 1.80–2.21 (m, 1 H) 5.86 (s, 10 H) 6.78 (m, 1 H) other vinylic resonance obscured by Cp
a 	 **1d**	0.92–1.91 (m, 17 H) 3.25–4.08 (m, 3 H) 4.58–5.17 (m, 1 H) 5.86 (2 s, 10 H, obscures 1 vinylic H) 6.65–6.95 (d of d, 1 H, J_{ab} = 18, J_{bc} = 3 Hz)
b 	 **1e**	0.27 (2 s, 6 H), 1.12 (s, 9 H), 0.87–1.82 (m, 11 H) 3.82–4.22 (m, 1 H), 5.97 (s, 10 H) 6.90 and 6.60 (br d, J_{ab} = 18 Hz) other vinylic H obscured by Cp resonance
c 	 **1f**	0.83–1.82 (m, 11 H), 3.92–4.22 (m, 2 H) 4.52–5.30 (m, 4 H), 6.00 (s, 10 H) 6.87 and 7.17 (d, 1 H, J = 18 Hz) 7.20–7.67 (m, 5 H) other vinylic resonance obscured by Cp
d $HC{\equiv}C(CH_2)_4OSi(CH_3)_2$-*t*-Bu	 **1g**	0.08 (s, 6 H) 0.98 (s, 9 H) 1.22–2.27 (m, 6 H) 3.42–3.82 (m, 2 H) 5.88 (s, 10 H) 6.70 and 7.00 (br d, 1 H, J = 18 Hz) other vinylic resonance obscured by Cp
e 	 **1h**	1.37 (s, 9 H) 1.55–2.43 (m, 6 H) 5.90 (s, 10 H) 6.67 and 6.95 (d of t, 1 H, J_{ab} = 16, J_{bc} = 2 Hz) other vinylic resonance obscured by Cp

[a] References 10 and 34. [b] References 38 and 39. [c] References 34 and 35. [d] Reference 39. [e] Reference 40.

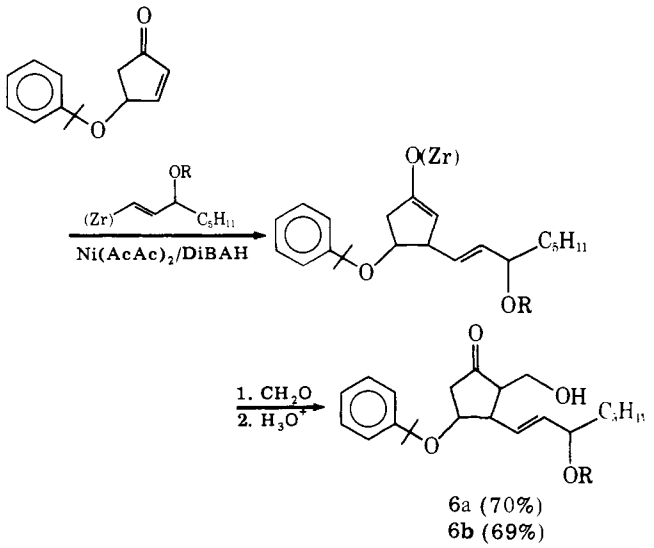
these enolates leads to α-methylene ketones which can then be used for further extension of the carbon skeleton. Reaction between zirconium enolate conjugate addition products and formaldehyde gave, in high yield, the desired α-hydroxy methyl ketone on hydrolysis. When enolate **4c** is treated with formaldehyde, the resulting ketone, **6a**, is obtained in 70% yield (Scheme VI).

Other products of formaldehyde condensation reactions are listed in Scheme VI.[32,33] Thus, the sequence shown provides an alternative route to **6b**, originally prepared by Stork in conjunction with his synthesis of $PGF_{2\alpha}$.[34,35] Conversion of **6a** and **6b** to the α-methylene ketones **2d** and **2e** can then be followed by further conjugate addition of an α side chain, making convergent syntheses of prostaglandin analogues possible. Two examples of such syntheses are shown in Scheme VII. Thus reaction of zirconium alkenyl **1h** with α-methylene ketone **2e** (obtained from **6b** in 80% yield according to literature procedures)[34,35] gave prostaglandin analogue precursor **3m** (61%), which was converted[34,35] to 5(E)-$PGF_{2\alpha}$.[36,37] It is interesting to note that hydrozirconation of the *tert*-butyl ester of 5-hexynoic acid proceeds in 81% yield with little discernible competitive reduction of the ester functional group (to the alcohol). Comparative hydrozirconation of the methyl ester gave only 41% of the desired zirconium alkenyl; here a large amount of reduced carboxylate product was obtained. The yield of **3m** is slightly lower than that obtained for unsubstituted cyclic enones; this may be due to steric hindrance from the β side chain on the C-5 ketone ring.

IV. Experimental Section

All experiments were performed under an atmosphere of nitrogen or argon from which oxygen was removed by passing through a bed of BTS catalyst in reduced form (previously heated under a CO stream) and from which water was removed by passing through a column of Matheson size 4A molecular sieves. The atmosphere was introduced by repeated evacuation and addition of gas to thoroughly dried glassware. Liquid transfers were performed by syringe, and solid transfers were performed under a stream of inert gas or in a drybox. All ether and routinely used hydrocarbon solvents were distilled, just prior to use, under argon or nitrogen, from sodium/benzophenone ketyl. Approximately 5% tetraglyme was added to hydrocarbon solvents to ensure solubility of the ketyl. All other solvents were distilled under argon or nitrogen from the proper drying agents (calcium hydride or lithium aluminum hydride). Commercially obtained organic

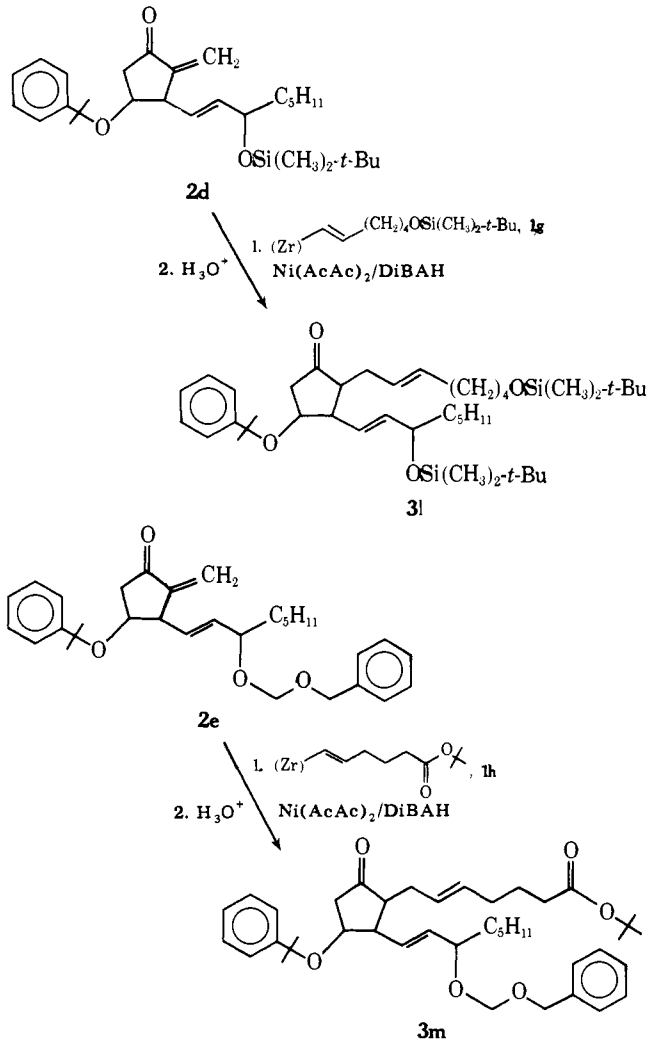
Scheme VI



6a (70%)
6b (69%)

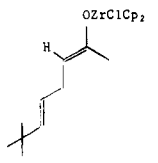
4c, 6a, R = $Si(CH_3)_2$-*t*-Bu
4d, **6b**, R = $CH_2OCH_2C_6H_5$

Scheme VII



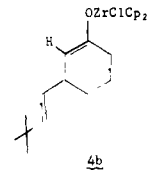
compounds were dried by the appropriate method and, if liquid, distilled under argon or nitrogen directly prior to use.

Infrared (IR) spectra were obtained with a Perkin-Elmer 283 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken on either a Varian A-60A spectrometer or a Perkin-Elmer R-32 90-MHz spectrometer, and are reported downfield from tetramethylsilane (Me_4Si) in units of δ in the order multiplicity, intensity (and identity). ^{13}C NMR spectra were obtained with a Varian XL-100 spectrometer equipped with a pulsed Fourier transform system. Mass spectra were recorded on an E.E.I.-MS 9. Elemental analyses were performed by Hoffman-La Roche, Inc., Nutley, N.J.



4a

δ 6.02 (s, 10)
5.18-5.83 (m, 2)
4.12-4.35 (t, 1, J = 7 Hz)
2.55-2.97 (m, 2)
1.67 (s, 3)
1.00 (s, 9)



4b

δ 5.96 (s, 10)
5.18-5.80 (m, 2)
4.57-4.67 (br d, 1, J = 5 Hz)
2.68-3.17 (m, 1)
1.35-2.42 (m, 6)
0.98 (s, 9)

Figure 1. ^1H NMR spectral data (in C_6D_6) for zirconium enolates **4a** and **4b.**

Analytical thin layer chromatography was performed on Whatman MK6F 1 × 3 in. plates. Preparative liquid chromatography was performed by using a Waters Associates refractive index detection Model R403 and a Fluid Metering, Inc., solvent delivery system. Samples were run through two EM Laboratories silica gel columns. The first, a scrubber column, was filled with EM Laboratories silica gel Type 60; the second was a LOBAR prepacked column, size B, 25 × 310 mm, also filled with silica gel Type 60. Samples were eluted with varying percentages of reagent grade hexane and ethyl acetate.

Analytical vapor phase chromatography (VPC) was performed on a Hewlett-Packard 402 instrument equipped with a flame ionization detector. The column used was a 1/4 in. × 8 ft 5% DEGS on Chromosorb P NAW 80–100. Preparative gas chromatography was carried out on a Perkin-Elmer 3920 thermal conductivity instrument, using a 3/8 in. × 8 ft 10% DEGS on Chromosorb P NAW 60–80. VPC yields were derived from the weights of peak areas of products vs. that of internal standards and were adjusted with the appropriate response factors. Response factors were determined by using standard solutions of known compounds or compounds prepared specifically for that purpose. Products were identified by coinjection with known samples unless otherwise specified. All yields are isolated unless otherwise noted.

Preparation of Anhydrous Nickel(II) 2,4-Pentanedionate, Ni(AcAc)$_2$. Nickel(II) 2,4-pentanedionate (Alfa) was dissolved in ether and filtered to remove ether-insoluble impurities. The ether was removed in vacuo and the bright green solid was dried overnight in vacuo at 80 °C. The resulting pale green solid was stored in a desiccator over $CaCl_2$.

Preparation of Chlorobis(η^5-cyclopentadienyl)hydridozirconium, Cp_2ZrHCl. This compound was prepared from dichlorobis(η^5-cyclopentadienyl)zirconium (Cp_2ZrCl_2) (Boulder Scientific) by the method of Wailes and analyzed for purity.[17]

Preparation of Alkyl- and Alkenylzirconium Compounds. These compounds were prepared according to a published procedure.[17] Zirconium alkenyls synthesized for this study, together with their NMR spectra, are reported in Table I.

Reaction of 1a with Cu_2Cl_2 in THF. Complex **1a** (174 mg, 0.51 mmol) and Cu_2Cl_2 (57 mg, 0.29 mmol) were dissolved in THF (5 mL). The mixture immediately turned yellow-green and gradually became brown. A copper mirror slowly deposited on the flask. The reaction mixture was stirred overnight, giving a colorless solution. This reaction mixture was hydrolyzed with water and extracted with ether. The organic layer was dried ($MgSO_4$) after the addition of dodecane (19 mg, as VPC standard). The solvent was removed in vacuo and the residual material was flash distilled to give 57 mg of an oil containing dodecane (19 mg) and 2,2,7,8-tetramethyl-3,5(*E,E*)-octadiene (38 mg, 0.23 mmol) (90%).[41]

Preparation of 3a from 1a and Methyl Vinyl Ketone, Using Cu(OSO_2CF_3) and LiI. Complex **1a** (0.402 g, 1.18 mmol), LiI (0.171 g, 1.28 mmol), and methyl vinyl ketone (0.125 g, 1.79 mmol) were dissolved in THF (10 mL) and cooled to −78 °C. A cold (−78 °C) so-

lution of $Cu(OSO_2CF_3)$, freshly prepared from Cu_2O and trifluoromethanesulfonic anhydride, was then added.[42]

The yellow reaction mixture slowly turned orange. After stirring for 2 h at −78 °C, it was warmed to −35 °C and kept at this temperature overnight. The resulting red reaction mixture was then warmed to room temperature. Hydrolysis with aqueous NH_4Cl, extraction with ether, drying, and removal of solvent, followed by analytical VPC, showed **3a** (73%). The same procedure using Cu_2Cl_2 also gave **3a** (39%). A sample was collected using preparative VPC: ^1H NMR (60 MHz, CCl_4) δ 0.96 (s, 9 H), 2.03 (s, 3 H), 2.33 (m, 4 H), 5.40 (m, 2 H); IR (CCl_4) CO 1720 cm^{-1}.

Preparation of 7,7-Dimethyloct-5-en-2-one (3a) Using a Stoichiometric Amount of $Ni(AcAc)_2$. Complex **1a** (1.049 g, 3.09 mmol) was dissolved in 10 mL of THF. Methyl vinyl ketone (0.35 mL) was added, as was dodecane (0.049 g, 0.29 mmol, VPC standard). This solution was cooled to −78 °C. $Ni(AcAc)_2$ (0.711 g, 2.77 mmol) was added, and the reaction mixture was slowly warmed to room temperature overnight. Saturated aqueous NH_4Cl was added, and the hydrolyzed reaction mixture was extracted with ether. The ether extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried (Na_2SO_4). After filtration, VPC analysis (95 °C) of the ether extracts showed **3a** (>95%).

Preparation of 3a Using a Catalytic Amount of $Ni(AcAc)_2$. The procedure and conditions above were used. Complex **1a** (0.933 g, 2.75 mmol), methyl vinyl ketone (0.25 mL), and dodecane (0.038 g, 0.22 mmol) were dissolved in 10 mL of THF. $Ni(AcAc)_2$ (0.071 g, 0.28 mmol) was added. VPC analysis (95 °C) showed **3a** (>95%).

Preparation of 3-(*trans*-4,4-Dimethylbuten-1-yl)cyclohexanone (3b) by $Ni(AcAc)_2$-Catalyzed Conjugate Addition of 1a. Complex **1a** (1.924 g, 5.67 mmol) and 2-cyclohexen-1-one (0.623 g, 6.48 mmol) were dissolved in 30 mL of THF and cooled to 0 °C. $Ni(AcAc)_2$ (0.151 g, 0.59 mmol) was added and the reaction mixture was stirred at 0 °C for 6.5 h. The reaction mixture was hydrolyzed and treated as described above. Compound **3b** was isolated by distillation of the ethereal solvent, followed by preparative liquid chromatography of the resulting oil. Distillation of solvent from the product fraction gave 0.744 g **3b** (73%): ^1H NMR (60 MHz, CCl_4) δ 1.00 (s, 9 H), 1.60-2.55 (m, 9 H), 5.36-5.40 (m, 2 H); IR (CCl_4) CO 1718 cm^{-1}. Anal. ($C_{12}H_{20}O$) C, H.

Preparation of 3b by $Ni(mesal)_2$-Catalyzed Conjugate Addition of 1a. Complex **1a** (0.349 g, 1.03 mmol) and 2-cyclohexen-1-one (0.071 g, 0.74 mmol) were dissolved in 10 mL of THF. $Ni(mesal)_2$[28] (0.062 g, 0.21 mmol) was added. After 30 min at room temperature, the solution had become dark brown. Hydrolysis of an aliquot after 4 h showed no remaining starting material in an NMR spectrum of the reaction mixture. Standard workup of the remaining reaction mixture, followed by preparative liquid chromatography, afforded 82.4 mg of **3b** (62%).

Preparation of 3b Using $Ni(mesal)_2$/DiBAH as Catalyst. $Ni(mesal)_2$ (0.062 g, 0.21 mmol) was dissolved in 3 mL of THF and cooled to 0 °C. DiBAH (0.39 mL of a 0.53 M THF solution) was added (0.21 mmol). The mixture turned dark brown immediately. A solution of 2-cyclohexen-1-one (0.074 g, 0.77 mmol) and **1a** (0.346 g, 1.03 mmol) in 15 mL of THF was added to the $Ni(mesal)_2$/DiBAH solution over 15 min and the resulting reaction mixture was stirred for 4 h at 0 °C. Standard workup, followed by preparative liquid chromatography, gave 101 mg of **3b** (76%). Similar procedures[43] using $Co(AcAc)_2$/DiBAH or $Pd(AcAc)_2$/DiBAH were employed and gave comparable results.

3-(*trans*-3,3-Dimethylbuten-1-yl)cyclopentanone (3c). The procedure for preparation of **3a** was followed, using **1a** (0.674 g, 1.99 mmol), 2-cyclopenten-1-one (0.2 mL), and dodecane (34 mg, internal VPC standard) dissolved in 10 mL of THF. $Ni(AcAc)_2$ (0.054 g, 0.21 mmol) was added and the reaction mixture was warmed to 0 °C gradually over 20 h. VPC analysis of a hydrolyzed aliquot showed **3c** (79%): IR (CCl_4) CO 1748 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.02 (s, 9 H), 1.75-3.00 (m, 7 H), 5.37-5.45 (m, 2 H). Anal. ($C_{11}H_{18}O$) C, H.

2-Methyl-3-(*trans*-3,3-dimethylbuten-1-yl)cyclopentanone. Complex **1a** (1.252 g, 3.69 mmol) and 2-methylcyclopent-2-enone (370 mg) were dissolved in 15 mL of THF. The solution was cooled to −78 °C for 30 min and then warmed to room temperature over 2 h. Standard workup, followed by preparative VPC, gave the desired compound (yield not determined quantitatively, homogeneous by analytical VPC): ^1H NMR (60 MHz, CCl_4) δ 1.01 (s, obscures d, 12 H), 1.50-2.47 (m, 6 H), 5.00-5.75 (m, 2 H); ^1H NMR (270 MHz, $CDCl_3$) δ 1.00 (s, obscures d, 12 H), 1.51-1.70 (m, 1 H), 1.70-1.91 (m, 1 H), 1.92-2.26 (m, 3 H), 2.26-2.48 (m, 1 H), 5.11-5.31 (d of d, 1 H, J_1 = 17, J_2 = 7 Hz), 5.50-5.61 (d, 1 H, J = 17 Hz).

$Ni(AcAc)_2$-Catalyzed Preparation of 3-(3-Hexen-3-yl)cyclohexanone (3d). Complex **1b** (0.668 g, 1.97 mmol) and 2-cyclohexen-1-one (0.189 g, 1.97 mmol) were dissolved in 10 mL of THF and cooled to −78 °C. $Ni(AcAc)_2$ (0.514 g, 2 mmol) was added with hexadecane (46 mg, internal VPC standard). The reaction mixture was stirred at 0 °C for 8 h. VPC analysis of a hydrolyzed aliquot showed **3d** (6%): IR (CCl_4) 1718 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.97 (t, 6 H, J = 7.5 Hz), 1.42-2.83 (m, 13 H), 5.13 (t, 1 H, J = 7 Hz). For distilled sample: Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C 80.80; H, 11.02.

$Ni(AcAc)_2$/DiBAH (1:1)-Catalyzed Preparation of 3d. $Ni(AcAc)_2$ (0.133 g, 0.52 mmol) was dissolved in 5 mL of THF and cooled to 0 °C. DiBAH (1.01 mL of a 0.5 M solution in THF, 0.505 mmol) was added. In a second flask **1b** (1.725 g, 5.08 mmol) and 2-cyclohexen-1-one (0.319 g, 3.33 mmol) were dissolved in 20 mL of THF. This solution was added dropwise to the catalyst solution over 20 min. The mixture was stirred for 4 h at 0 °C, then worked up in standard fashion. Preparative liquid chromatography gave 0.311 g of **3d** (52%).

3-(1-Ethoxyethoxyocten-1-yl)cyclopentanone (3e). Complex **1d** (1.826 g, 4.04 mmol) and 2-cyclopenten-1-one (0.42 mL) were dissolved in 20 mL of THF and cooled to 0 °C. $Ni(AcAc)_2$ (0.738 g, 2.87 mmol) was added and the reaction mixture was stirred at 0 °C for 6.5 hr. Standard workup, followed by preparative liquid chromatography, gave 426 mg of **3e** (59%): ^1H NMR (60 MHz, CCl_4) δ 0.70-2.33 (m, 17 H), 2.34-3.10 (m, 1 H), 3.10-3.68 (m, 2 H), 3.68-4.18 (m, 1 H), 4.41-4.76 (br q, 1 H, J = 6 Hz), 4.95-5.65 (m, 2 H); IR (CCl_4) CO 1750 cm^{-1}. For distilled sample: Anal. ($C_{17}H_{30}O_3$) H; C: calcd, 72.30; found, 71.06.

3-(1-Octen-1-yl)cyclopentanone (3f). The above procedure was followed using **1c** (1.364 g, 3.73 mmol), 2-cyclopenten-1-one (0.336 g, 4.10 mmol), and $Ni(AcAc)_2$ (0.097 g, 0.38 mmol), stirred for 8 h at 0 °C. Standard workup, followed by preparative liquid chromatography, gave 0.334 g of **3f** (49%): ^1H NMR (60 MHz, CCl_4) δ 0.67-1.08 (m, 3 H), 1.08-1.58 (m, 8 H), 1.58-2.45 (m, 8 H), 2.45-3.03 (m, 1 H), 5.38-5.57 (m, 2 H); IR (CCl_4) CO 1743 cm^{-1}. For distilled sample: Anal. ($C_{13}H_{22}O$) H; C: calcd, 80.35; found, 79.42.

9-(*trans*-3,3-Dimethyl-1-buten-1-yl)-$\Delta^{1(9)}$-octalone-2 (3g). The procedure above for preparation of **3e** was followed, using **1a** (0.710 g, 2.09 mmol), $\Delta^{1(9)}$-octalone-2 (0.474 g, 3.16 mmol), and $Ni(AcAc)_2$ (0.054 g, 0.21 mmol), dissolved in 20 mL of THF. This mixture was stirred for 4 h at 0 °C. Preparative liquid chromatography gave 0.158 g of **3g** (32%): ^1H NMR δ 0.98 (s, 9 H), 1.28-2.75 (m, 15 H), 4.92-5.63 (m, 2 H); IR (CCl_4) CO 1710 cm^{-1}.

9-(*trans*-3,3-Dimethyl-1-buten-1-yl)-10-methyl-$\Delta^{1(9)}$-octalone-2 (3h). The procedure for preparation of **3e** was followed, using **1a** (0.613 g, 1.81 mmol), 10-methyl-$\Delta^{1(9)}$-octalone-2 (0.359 g, 2.18 mmol), and $Ni(AcAc)_2$ (0.052 g, 0.20 mmol) dissolved in 20 mL of THF. This mixture was stirred at 0 °C for 9 h. VPC analysis (170 °C) showed a low (<10%) yield of **3h**. A sample was collected by preparative VPC (170 °C): ^1H NMR δ 1.00 (s, 12 H), 1.32-2.45 (m, 14 H), 5.13-5.75 (m, 2 H); IR (CCl_4) CO 1714 cm^{-1}. For distilled sample: Anal. ($C_{17}H_{28}O$) H; C: calcd, 83.40; found, 81.92.

3-(*trans*-3,3-Dimethylbuten-1-yl)-4-*tert*-butoxycyclopentanone (3i). Complex **1a** (0.552 g, 1.63 mmol) and 4-*tert*-butoxycyclopent-2-enone (0.172 g, 2.09 mmol) were dissolved in 20 mL of THF and cooled to 0 °C. $Ni(AcAc)_2$ (0.085 g, 0.33 mmol) was added and the resulting solution was stirred for 18.5 h at 0 °C. Standard workup, followed by preparative liquid chromatography, gave 205 mg of **3k** (77%): ^1H NMR δ 1.03 (s, 9 H), 1.18 (s, 9 H), 1.69-2.78 (m, 6 H), 3.66-3.95 (q, 1 H, J = 8 Hz), 5.13-5.65 (m, 2 H); IR (CCl_4) CO 1728 cm^{-1}.

3-(*trans*-3,3-Dimethylbuten-1-yl)-4-cumyloxycyclopentanone (3j). Complex **1a** (0.478 g, 1.41 mmol) and 4-cumyloxy-2-cyclopenten-1-one (**2a**, 0.222 g, 1.03 mmol) were dissolved in 15 mL of glyme. In a second flask $Ni(AcAc)_2$ (0.038 g, 0.14 mmol) was dissolved in 5 mL of ether and cooled to 0 °C. DiBAH (0.3 mL of a 0.47 M solution in toluene, 0.141 mmol) was added to the $Ni(AcAc)_2$ solution, followed by addition of the solution of **1a** and **2a**, dropwise over 15 min. The reaction mixture was stirred at 0 °C for 3 h. Standard workup, followed by preparative liquid chromatography, gave 0.234 g of **3j** (80%): ^1H NMR (60 MHz, CCl_4) δ 1.00 (s, 9 H), 1.51 (s, 6 H), 1.85-2.35

(m, 4 H), 2.48–2.98 (m, 1 H), 3.43–3.83 (q, 1 H, $J = 7$ Hz), 4.95–5.70 (m, 2 H), 7.10–7.55 (m, 5 H); IR (neat) CO 1754 cm^{-1}. Anal. ($C_{20}H_{28}O_2$) C, H.

3-(*trans*-3-*tert*-Butyldimethylsiloxyocten-1-yl)-4-cumyloxycyclopentanone (3k). Complex **1e** (1.217 g, 1.71 mmol) and **2a** (0.245 g, 1.13 mmol) were dissolved in 15 mL of THF. This solution was added dropwise over 0.5 h to a second flask containing $Ni(AcAc)_2$ (0.066 g, 0.26 mmol) and DiBAH (0.27 mL of a 0.94 M solution in THF, 0.25 mmol) dissolved in 4 mL of THF at 0 °C. The resulting solution was stirred for 4 h at 0 °C. Standard workup, followed by preparative liquid chromatography, gave 0.411 g of **3k** (84%): ^1H NMR (60 MHz, CCl_4) δ 0.00–0.13 (m, 6 H), 0.68–1.68 (m, 11 H), 1.53 (s, 6 H), 1.87–2.43 (m, 4 H), 2.60–2.95 (m, 1 H), 3.50–3.88 (m, 1 H), 3.88–4.22 (m, 1 H), 5.37–5.52 (m, 2 H), 7.01–7.58 (m, 5 H); ^{13}C NMR (CD_2Cl_2) δ 214*, 146*, 135*, 130*, 128, 127, 126, 77*, 75*, 73*, 53 (solvent), 47, 47, 42, 38, 32, 29, 26, 25, 23, 18, 14, −3, −3. (Asterisked signals are doubled owing to the presence of two diastereomers having the natural and epi configuration at C-15.) IR (CCl_4): CO 1750 cm^{-1}. Anal. ($C_{28}H_{46}O_3Si$) C, H.

Recommended Method for Preparation of a Dry Formaldehyde Solution.[32] Paraformaldehyde (Aldrich) is predried in vacuo at 60 °C overnight, then stored in a desiccator. The following apparatus is used for preparing the solution of formaldehyde: a three-necked, 100-mL, round-bottomed flask is equipped with an N_2 inlet, stopper, and oil bath and connected via Tygon tubing to a trap, which may be cooled by immersion in a Dewar flask. This trap is then connected to a three-way stopcock, which may either vent the system to the air through a $CaCl_2$ drying tube or to a tube which can bubble gas into a second three-necked, round-bottomed flask, equipped with a magnetic stirrer, a rubber serum cap, and a stopcock which can vent the system to air through another drying tube. This flask must also be cooled.

The entire system is evacuated and filled with N_2. Paraformaldehyde is placed in the first flask and depolymerized in a stream of N_2 by heating to 180 °C with the system open to the atmosphere at the first stopcock. CH_2O is collected as a liquid in the trap, which is cooled to −78 °C. When the desired volume of liquid formaldehyde is condensed, the oil bath is removed, the three-way stopcock is turned to the bubbler, and dry ether is added to the second flask via syringe. The ether is cooled to −78 °C, and then the second stopcock is opened, as the liquid CH_2O is boiled off and bubbled into the ether by warming the trap to −15 °C. The resulting ether solution of dry CH_2O can then be used in further reactions.

2-Hydroxymethyl-3-(*trans*-3-benzyloxymethoxyocten-1-yl)-4-cumyloxycyclopentanone (6b). Ketone **2a** (994 mg, 4.82 mmol) and **1f** (2.91 g, 5.80 mmol) were dissolved in 25 mL of THF. In a second flask $Ni(AcAc)_2$ (266 mg, 1.03 mmol) was dissolved in 15 mL of THF at 0 °C and DiBAH (1.6 mL of a 0.6 M solution) was added, followed by dropwise addition of the solution of **2a** and **1f**. The mixture was stirred for 1 h at 0 °C and then quenched with formaldehyde in ether solution (using a large excess of CH_2O). Standard workup, followed by preparative liquid chromatography, gave **6b** (69%). The ^1H NMR is in agreement with that given by Stork.[34,35] IR (CCl_4): CO 1742 cm^{-1}.

The two C-15 diastereomers of this product were separated by preparative liquid chromatography. If the natural configuration at C-15 is assigned to the less polar diastereomer, as Stork has done,[44] the ratio of the natural configuration to the epi was found to be ~1.5:1.

2-Hydroxymethyl-3-(*trans*-3-*tert*-butyldimethylsiloxyocten-1-yl)-4-cumyloxycyclopentanone (6a). A solution of **2a** (648 mg, 3 mmol) and **1e** (1.67 g, 3.36 mmol) in THF (20 mL) was added dropwise over 1 h to a solution of $Ni(AcAc)_2$ (196 mg, 0.75 mmol) and DiBAH (1 mL of a 0.6 M solution in toluene, 0.6 mmol) at 0 °C. Analytical TLC showed that reaction was complete in 3.5 h. The reaction mixture was then cooled to −70 °C, and a solution of formaldehyde (30 mL of ~1 M solution in ether) was added. Standard workup, followed by preparative liquid chromatography, gave 474 mg of **6a** (70%): ^1H NMR (60 MHz, CCl_4) δ 0.05–0.08 (2 s, 6 H), 0.88 (s, obscures t, 12 H), 1.15–1.72 (m, with s at 1.55, 14 H), 1.85–2.40 (m, 3 H), 2.47–3.02 (m, 1 H), 3.45–3.90 (m, 3 H), 3.91–4.30 (m, 1 H), 5.38–5.65 (m, 2 H), 7.13–7.58 (m, 5 H); IR (CCl_4) CO 1735 cm^{-1}.

2-Methylene-3-(*trans*-3-*tert*-butyldimethylsiloxyocten-1-yl)-4-cumyloxycyclopentanone (2d). To a cooled solution of **6a** (206 mg, 0.42 mmol) and triethylamine (172 mg, 1.7 mmol) in CH_2Cl_2 (3 mL) was added dropwise a solution of CH_3SO_2Cl (73 mg, 0.63 mmol) in CH_2Cl_2 (1.5 mL) at −25 °C. Reaction was complete after 1 h. The solution was poured into 30 mL of ice water and extracted with ether. The combined ether extracts were washed with water and brine to give 177 mg of **2d** (89%): ^1H HMR (60 MHz, CCl_4) δ 0.50–0.10 (2 s, 6 H), 0.92 (s, obscures t, 12 H), 1.13–1.75 (m, with s at 1.57, 14 H), 2.05–2.45 (m, 2 H), 3.17–3.55 (m, 1 H), 3.37–3.92 (m, 1 H), 3.93–4.32 (m, 1 H), 5.05–5.23 (m, 1 H), 5.32–5.63 (m, 2 H), 5.90–6.08 (m, 1 H), 7.12–7.58 (m, 5 H); IR (CCl_4) CO 1712 cm^{-1}.

(±)-2-Decarboxy-2-*tert*-butyldimethylsiloxymethyl-5-(*E*)-prostaglandin E_2 9-Cumyl Ether 15-*tert*-Butyldimethylsilyl Ether (3l). Complex **1g** (0.598 g, 1.08 mmol) and **2d** (330 mg, 0.703 mmol) were dissolved in 10 mL of THF. This solution was added dropwise over 20 min to a solution to $Ni(AcAc)_2$ (0.042 g, 0.163 mmol) and DiBAH (0.17 mL of a 0.94 M solution in toluene) in 5 mL of THF at 0 °C. Standard workup, followed by preparative liquid chromatography, gave 0.234 g of **3l** (49%): ^1H NMR (CCl_4, 60 MHz) δ 0.07 (s, 12 H), 0.93 (s, obscures triplet, 21 H), 1.17–1.75 (m, with s at 1.55, 18 H), 1.83–2.50 (m, 8 H), 3.43–3.78 (m, 3 H), 3.93–4.25 (m, 1 H), 5.25–5.58 (m, 4 H), 7.07–7.50 (m, 5 H); ^{13}C NMR (CD_2Cl_2) δ −4, −4, −5, 15, 19, 23, 26*, 29*, 30*, 31, 33, 39, 39, 48, 52*, 54, 64, 73*, 74*, 78*, 127, 128, 128, 129, 130, 134*, 137*, 147*, 215. (Asterisked signals are doubled owing to the presence of two diastereomers, having the natural and epi configurations at C-15.) IR (CCl_4): CO 1752 cm^{-1}.

(±)-5-(*E*)-Prostaglandin E_2 *tert*-Butyl Ester 9-Cumyl Ether 15-Benzyloxymethyl Ether (3m). Enone **2e** (130 mg, 0.280 mmol) and complex **1h** (0.39 mmol) were dissolved in 5 mL of THF. This solution was added to a mixture of $Ni(AcAc)_2$ (65 mg, 0.253 mmol) and DiBAH (0.35 mL of a 0.6 M solution in THF) in 6 mL of THF at room temperature. The reaction mixture was stirred for 2 h. Standard workup, followed by preparative liquid chromatography, gave 119 mg of **3m** (66%): ^1H NMR (90 MHz, CCl_4) δ 0.90 (m, 3 H), 1.07–1.83 (m, 25 H), 1.83–2.65 (m, 9 H), 3.40–3.73 (m, 1 H), 3.78–4.25 (m 1 H), 4.40–4.91 (m, 4 H), 5.00–5.58 (m, 4 H), 6.90–7.45 (m, 10 H); IR (CCl_4) CO 1730, 1743 cm^{-1}.

4-*tert*-Butoxycyclopent-2-enone.[45] Cyclopentadiene (4.2 mL, 0.05 mmol) was collected just prior to use by cracking the dimer at 180–200 °C. The cyclopentadiene was distilled through a short (8 cm) column of glass helices at 41 °C. The cyclopentadiene was added to a solution of $Cu(OAc)_2 \cdot H_2O$ (5.5 g, 0.02 mol) and *tert*-butyl hydroperoxide (5.4 g, 70%, 0.02 mol) in glacial acetic acid (15 mL). This solution was cooled to 10 °C, and a solution of $FeSO_4 \cdot 7H_2O$ (7.7 g, 0.03 mol, in 30 mL of H_2O) was added over 1 h. The mixture was then stirred for 1 h at room temperature. It was extracted three times with 50 mL of ether. The combined ether layers were washed with saturated aqueous sodium bicarbonate until the water layer was basic. The ether layers were concentrated, then dissolved in 60 mL of 10% methanolic KOH and stirred overnight. The resulting dark brown solution was extracted with ether. The ether extracts were dried and concentrated on the rotary evaporator. Distillation gave a clear liquid, bp 44–46 °C (0.05 mm).

This product, 4-*tert*-butoxycyclopent-2-en-1-ol (3.42 g, 22 mmol), was oxidized with 11.16 mL of Jones reagent (10% excess) (prepared by dissolving 10.2 g of CrO_3 in H_2O, adding 8.5 mL of H_2SO_4, and diluting to 75 mL with H_2O) added dropwise to a solution of the alcohol in an equal volume of acetone at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. Then 1.5 g of $NaHSO_3$ was added and the reaction mixture stirred at room temperature overnight.

The product was isolated by extracting the reaction mixture with hexane, washing the organic layer with saturated aqueous $NaHCO_3$ and brine, drying (Na_2SO_4), and concentrating the hexane solution under reduced pressure to give 2.30 g of product (56%): ^1H NMR (90 MHz, CCl_4) δ 1.20 (s, 9 H), 1.83–2.83 (m, 2 H), 4.75 (m, 1 H), 6.00 (m, 1 H), 7.25 (m, 1 H).

V. Conclusions

Organozirconium species Cp_2ZrRCl were found *not* to undergo conjugate addition to α,β-enones in acceptable yield. Through nickel catalysis trans (alkenylzirconium) complexes could be used as readily accessible reagents for high-yield conjugate addition to α,β-enones. The utility of this mixed-metal sequence was demonstrated by its application to a convenient synthesis of prostaglandin analogues.

The discovery that Cu(I) salts activate Grignard reagents toward 1,4 addition to α,β-enones led to the development of

organocuprate chemistry and the discovery that these copper species are versatile reagents for other types of synthetic transformations. Here zirconium alkenyls, normally inert to α,β-unsaturated ketones, have been activated toward conjugate addition by the addition of a reduced nickel catalyst system. Much of the chemistry of organozirconium reagent systems so activated remains to be studied. Further investigations in this area will undoubtedly uncover new methods for activation of organozirconium compounds. This, in turn, will enable development of other carbon–carbon bond forming reactions and extend the utility of these organometallic reagents.[46]

Acknowledgments. The authors acknowledge generous support for this research given by the National Science Foundation (CHE-76-02130) and the National Institutes of Health (HL 22612). One of us (M.J.L.) acknowledges support as a National Cancer Institute Trainee.

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Catalysis of Transimination by Rate-Limiting Proton Transfer to Buffer Bases[1]

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Abstract: General base catalysis of the hydroxylaminolysis of benzhydrylidenedimethylammonium ion gives a Brønsted plot that follows the Eigen curve expected for rate-determining trapping of the initially formed addition intermediate by proton transfer to a buffer base or water. The solvent deuterium isotope effects for catalysis by oxy anions exhibit a maximum at the break point of the Eigen curve, close to the estimated pK_a for the addition intermediate. This maximum can be accounted for by a partial change in rate-limiting step of the proton-transfer process near $\Delta pK = 0$. Water shows a positive deviation from the Brønsted plot and a solvent isotope effect of $k_{H_2O}/k_{D_2O} = 4.7$ that provide additional evidence for the trapping mechanism. The addition of glycerol increases the rate of the base-catalyzed reaction; much larger increases are observed with ethylene glycol and methanol. In contrast, the base-catalyzed hydrolysis of the cationic imine follows a linear Brønsted plot ($\beta = 0.24$), with a negative deviation for catalysis by water, and gives a constant value of $k_{H_2O}/k_{D_2O} = 1.9 \pm 0.2$. A concerted mechanism of base-catalyzed attack by water is suggested for this reaction.

Evidence for catalysis of the transimination of **1** through trapping the initial addition intermediate by buffer acids and bases was provided by the observation of a change in rate-determining step with increasing buffer concentration.[2] The relative catalytic activities of different acids and bases are consistent with trapping through simple proton transfer to or from the intermediate and with bifunctional acid–base catalysis by carboxylic acids, but it was not possible to obtain a satisfactory Brønsted plot for the reaction because of the change in rate-determining step.

0002-7863/80/1502-1340$01.00/0