search Corporation, and from the University of Utah Research Committee.

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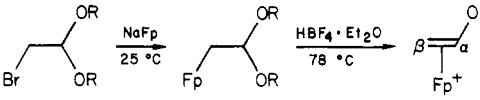
Enol Ether-Iron Complexes as Vinyl Cation Equivalents. Vinylation of Enolates

Sir:

While vinyl anion reagents are common synthetic components,[1] vinyl cations are known only as reactive intermediates in solvolysis reactions.[2] Cationic reagents which function as equivalents of vinyl cations would consequently provide a valuable charge-reversal complement in synthesis, especially for the vinylation of enolizable centers.[3] We report here on the use of Fp(alkyl vinyl ether), [Fp = $C_5H_5Fe(CO)_2$] complexes as vinyl cation equivalents for the regio- and stereospecific vinylation of enolates under mild conditions.

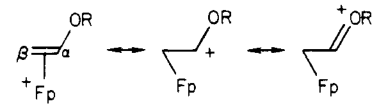
Fp(vinyl ether) complexes are readily available by metalation of α-bromo acetals or ketals by NaFp, followed by acid-promoted alcohol elimination (eq 1), and are obtained as yellow crystalline



(1)

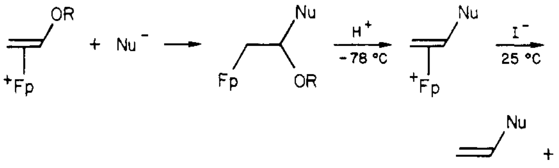
materials, which may be stored for prolonged periods of time at 0 °C without appreciable decomposition.[4]

By contrast with alkyl-substituted Fp(olefin) cations, which react with nucleophiles with low regiospecificity, nucleophilic addition to vinyl ether complexes occurs with high regiospecificity at the α carbon atom due to localization of charge at this site (eq 2).



(2)

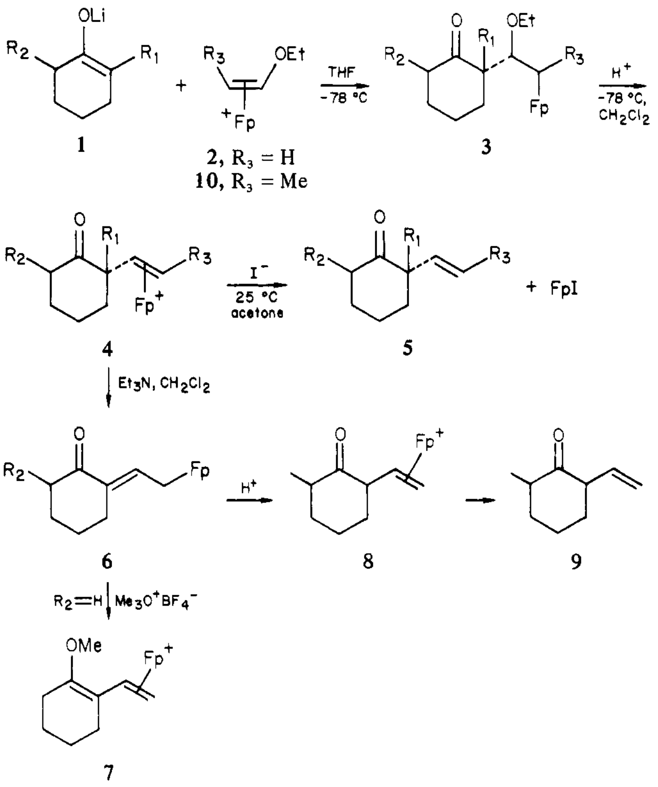
Transformation of the adduct to the vinylated product is then readily accomplished by low-temperature protonation, followed by brief exposure of the resulting cationic olefin complex to iodide (eq 3).



(3)

The use of this sequence for the vinylation of ketones is illustrated with cyclohexanone-derived enolates (Scheme I). Thus, cyclohexenone lithium enolate[5] (**1a**) reacts rapidly in THF solution at −78 °C with Fp(ethyl vinyl ether)BF_4 (**2**)[4] to give the adduct **3a** as amber crystals (89%) as a single stereoisomer.[6] Protonation of **3a** in CH_2Cl_2 solution at −78 °C with $HBF_4{\cdot}Et_2O$ gave the salt **4a** as an unstable yellow solid (90%), and this on brief exposure to NaI (acetone, 25 °C, 0.5 h) liberated the free vinyl ketone[7-9] (**5a**, 68% isolated). The proton at C-2 in **4a** is highly acidic due to activation by the adjacent cationic and carbonyl centers, so that brief treatment with 1 equiv of triethylamine (CH_2Cl_2, 25 °C) converts it entirely to the conjugated enone **6a**.[10] While pro-

Scheme I



a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_3 = H, R_2 = Me$
c, $R_1 = Me, R_2 = R_3 = H$
d, $R_1 = R_3 = Me, R_2 = H$

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[3] A few uncharged vinyl cation equivalents are known, and the vinylation of lithium ester enolates, employing vinyl halides and a nickel catalyst, has recently been described: Hudrlik, P. F.; Peterson, D.; Rona, R. J. *J. Org. Chem.* **1975**, *40*, 2263. Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 1993. Eisch, J. J.; Galle, J. E. *Ibid.* **1976**, *41*, 2615. Oishi, T.; Takechi, H.; Ban, Y. *Tetrahedron Lett.* **1974**, 3757. Metcalf, B. W.; Bonilavri, E. *J. Chem. Soc., Chem. Commun.* **1978**, 914. Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833.

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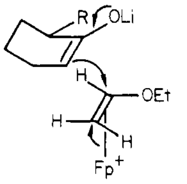
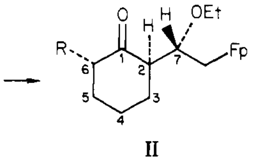
[5] House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

[6] On the basis of the ^1H and ^{13}C NMR spectra of the adduct. The stereochemistry assigned to this substance at C-2 and C-7 (II; R = H, Me) is based on the assumption of a sterically preferred orientation (I) of reacting components in the transition state.



I



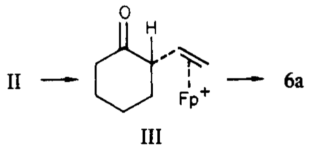
II

[7] (a) Marvell, E. N.; Russay, R. *J. Org. Chem.* **1977**, *42*, 3336. (b) Crandall, J. K.; Arrington, J. P.; Hen, J. *J. Am. Chem. Soc.* **1967**, *89*, 6208.

[8] IR (CH_2Cl_2) 1700, 1630, 990, 930 cm^{-1}; NMR ($CDCl_3$) δ 6.0 (q, $|J_{AX} + J_{BX}| = 28$ Hz, CH=), 5.05 (t, $J_{AB} < 1$ Hz, CH_2=).

[9] A satisfactory elemental analysis was obtained for this substance.

[10] This substance exhibits vinyl proton resonance at δ 7.15 (t, $J = 9$ Hz), which may be compared with resonances reported for *cis*- and *trans*-2-ethylidenecyclohexanone (δ_{cis} 5.6; δ_{trans} 6.6).[7b] The exclusive formation of the anti-isomer as a kinetic product is plausible in terms of the relative configurations assigned to the two chiral centers in II (R = H).[6] Trans elimination of ethanol[11] from it would give a vinyl complex with stereochemistry III, and stereospecific trans deprotonation[12] of this gives **6a**.



III

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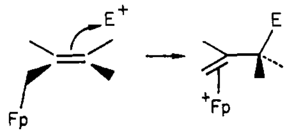
tonation of this substance regenerates the cationic olefin complex (**4a**), alkylation of **6a** with $Me_3O^+BF_4^-$ results in the exclusive formation of the methoxy diene complex (**7**, 24%).

The high reactivity of Fp(vinyl ether) complexes ensures stereospecific and regiospecific alkylation of kinetically generated enolates, free of complications due to equilibration of the enolate or to proton exchange.[5,13] Thus, enolate **1b**[14] gave adduct **3b** (90%) as a single stereoisomer[6] on reaction with **2** (THF, −78 °C, 1 h). This substance is assigned trans C-2,6 stereochemistry, assuming preferential axial attack of the vinyl cation on the enolate anion.[15] Treatment of **3b** with $HBF_4 \cdot Et_2O$ (CH_2Cl_2, −78 °C, 0.5 h), followed by decomposition of the salt **4b** with NaI, gave *trans*-2-vinyl-6-methylcyclohexane **5b**[9,16] in 79% overall yield from **1b**. The sequence thus allows the isolation of the isomer, which is thermodynamically disfavored on conformational as well as on structural grounds.

Surprisingly, only partial isomerization of **4b** to the cis isomer **8** may be achieved through deprotonation (Et_3N, CH_2Cl_2, 25 °C, 2 h) to **6b**,[17] followed by reprotonation ($HBF_4 \cdot Et_2O$, CH_2Cl_2, −78 °C, 0.5 h). The product, 78% yield after demetalation (NaI, acetone, 25 °C, 0.5 h), is a mixture of *cis*- and *trans*-2-vinyl-6-methylcyclohexanones (**9** and **5b**) in a ratio of 1:2.[18] Protonation, unlike the alkylation of **6a**, may take place preferentially at C-2 rather than at the carbonyl oxygen, since in the latter circumstance tautomerization of the resulting dienol complex (**7**, H in place of Me) would be expected to give the more stable cis-2,6-disubstituted cyclohexanone. The ratio of cis and trans isomers may instead reflect stereochemical control of kinetic protonation at C-2 through the spatial orientation of the Fp group, which is known to direct electrophillic attack in (η^1-allyl)-[19] and (η^1-propargyl)Fp[20] complexes trans to the Fp–C bond (eq 4).



(4)

The reactivity of **2** is sufficiently great that reaction is not measurably impeded by full substitution at the enolate carbon center. Thus, the enolate **1c**[21] reacts smoothly with **2** (THF, −78 °C, 1 h) to give the adduct **3c** in 90% yield as a 2:3 mixture of stereoisomers.[22] Protonation of this product ($HPF_6 \cdot Et_2O$, −78 °C, 0.5 h), followed by treatment of the resulting salt **4c** with NaI (acetone, 25 °C, 0.25 h), gave the free enone **5c**[7a] as a colorless oil (88%).[9,23]

Finally, the introduction of a *trans*-propenyl group at C-2 in 2-methylcyclohexanone is readily achieved by using the electrophile complex **10**. This substance is prepared from 2-bromopropionaldehyde diethyl acetal by metalation with NaFp, followed by treatment of the product with HBF_4,[4] and is obtained exclusively as the cis isomer.[24] Reaction of enolate **1c** with cation **10** (THF, −78 °C, 1 h) gave the adduct **3d** as a yellow oil. This was converted to the salt **4d** ($HBF_4 \cdot Et_2O$, CH_2Cl_2, −78 °C, 0.5 h) and then to the free enone (NaI, acetone, 25 °C, 0.5 h). Kugelrohr distillation gave the product in 78% overall yield as a colorless oil.[9,27] Spin decoupling shows the product to be entirely the *trans*-propenyl ketone, a stereochemical outcome expected for preferential trans addition of the nucleophile to the Fp(olefin) cation[28] and trans elimination of ethanol from the adduct.[11]

We are currently examining some further elaborations and synthetic applications of these reactions.

Acknowledgments. This research was supported by grants from the National Institutes of Health (GM-16395) and the National Science Foundation (MPS-75-09590) which are gratefully acknowledged.

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(16) NMR ($CDCl_3$) δ 6.3–5.8 and 5.2–4.8 (ABX multiplets, $CH{=}CH_2$), 1.02 (d, $J = 6$ Hz, CH_3).

(17) NMR ($CDCl_3$) δ 7.15 (t, 1, $J = 9$ Hz, $CH{=}$).[6b]

(18) Methyl doublet; δ_{cis} 1.07, δ_{trans} 0.97. Compare the C-2 methyl-doublet resonances in 2,3-dimethylcyclohexanone; δ_{cis} 0.93, δ_{trans} 0.97: Pfeffer, P. E.; Osman, S. F. *J. Org. Chem.* **1972**, *37*, 2425.

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(22) The isomers were separated by TLC: NMR (major isomer, $CDCl_3$) δ 4.80 (s, 5, Cp), 3.75 (m, 4, CH_2O, CHO), 2.40 (m, 2, CH_2CO), 2.2–1.5 (m, 8, CH_2), 1.17 (t, 3, $J = 7$ Hz, CH_3), 1.06 (s, 3, CH_3); (minor isomer, $CDCl_3$) δ 4.87 (s, 5, Cp), 3.70 (m, 3, OCH_2, OCH), 2.45 (m, 2, CH_2CO), 1.70 (m, 8, CH_2), 1.22 (t, 3, $J = 7$ Hz, CH_3), 1.15 (s, 3, CH_3).

(23) NMR ($CDCl_3$) δ 6.02 (q, 1, $|J_{Ax} + J_{Bx}| = 28$ Hz, $CH{=}$), 5.1 (t, 2, $|J_{AB}| = 1$ Hz, $CH_2{=}$), 2.4 (m, 2, CH_2CO), 1.21 (m, 6, CH_2), 1.18 (s, 3, CH_3).

(24) The formation of the cis isomer in this sequence is most likely the result of thermodynamic rather than kinetic control as had earlier been proposed.[4] The rotational barrier about the putative double bond in these vinyl ether complexes is relatively low (<25 kcal/mol),[25] and hence, cis–trans isomerization should be facile. Moreover, cis olefin complexes of several transition metals are generally found to be more stable than their trans isomers.[26]

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(27) NMR ($CDCl_3$) δ 5.8–5.2 (m, 2, $CH{=}$), 2.34 (m, 2, CH_2CO), 2.1–1.5 (m, 6, CH_2), 1.68 (d, 3, $J = 6$ Hz, $CH_3C{=}$), 1.14 (s, 3, CH_3).

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A New Soft Ionization Technique for Mass Spectrometry of Complex Molecules

Sir:

In a number of areas of organic and biochemical research, there is a growing need for high mass, high sensitivity mass spectrometry applicable to thermally labile molecules of low volatility.[1] In particular, it is often very important to obtain easily identifiable ions characteristic of the intact molecule so that the molecular weight can be determined. In response to this need, several new techniques have been developed. These include field desorption,[2] chemical ionization,[3] plasma desorption,[4] laser desorption,[5] and organic SIMS.[6] All of these techniques show some promise for at least partially fulfilling the above-stated need, but only the first two have as yet been widely applied. We have recently been engaged in developing a new combined liquid chromatograph–mass spectrometer (LC–MS) system suitable for application to involatile molecules. In the course of this work, we have discovered a new ionization technique which appears widely applicable to mass

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