Geminal Acylation–Alkylation at a Carbonyl Carbon via Regiospecifically Generated Metalloenamines[1]

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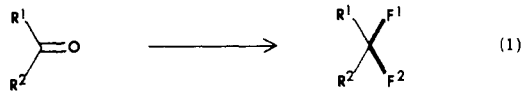
Abstract: A useful procedure for effecting geminal disubstitution at the carbonyl carbon atom of aldehydes and ketones has been developed in which the sequence of reactions results in the replacement of the two carbon–oxygen bonds of the carbonyl function with an acyl group and an alkyl or hydroxyalkyl group. Of particular importance is the facile application of these procedures to the efficient construction of quaternary carbon atoms that bear alkyl appendages containing differentiated functionality. This novel methodology features the initial conversion of carbonyl compounds **1** into the substituted 2-azadienes **10** or **11** by a Wittig–Horner reaction. Subsequent reaction of these 2-azadienes produced in situ with *n*-butyllithium results in the formation of the metalloenamines **12** and **13** (R^4 = *n*-Bu) which undergo reactions with a wide variety of electrophiles to give, after hydrolysis of the intermediate imines, the α-substituted aldehydes **14** or the α-substituted ketones **15** in good to excellent overall yields. New procedures for the annelation of cyclopentenones such as **22** and cyclohexenones **26** at the carbonyl carbon of ketones are described as is an important variant of a directed aldol reaction, **1** → **28**. Although a number of individual manipulations are necessary to effect the geminal disubstitution of a carbonyl functional group, it is generally feasible to execute the entire sequence of reactions in a single flask, thereby rendering this methodology very convenient to implement in practice.

Since a quaternary carbon atom that bears alkyl appendages containing differentiated functionality is a structural element common to a host of natural and unnatural products possessing complex molecular frameworks, the task of creating such centers is frequently encountered in synthesis. The assemblage, however, of a fully substituted carbon atom ranks among the most restricted constructions in synthetic organic chemistry.[2] Inasmuch as the carbonyl function is one of the most accessible and important functional groups in organic chemistry, a general procedure for the facile conversion of a ketone carbonyl group into a quaternary carbon atom by the net replacement of both of the carbon–oxygen bonds with dissimilarly functionalized alkyl substituents (eq 1) would possess substantive synthetic utility.

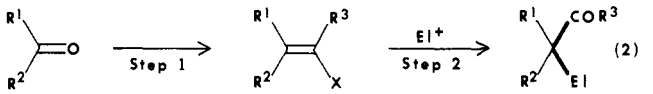


(1)

R^1, R^2 = H, alkyl, aryl

F^1, F^2 = functionalized alkyl

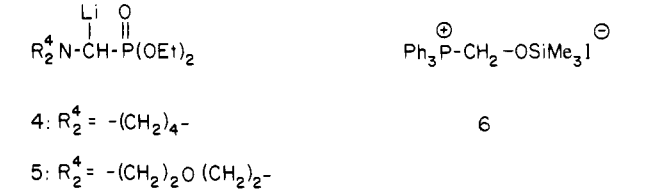
Indeed a number of methods that result in the geminal disubstitution at a carbonyl center have already been developed,[3,4] but most of these procedures are multistep processes which require the isolation of one or more intermediates. Thus, a procedure for effecting this important transformation wherein the entire series of operations could be conveniently executed in a single flask would be desirable. In accordance with this objective we have devised an appealing strategy for introducing two new alkyl appendages which contain differentiated functionality at a carbonyl carbon. The synthetic sequence (eq 2) commences with the olefination of a carbonyl compound **1** to produce the enolate, enamine, or metalloenamine **2** (X = O^-, R_2^4N, R^4N^-, respectively) (or their



(2)

1 2: X = O^-; R_2^4N; R^4N^- 3

immediate precursors) of a higher aldehyde or ketone.[5] The subsequent formation of the second carbon–carbon bond at the original electrophilic center of the carbonyl function would then be expeditiously achieved by the reaction of these nucleophilic derivatives of carbonyl compounds with suitable electrophiles. For example, we have recently discovered that the reaction of ketones with the lithiated dialkylaminomethylphosphonates **4** and **5** fol-



4: R_2^4 = $-(CH_2)_4-$

5: R_2^4 = $-(CH_2)_2O(CH_2)_2-$

6

lowed by the reaction of the enamines[6] **2** (X = NR_2^4) thereby generated in situ with allyl bromide,[3a] methyl vinyl ketone,[3b] and

(1) A preliminary account of portions of this work has previously appeared. Martin, S. F.; Phillips, G. W. *J. Org. Chem.* **1978**, *43*, 3792.

(2) For a review of methodology for the construction of quaternary carbon atoms see: Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(3) (a) Martin, S. F.; Gompper, R. *J. Org. Chem.* **1974**, *39*, 2814. (b) Martin, S. F. *Ibid.* **1976**, *41*, 3337. (c) Martin, S. F.; Chou, T.; Payne, C. W. *Ibid.* **1977**, *42*, 2520.

(4) For other procedures for the geminal disubstitution of carbonyl compounds see: (a) Corey, E. J.; Shulman, J. I. *J. Am. Chem. Soc.* **1970**, *92*, 5522. (b) Trost, B. M. *Acc. Chem. Res.* **1974**, *7*, 85. (c) Trost, B. M.; Bogdanowicz, M. J.; Kern, J. *J. Am. Chem. Soc.* **1975**, *97*, 2218. (d) Trost, B. M.; Preckel, M.; Leichter, L. M. *Ibid.* **1975**, *97*, 2224. (e) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bodganowicz, M. J. *Ibid.* **1977**, *99*, 3088. (f) Ziegler, F. E.; Wender, P. A. *J. Org. Chem.* **1977**, *42*, 2001. (g) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453. (h) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 5, 9, 13.

(5) For a review of methodology for the chain extension of the carbonyl group to give carbonyl and acyl compounds see: Martin, S. F. *Synthesis* **1979**, 633.

(6) Recent results obtained in other laboratories[7] have revealed the distinct possibility that the reaction of carbonyl compounds with metalated dialkyl aminoalkylphosphonates such as **4** and **5** may not be as straightforward as once envisioned.[3] While it is clearly evident that such carbanions add readily to carbonyl compounds, the subsequent elimination of dialkyl phosphate to produce the enamine may not always readily occur. For example, the morpholine enamines obtained by the reaction of **5** with ketones may be isolated without difficulty by evaporation of the excess solvents from the crude reaction mixture followed by flash distillation (125–200 °C pot temperature at 0.1 mm) of the volatile materials from the viscous residue.[3b] In these cases it is certainly conceivable that the elimination of phosphate was thermally induced. However, in several instances where the elimination of phosphate produced an enamine that was conjugated with an aromatic ring or a carbon–carbon double bond, the morpholine enamines could be isolated upon an aqueous workup of the reaction mixture (1 N KOH in cold saturated brine). The pyrrolidine enamines obtained upon reaction of **4** with ketones could also be isolated from the crude reaction mixture by flash distillation, albeit in lower yields. It may also be noted that in early experiments[3a] the yields of the α-allyl aldehydes did not change substantially if the reaction mixture obtained after the addition of **4** to a ketone was heated at reflux prior to the addition of allyl bromide. Further investigations will undoubtedly lead to a greater understanding of the mechanistic details of these reactions.

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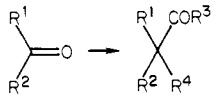
2,3-dibromopropene[3c] has resulted in procedures for the facile construction of quaternary carbon atoms bearing substituents suitably functionalized for subsequent synthetic transformations, including the annelation of cyclohexenones and cyclopentenones. The utility of several of these methods has been demonstrated by their successful application to the total syntheses of selected natural products.[8,9] Unfortunately, the reaction of metalated dialkylaminoalkylphosphonates related to **4** and **5** with carbonyl compounds does not always proceed to give enamines in a completely satisfactory fashion.[6,7] Moreover, owing to the low nucleophilicity of enamines coupled with the pronounced tendency for the enamines of α,α-disubstituted aldehydes to undergo irreversible N-alkylation with many simple alkylating agents,[10] it became obvious that there were several inherent limitations in these methods involving enamine intermediates which would likely attenuate their general utilization in organic synthesis. Investigations were then directed toward the development of procedures for the conversion of carbonyl compounds **1** into precursors of the enolates **2** (X = O^-), but preliminary studies indicated that the ylide generated by deprotonation of the phosphonium salt **6** did not undergo reaction with ketones such as acetophenone or cyclohexanone to give the expected trimethylsilyl enol ethers **2** (X = $OSiMe_3$) in a reproducible manner.[11]

At this juncture our attention was focused upon the development of a method for the olefination of a carbonyl compound **1** into a metalloenamine **2** (X = R^4N^-). Indeed, of the nucleophilic derivatives of aldehydes and ketones, metalloenamines[12,13] are often superior to the related enolates and enamines for the construction of a new bond α to a carbonyl function since they (1) are more nucleophilic, (2) usually undergo highly regioselective reaction with electrophiles at carbon, and (3) exhibit a low tendency to suffer equilibration by proton-transfer processes.[13b,n,q] Furthermore, the alkylation of the tertiary metalloenamines derived from α,α-disubstituted aldehydes is not normally subject to the troublesome side reactions which frequently accompany the alkylation of the corresponding enolates.[13d,14] We now wish to report the details of a general procedure for effecting the geminal disubstitution of a carbonyl group according to eq 2 wherein metalloenamines are employed as the key synthetic intermediates.[1]

Table I. Geminal Acylation–Alkylation of Carbonyl Compounds **1** → **16**

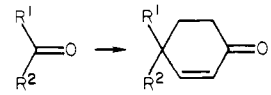


1 **16**

entry	R^1	R^2	R^3	R^4[a]	% overall yield[b]
a	*n*-C_6H_{13}	H	H	Me	34
b	c-C_6H_{11}	H	H	Me	43
c	c-C_6H_{11}	H	Me	Me	41
d	Ph	H	H	Me	39 (33)
e	Ph	H	Et	Me	35
f	*n*-Pr	*n*-Pr	H	Me	58
g	$-(CH_2)_5-$		H	$CH_2CH{=}CH_2$	51
h	$-(CH_2)_2CH(t\text{-Bu})-(CH_2)_2-$		H	Me	63[c]
i	$-(CH_2)_2CH(t\text{-Bu})-(CH_2)_2-$		H	$CH_2CH{=}CH_2$	51[d]
j	$-(CH_2)_2CH(t\text{-Bu})-(CH_2)_2-$		H	SMe	40[e]
k	$-(CH_2)_2CH(t\text{-Bu})-(CH_2)_2-$		Me	Me	60
l			H	Me	80
m	Ph	Me	H	Me	77 (67)
n	Ph	Me	H	$CH_2CH{=}CH_2$	81
o	Ph	Me	Me	Me	63

[a] Electrophiles employed were MeI (R^4 = Me), EtI (R^4 = Et), $CH_2{=}CHCH_2Br$ ($R^4 = CH_2CH{=}CH_2$), and $(MeS)_2$ (R^4 = SMe). [b] Yields are of distilled product based on starting ketones but are not fully optimized; values in parentheses correspond to those cases in which Super Hydride was used to generate the metalloenamine. [c] As ca. 79:21 mixture of diastereomers. [d] As ca. 75:25 mixture of diastereomers. [e] As ca. 55:45 mixture of diastereomers.

Table II. Conversion of Ketones to Cyclohexenones **1** → **26**



1 **26**

entry	R^1	R^2	% overall yield[a]
a	$-(CH_2)_5-$		55
b	$-(CH_2)_2CH(t\text{-Bu})(CH_2)_2-$		57
c			65
d	Ph	Me	59
e	3,4-$(OMe)_2C_6H_3-$	$CH_2CH_2NMeCO_2Me$	50[b]

[a] Yields are of chromatographically purified and distilled product but are not fully optimized. [b] Reference 8b.

Results and Discussion

Our strategy for the generation of metalloenamines from intermediates that were prepared by carbonyl olefination operations was based upon the prediction that 2-azadienes such as **10** and **11** should suffer highly regioselective attack by organometallic reagents and certain hydride reducing agents to give the metaloenamines of higher aldehydes **12** or ketones **13**, respectively (Scheme I).[15] In order to test the viability of this hypothesis, the requisite 2-azadienes **10** were prepared by allowing aldehydes and ketones **1** to react with diethyl *N*-benzylidenaminolithio-

(7) (a) Broekkof, N. L. J. M.; Jonkers, F. L.; van der Gen, A. *Tetrahedron Lett.* **1979**, 2433. (b) Koenigkramer, R. E.; Zimmer, H. "Abstracts of Papers", 178th National Meeting of the American Chemical Society, Washington, D.C., Sept 1979; American Chemical Society: Washington, D.C., 1979; ORGN 67.

(8) Martin, S. F.; Puckette, T. A. *Tetrahedron Lett.* **1978**, 4229. Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391.

(9) Martin, S. F.; Chou, T. S. *J. Org. Chem.* **1978**, *43*, 1027.

(10) For a discussion see: Curphey, T. J.; Hung, J. C.; Chu, C. C. C. *J. Org. Chem.* **1975**, *40*, 607.

(11) For accounts of related phosphonate anions see: (a) Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847. (b) Koenigkramer, R. E.; Zimmer, H. *Tetrahedron Lett.* **1980**, 1017.

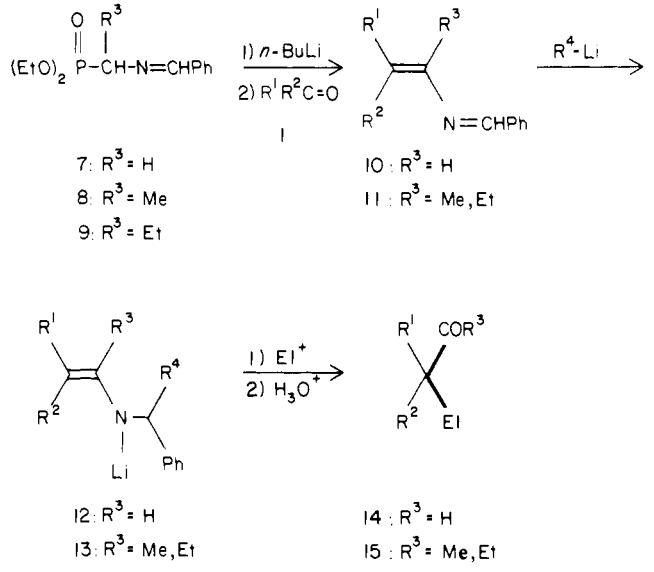
(12) (a) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178. (b) Wittig, G.; Frommeld, H. D.; Suchanek, P. *Angew. Chem.* **1963**, *75*, 978. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 683. (c) Wittig, G. *Top. Curr. Chem.* **1976**, *67*, 2, and references cited therein.

(13) For other recent examples of the synthetic utility of metalloenamines and related compounds see: (a) Evans, D. A. *J. Am. Chem. Soc.* **1970**, *92*, 7593. (b) Stork, G.; Benaim, J. *Ibid.* **1971**, *93*, 5938. (c) Wittig, G.; Fischer, S.; Tanaka, M. *Justus Liebigs Ann. Chem.* **1973**, 1075. (d) House, H. O.; Liang, W. C.; Weeks, P. D. *J. Org. Chem.* **1974**, *39*, 3102. (e) Hudrlik, P. F.; Wan, C. N. *Ibid.* **1975**, *40*, 2963. (f) Cuvigny, T.; Larcheveque, M.; Normant, H. *Justus Liebigs Ann. Chem.* **1975**, 719. (g) Larcheveque, M.; Valette, G.; Cuvigny, T. *Tetrahedron* **1979**, *35*, 1745. (h) Le Borgne, J. F. *J. Organomet. Chem.* **1976**, *122*, 123, 129, 139. (i) Kieczykowski, G. R.; Schlessinger, R. H.; Sulsky, R. B. *Tetrahedron Lett.* **1976**, 597. (j) Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032. (k) Whitesell, J. K.; Whitesell, M. A. *J. Org. Chem.* **1977**, *42*, 377. (l) Jacobson, R. M.; Raths, R. A.; McDonald, III, J. H. *Ibid.* **1977**, *42*, 2545. (m) Enders, D.; Eichenauer, H. *Tetrahedron Lett.* **1977**, 191. (n) Wender, P. A.; Eissenstat, M. A. *J. Am. Chem. Soc.* **1978**, *100*, 292. (o) Hashimoto, S. I.; Koja, K. *Tetrahedron Lett.* **1978**, 573. (p) Enders, D.; Weuster, P. *Ibid.* **1978**, 2853. (q) Wender, P. A.; Schaus, J. M. *J. Org. Chem.* **1978**, *43*, 782. (r) Meyers, A. I.; Poindexter, G. S.; Brich, Z. *Ibid.* **1978**, *43*, 892. (s) Meyers, A. I.; Williams, D. R. *Ibid.* **1978**, *43*, 3245. (t) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337, 1362. (u) Eichenauer, H.; Friedich, E.; Lutz, W.; Enders, D. *Angew. Chem.* **1978**, *90*, 219; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 206. (v) Fraser, R. R.; Banville, J.; Dhawan, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7999. (w) Fraser, R. R.; Banville, J. *J. Chem. Soc., Chem. Commun.* **1979**, 47. (x) Meyers, A. I. *Pure Appl. Chem.* **1979**, *51*, 1255. (y) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933.

(14) Cf. Groenewagen, P.; Kallenberg, H.; van der Gen, A. *Tetrahedron Lett.* **1978**, 491.

(15) During the course of our investigations there were two other reports of the usage of 2-azadienes as precursors to metalloenamines.[13n,q]

Scheme I



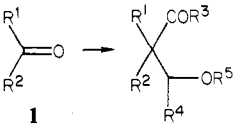
methylphosphonate which was generated by metalation of **7**[16,17] with *n*-butyllithium.[19] An important variant of this procedure involves the reaction of carbonyl compounds with the anions of the alkyl-substituted *N*-benzylidenaminophosphonates **8** and **9**, which may be conveniently prepared from **7** by sequential metalation and alkylation,[19a,20] to afford the 3-alkyl-2-azadienes **11**. Although 2-azadienes such as **10** and **11** may be isolated,[19] it was judged both more expedient and efficient to treat them in situ with *n*-butyllithium, thereby producing the metalloenamines **12** and **13** (R^4 = *n*-Bu). *n*-Butyllithium was usually employed as the nucleophilic reagent for the generation of these intermediate metalloenamines, but hydride reducing agents such as Super Hydride and L-Selectride may also be effectively used to produce the metalloenamines **12** (R^4 = H). The production of metalloenamines by the reduction of certain 2-azadienes with lithium–ammonia has also been reported.[13n] Grignard reagents appear less reactive and do not add readily to the 2-azadienes. The subsequent reaction of the metalloenamines **12** and **13** with a diverse array of electrophiles (El^+) including alkylating agents and aldehydes afforded, after hydrolysis of the intermediate imines, the geminally disubstituted aldehydes **14** and ketones **15** in good to excellent overall yields (Tables I–III). It should also be recognized that the hydrolysis of the 2-azadienes **10** and **11** should afford the carbonyl compounds **14** and **15** (El = H),[19a] the products of the one carbon chain extension of the starting aldehyde or ketone **1**.

Geminal Acylation–Alkylation. In order to delineate the scope and limitations of this novel methodology for effecting the geminal disubstitution of aldehydes and ketones according to Scheme I, a number of representative cases were investigated in which the *N*-benzylidenaminoalkylphosphonates **7–9**, the carbonyl compound **1**, and the alkylating agent (El^+) were varied. In those conversions involving the use of the phosphonate **7**, an examination of Table I reveals that it is possible to effect the geminal disubstitution of a selection of structurally different aldehydes and ketones to give the aldehydes **16** (R^3 = H) in good to excellent overall yields. Furthermore, it appears that the aldehydes **16** (R^3 = H) are generally produced in higher yields when ketones are the starting carbonyl compounds, and the lowest yields are obtained from α-monosubstituted aldehydes. Thus, this new procedure seems especially well suited for the construction of quaternary carbon atoms. When the anions of the homologous phosphonates **8** and **9** are employed in the first step of the synthetic sequence, the overall yields of the ketones **16** (R^3 = Me or Et) from a given carbonyl precursor **1** tend to be lower than the yields of the corresponding aldehydes **16** (R^3 = H). The reaction of the anion derived from the phosphonate **9** with ketones such as cyclohexanone and acetophenone does not proceed cleanly to give the 2-azadienes **11** (R^3 = Et), but this limitation in the present methodology is not unexpected since the construction of tetrasubstituted alkenes by the Wittig and related reactions is frequently subject to similar constraints. Significantly, a variety of mono- and difunctional alkylating agents may be successfully employed as the electrophilic partners in these reactions, thereby allowing the introduction of two new alkyl appendages containing differentiated functionality at a carbonyl center (vide infra). The sulfenylation of the intermediate metalloenamines (entry **j**) with the relatively unreactive electrophile methyl disulfide is also noteworthy since subsequent oxidation and elimination of methylsulfenic acid should result in the formation of an α,β-unsaturated carbonyl compound.[21]

That the generation and trapping of the metalloenamines of unsymmetrical ketones **13** is highly regioselective is clearly established by entries **c**, **e**, **k**, and **o**. There was no evidence for the formation of products derived from the alkylation of the isomeric metalloenamines. It is not generally possible to attain the same regiocontrol by the simple deprotonation of the corresponding ketimines since such deprotonation and hence subsequent carbon–carbon bond formation usually occur at the less substituted α carbon atom.[13f,g] If each of the α carbon atoms were equally substituted, a mixture of imine anions would probably be produced. In analogy with previous reports,[13b,n,q] the low propensity for metalloenamines to suffer equilibration by proton-transfer processes and thus undergo C-alkylation with complete regiocontrol is also clearly evident from these examples.

Another important feature of this new methodology for the geminal acylation–alkylation of carbonyl compounds is that a reasonable number of functional groups may be tolerated on the ketone and/or the alkylating agent. A dramatic illustration of this fact is provided by the conversion of the monoprotected 1,4-dione **17** into the cyclohexenone **18**, a key step in our recent synthesis of mesembrine,[8b] wherein methyl *N*-(2-bromoethyl)-*N*-

Table III. Geminal Acylation–Hydroxyalkylation of Carbonyl Compounds **1** → **28**



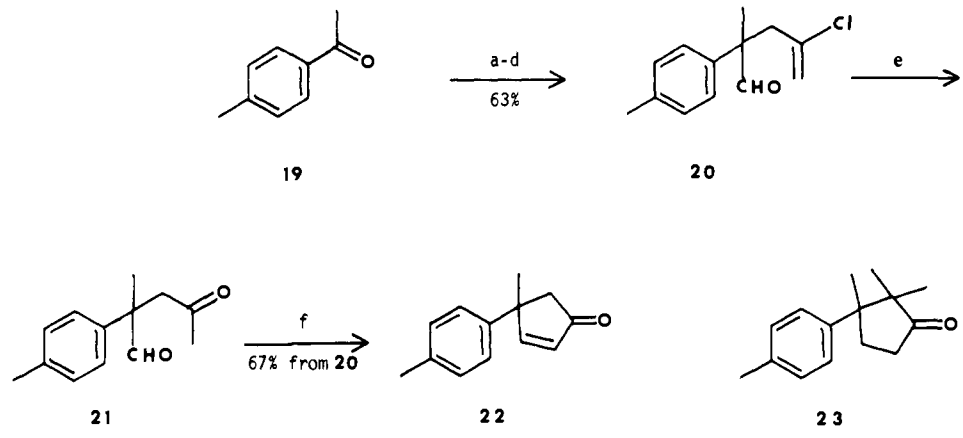
1 **28**

entry	R^1	R^2	R^3	R^4	R^5	% overall yield[a]
a	*n*-Pr	*n*-Pr	H	Ph	CO_2Me	56
b	$-(CH_2)_5-$		H	*n*-Pr	CO_2Me	45
c	$-(CH_2)_5-$		H	Ph	CO_2Me	47
d			H	Ph	CO_2Me	59[b]
e			H	Ph	CH_2OMe	42[b]
f	Ph	Me	H	*n*-Pr	CO_2Me	49[b]
g	Ph	Me	H	Ph	CO_2Me	62[b]
h	Ph	Me	Me	Ph	CO_2Me	51[b]

[a] Yields are of chromatographically purified and distilled product but are not fully optimized. [b] Obtained as a mixture of diastereomers; see Experimental Section for ratio.

(16) Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 4645.
(17) In our hands, the intermediate diethyl aminomethylphosphonate was more satisfactorily prepared by the hydrazinolysis of diethyl phthalimidomethylphosphonate.[18]
(18) Yamauchi, K.; Mitsuda, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3285.
(19) For other related syntheses of 2-azadienes see: (a) Dehnel, A.; Finet, J. P.; Lavielle, G. *Synthesis* **1977**, 474. (b) Kauffmann, T.; Koch, U.; Steinseifer, F.; Vahrenhorst, A. *Tetrahedron Lett.* **1977**, 3341. (c) Kauffman, T.; Berg, H.; Koppelmann, E.; Kuhlmann, D. *Chem. Ber.* **1977**, *110*, 2659.
(20) See also: Dehnel, A.; Lavielle, G. *Bull. Soc. Chim. Fr.* **1978**, 95.
(21) For example, see: Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

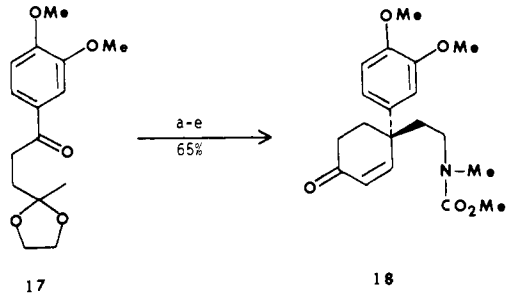
Scheme II



19 20 21 22 23

[a] $(EtO)_2\overset{O}{\overset{\|}{P}}CHLiN{=}CHPh/THF/-78^{\circ}\rightarrow reflux$; [b] n-BuLi/-78°; [c] $CH_2{=}CClCH_2Cl/THF/HMPA/-78^{\circ}\rightarrow RT$; [d] H_3O^+/RT; [e] $Hg(OAc)_2/HCO_2H/RT$; [f] KOH/aq MeOH/RT.

methylcarbamate served as the electrophilic partner for the intermediate metalloenamine.



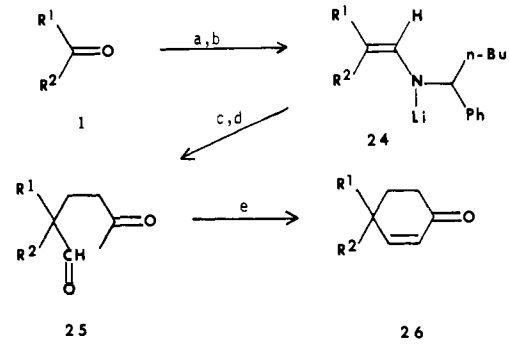
17 18

[a] $(EtO)_2\overset{O}{\overset{\|}{P}}CHLiN{=}CHPh/THF/-78^{\circ}\rightarrow reflux$; [b] n-BuLi/-78°; [c] $BrCH_2CH_2NMeCO_2Me/-78^{\circ}\rightarrow RT$; [d] H_3O^+/RT; [e] KOH/aq MeOH/RT.

Construction of Cyclopentenones and Cyclohexenones at a Carbonyl Carbon. When the electrophile employed in the alkylation stage of these sequences is properly selected, it is possible to replace each of the carbon–oxygen bonds of the starting carbonyl compound with alkyl substituents that are suitably functionalized for subsequent annelation operations. For example, the 2-(2′-chloropropenyl)aldehydes formed upon reaction of the metalloenamines **12** with 2,3-dichloropropene are smoothly converted upon treatment with mercuric acetate in formic acid[22] into γ-keto aldehydes which then undergo base-catalyzed cycloaldolization and dehydration to give 4,4-disubstituted cyclopentenones. A practical illustration of this useful procedure for the annelation of a cyclopentenone ring at a carbonyl carbon atom is provided by the facile conversion of *p*-methylacetophenone (**19**) into the cyclopentenone **22**, an intermediate in a recent synthesis of α-cuparenone (**23**)[23] (Scheme II).

A useful method for the annelation of a cyclohexenone **26** at a carbonyl carbon atom has also been developed (Scheme III). Although there exist a variety of alkylating agents that have been commonly used for the introduction of a 3-oxobutyl side chain α to a carbonyl function,[24] we have discovered that the metalloenamines **24** undergo smooth alkylation with 2-(2′-bromoethyl)-2-methyl-1,3-dioxolane[25] in the presence of hexamethylphosphoramide (HMPA) to give, after acid-catalyzed hydrolysis

Scheme III



1 24 25 26

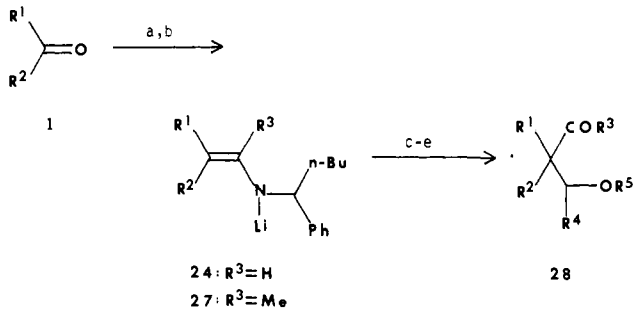
[a] $(EtO)_2\overset{O}{\overset{\|}{P}}CHLiN{=}CHPh/THF/-78^{\circ}\rightarrow reflux$; [b] n-BuLi/-78°; [c] $BrCH_2CH_2C(OCH_2CH_2O)CH_3$/THF/HMPA/$-78^{\circ}\rightarrow RT$; [d] H_3O^+/RT; [e] KOH/aq MeOH/RT.

of the imine and ketal moieties, the δ-keto aldehydes **25**. It has also proven possible to effect the selective hydrolysis of the imine function to give a δ-ketal aldehyde. Treatment of the intermediate δ-keto aldehydes **25** with aqueous methanolic potassium hydroxide produced the 4,4-disubstituted cyclohexenones **26** in very good overall yields (Table II). That other functional groups may be present in the ketonic substrate **1** is once again clearly manifested by entry e which represents an alternative route to the cyclohexenone **18**.[8b] Since it is a relatively poor alkylating agent, 2-(2′-bromoethyl)-2-methyl-1,3-dioxolane has rarely been used in annelation operations.[24] However, it now appears that when metalloenamines are the nucleophilic partners this reagent may be advantageously employed for the construction of cyclohexenones.

Geminal Acylation–Hydroxyalkylation. Although metalloenamines have been previously employed in directed aldol reactions,[12b,c,13t,u] we are unaware of any examples of the reaction of a β,β-disubstituted metalloenamine such as **24** or **27** (R^1, R^2 = alkyl) with a carbonyl compound to give an aldol product in which a quaternary carbon atom α to the carbonyl group has been constructed (Scheme IV). In order to assess the viability of such a directed aldol process, the metalloenamines **24** and **27** were prepared in the usual manner and allowed to react with aldehydes. If the reaction mixture containing the intermediate β-oxido imine was merely quenched with aqueous acid, the desired β-hydroxycarbonyl compounds **28** (R^5 = H) could not be isolated. Under the weakly acidic conditions employed for hydrolysis of the imine, it appears that extensive retro-aldolization occurs. Although suitable conditions for the selective hydrolysis of the imine moiety might be found, we discovered that this deleterious side reaction

(22) (a) Martin, S. F.; Chou, T. *Tetrahedron Lett.* **1978**, 1943. (b) Julia, M.; Blasioli, C. *Bull. Soc. Chim. Fr.* **1976**, 1941.
(23) Wenkert, E.; Buckwalter, B. L.; Craveiro, A. A.; Sanchez, E. L.; Sathe, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 1267.
(24) For a review of annelations using alkylating agents see: Jung, M. E. *Tetrahedron* **1976**, *32*, 3.
(25) Brown, E.; Dhal, R. *Bull. Soc. Chim. Fr.* **1972**, 4292.

Scheme IV



[a] $(EtO)_2P(O)CHLiN{=}CHPh$/THF/-78°→reflux; [b] n-BuLi/-78°; [c] R^4CHO/-78°; [d] MeOCOCl or $BrCH_2OMe$/-78°→RT; [e] H_3O^+/RT.

could be conveniently circumvented by the useful expedient of trapping the intermediate β-oxido imines at −78 °C either by O-acylation with methyl chloroformate or by O-alkylation with bromomethyl methyl ether. Subsequent, selective acid-catalyzed hydrolysis of the resulting imines afforded the protected β-hydroxycarbonyl compounds **28** (R^5 = CO_2Me or CH_2OMe, respectively) in good to very good overall yields (Table III). Preliminary results suggest that the tertiary metalloenamines **24** may not be trapped with enolizable ketones such as cyclohexanone.

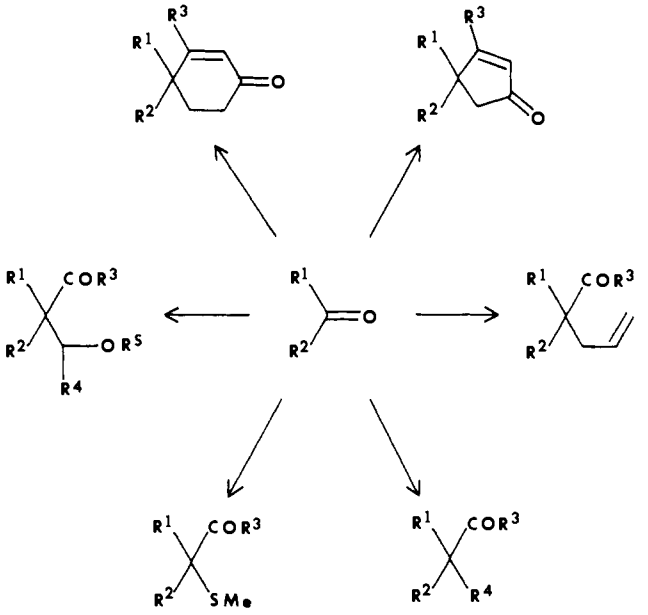
Conclusions

A general methodology has been developed that results in net geminal disubstitution at a carbonyl center via a reaction sequence which commences with the olefination of a carbonyl function to give a 2-azadiene which may be conveniently converted in situ into the metalloenamine of a higher aldehyde or ketone. In a subsequent step, a second carbon–carbon bond is formed at the original electrophilic center by either an alkylation or a directed aldol reaction. Using the methods detailed herein, it is clearly feasible to replace the two carbon–oxygen bonds of a carbonyl group with two alkyl appendages containing differentiated functionality that may be utilized in subsequent synthetic operations and transformations. Significantly these procedures appear to be admirably suited for the construction of quaternary carbon atoms. While several of the possible synthetic transformations are summarized in Scheme V, a number of others may be envisioned. There are a number of important advantages which attend the use of these procedures for the geminal acylation–alkylation and the geminal acylation–hydroxyalkylation of carbonyl compounds. (1) The requisite diethyl *N*-benzylidenaminoalkylphosphonate reagents such as **7–9** may be readily prepared on a large scale from inexpensive starting materials. (2) The key synthetic intermediates in these sequences are metalloenamines which are highly nucleophilic and generally undergo facile, regioselective reaction at carbon with a diverse array of weak and multifunctional electrophilic partners. (3) While a number of individual operations are required, *it is generally possible to execute the entire sequence of reactions in a single flask*. This is in marked contrast to other procedures which may give comparable overall yields but which are multistep *and* require the isolation of one or more intermediates. (4) The *overall* yields are good to excellent. (5) There is a reasonable degree of functional group compatibility which allows the extension of these procedures to the syntheses of molecules possessing complex molecular architecture. The feasibility of extending this methodology to the enantioselective construction of quaternary carbon centers is under active investigation.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. All boiling points are uncorrected. ^1H NMR spectra were determined on a Varian A-60A or HA100 spectrometer as solutions in $CDCl_3$, and the chemical shifts are reported in δ units with Me_4Si as the internal reference. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet; comp, complex multiplet. Coupling constants are given in hertz (Hz). The infrared spectra (IR) were determined as solutions in chloroform or as films on a Beckman IR-5A spectrophotometer. Low-resolution mass spectra were obtained on a Du Pont (CEC) 21-491 instrument at an ionizing voltage of 70 eV. Exact-mass determinations were obtained on a Du Pont (CEC) 21-110 instrument.

Scheme V



All experiments involving organometallic reagents were executed under an atmosphere of dry nitrogen, and the glassware was oven dried and flamed in a nitrogen stream prior to use. The tetrahydrofuran (THF) was freshly distilled from potassium–benzophenone, and the hexamethylphosphoric triamide (HMPA) was distilled from sodium under reduced pressure. All alkylating agents were freshly distilled (from calcium hydride) and filtered through basic alumina, and the methyl chloroformate was freshly distilled from calcium hydride prior to use. Preparative high-performance liquid chromatography (LC) was performed on a Waters Prep LC 500 instrument by using two Prep PAK columns.

Diethyl 1-(*N*-Benzylidenamino)ethylphosphonate (8). To a well-stirred solution of *n*-butyllithium (39.2 mmol, 3.3 N hexane) in anhydrous tetrahydrofuran (THF) (150 mL) under dry nitrogen at −78 °C was slowly added (ca. 10 min) a solution of diethyl *N*-benzylidenaminomethylphosphonate (**7**,[16] 10.0 g, 39.2 mmol) in anhydrous THF (15 mL) and the stirring was continued for 1 h at −78 °C. Methyl iodide (5.8 g, 41.2 mmol) was added, the cooling bath was removed, and the stirring was continued at room temperature for 2 h. Saturated sodium bicarbonate (50 mL) was added, and the aqueous layer was extracted with ether (3 × 100 mL). After the combined organic layers were dried ($MgSO_4$), the excess solvents were removed under reduced pressure, and the crude iminophosphonate **8** was purified by vacuum distillation, 9.2 g (87%), as a pale yellow oil, bp 124–126 °C (0.05 mm) [lit.[19a] 114–116 °C (0.1 mm)].

Diethyl 1-(*N*-Benzylidenamino)propylphosphonate (9). Alkylation of the anion obtained by metalation of **7** with ethyl iodide (1.05 equiv) according to the procedure detailed above for the preparation of **8** afforded a 71% yield of **9** as a pale yellow oil: bp 135–138 °C (0.07 mm); NMR δ 8.25 (d, 1 H, J = 4 Hz), 7.73 (m, 2 H), 7.37 (m, 3 H), 4.15 (p, 4 H, J = 7 Hz), 3.52 (m, 1 H), 2.04 (m, 2 H), 1.29 (br t, 6 H, J = 7 Hz), 0.91 (t, 3 H, J = 8 Hz); mass spectrum m/e 283.1334 ($C_{14}H_{22}NO_3P$ requires 283.1337), 180, 146 (base), 138.

Geminal Acylation–Alkylation of Carbonyl Compounds 1. General Procedure.[26] To a well-stirred solution of *n*-butyllithium (12.0 mmol,

(26) All reactions were carried out using a standard set of conditions, and no systematic effort was made in each case to evaluate the effect upon overall yield of varying the amounts of the reagents. However, a comparison of the various general procedures reveals that relative to the starting carbonyl compound **1** the following ratios of reagents are typical: phosphonate **7–9** (1.2 equiv); nucleophilic agent (*n*-butyllithium or Super Hydride) for metalloenamine generation (1.2–2.0 equiv); electrophilic partner (1.2–5.0 equiv). Conditions were optimized, however, for the preparation of compounds **18** (see ref 8b) and **20**.

3.3 N hexane) in anhydrous THF (50 mL) under dry nitrogen at −78 °C was slowly added (ca. 5 min) a solution of the diethyl *N*-benzylidenaminoalkylphosphonate **7**, **8**, or **9** (12.0 mmol) in anhydrous THF (5 mL), and the resulting red solution was stirred at −78 °C for an additional 1 h. The appropriate carbonyl compound **1** (10.0 mmol) in anhydrous THF (5 mL) was then added dropwise and the cooling bath removed, whereupon the reaction mixture was heated at reflux for 2 h. The resulting solution containing the azadiene **10** or **11** was cooled to −78 °C, and *n*-butyllithium (20.0 mmol, 3.3 N hexane) was slowly added (5 min), whereupon the dark burgundy solution of the metalloenamine **12** or **13** was stirred at −78 °C for an additional 1 h. The metalloenamine **12** could also be generated by the addition of Super Hydride (20.0 mmol, 1 M in tetrahydrofuran) to the solution of the azadiene **10** at −78 °C followed by stirring the resulting mixture at room temperature for 3 h and then cooling the solution to −78 °C. After the appropriate electrophile (30.0–50.0 mmol) was added, the cooling bath was removed and the reaction mixture was stirred at room temperature for 2–4 h. The solution was then added to 1 N HCl (50 mL), and the resulting heterogeneous mixture was stirred vigorously at room temperature for 2 h. Saturated sodium chloride (25 mL) was added, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with saturated sodium bicarbonate (1 × 75 mL) and dried ($MgSO_4$). Following removal of the excess solvents under reduced pressure, the crude product **16** was purified by vacuum distillation. The crude α,α-disubstituted aldehydes **16a** and **16d** were initially isolated as their bisulfite adducts prior to final purification by vacuum distillation.

3-Cyclohexyl-2-butanone (16c): 41%; bp 70–71 °C (2.8 mm); IR (film) 1706 cm^{-1}; NMR δ 2.28 (m, 1 H), 2.11 (s, 3 H), 1.02 (d, 3 H, J = 7 Hz), 0.87–1.92 (comp, 11 H); mass spectrum m/e 154.1361 ($C_{10}H_{18}O$ requires 154.1358), 111, 72 (base), 69, 55.

2-Methyl-2-(1-propyl)pentanal (16f): 58%; bp 60–61 °C (10.0 mm); IR (film) 1715 cm^{-1}; NMR δ 9.40 (s, 1 H), 0.80–1.60 (comp, 14 H), 0.98 (s, 3 H); mass spectrum m/e 142.1360 ($C_9H_{18}O$ requires 142.1358), 113, 100, 87, 71 (base), 57.

4-*tert*-Butyl-1-methylthiocyclohexanecarboxaldehyde (16j): 40% as a 45:55 mixture of diastereomers; bp 70–71 °C (0.1 mm); IR (film) 1706 cm^{-1}; NMR δ 9.05 (s, 0.55 H), 8.93 (s, 0.45 H), 1.80 (s, 1.35 H), 1.74 (s, 1.65 H), 1.30–1.85 (comp, 9 H), 0.90 (s, 4.95 H), 0.83 (s, 4.05 H); mass spectrum m/e 214.1395 ($C_{12}H_{22}OS$ requires 214.1391), 185 (base), 137, 81, 67, 57.

1,3,5,5-Tetramethyl-2-cyclohexenecarboxaldehyde (16l): 80%; bp 70–72 °C (1.7 mm); IR (film) 1724 cm^{-1}; NMR δ 9.41 (s, 1 H), 5.28 (br m, 1 H), 1.95 (d, 1 H, J = 14 Hz), 1.73 and 1.70 (2 s, 5 H), 1.17 (d, 1 H, J = 14 Hz), 1.05 (s, 6 H), 0.98 (s, 3 H), 0.79 (s, 3 H); mass spectrum m/e 166.1351 ($C_{11}H_{18}O$ requires 166.1358), 137 (base), 95, 81, 57.

2-Methyl-2-(*p*-tolyl)-4-chloro-4-pentenal (20). A solution of diethyl *N*-benzylidenaminomethylphosphonate (**7**, 3.06 g, 12.0 mmol) in anhydrous THF (5 mL) was added over 5 min to a stirred solution of *n*-butyllithium (12.0 mmol, 2.9 N hexane) in anhydrous THF (40 mL) at −78 °C under dry nitrogen. After 1 h, a solution of *p*-methylacetophenone (**19**, 1.34 g, 10.0 mmol) in anhydrous THF (5 mL) was added, and the resulting solution was heated at reflux for 2 h. This solution was cooled to −78 °C, *n*-butyllithium (15.0 mmol, 2.9 N hexane) was added (ca. 5 min), and the stirring was continued at −78 °C for 1 h. After the addition of freshly distilled hexamethylphosphoramide (HMPA, 20 mL), a solution of freshly distilled 2,3-dichloroprop-1-ene (3.3 g, 30.0 mmol) in anhydrous THF (5 mL) was added. The reaction mixture was then stirred at ambient temperature for 18 h, whereupon 1 N hydrochloric acid (50 mL) was added, and the stirring was continued at room temperature for 2 h. Saturated brine (50 mL) was added, and the aqueous layer was extracted with hexane (3 × 100 mL). The combined organic layers were washed with saturated sodium bicarbonate (1 × 100 mL) and saturated brine (1 × 100 mL). The organic solution was then dried ($MgSO_4$), and the excess solvents were removed under reduced pressure to provide the vinyl chloride **20** as a crude oil which was purified by high-performance liquid chromatography with hexane/ethyl acetate (8:1) as the eluting solvent to give 1.41 g (63%) of pure **20**: IR ($CHCl_3$) 1724, 1637 cm^{-1}; NMR δ 9.42 (s, 1 H), 7.12 (s, 4 H), 5.17 (m, 1 H), 2.99 (m, 2 H), 2.30 (s, 3 H), 1.52 (s, 3 H); mass spectrum m/e 222, 193, 157 (base), 119, 91. An analytical sample of the 2,4-dinitrophenylhydrazone was prepared, mp 160–161 °C (ethanol). Anal. ($C_{19}H_{19}N_4O_4Cl$) C, H, N.

4-Methyl-4-(*p*-tolyl)-2-cyclopenten-1-one (22). To a stirred solution of mercuric acetate (636 mg, 2.00 mmol) in formic acid (10 mL) under dry nitrogen at room temperature was added the vinyl chloride **20** (440 mg, 1.95 mmol). The resulting solution was stirred at room temperature for 21 h, whereupon the excess formic acid was removed in vacuo, and saturated aqueous sodium bicarbonate (20 mL) was added. The aqueous layer was extracted with methylene chloride (3 × 20 mL), and the combined organic layers were washed with brine (1 × 50 mL) and dried ($MgSO_4$). Evaporation of the excess solvents under reduced pressure afforded the crude γ-keto aldehyde **21**, which was dissolved in a mixture of methanol (5 mL) and 10% aqueous potassium hydroxide (5 mL), and the solution was stirred at room temperature for 2 h. The methanol was removed under reduced pressure, and saturated brine (30 mL) was added. The aqueous mixture was extracted with methylene chloride (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$). Removal of excess solvents afforded an oily residue which was purified by column chromatography (10 g of Florisil/benzene) to give 243 mg (67%) of pure **22**, semicarbazone mp 166–168 °C (H_2O/EtOH) (lit.[23] 168–169 °C).

Preparation of 4,4-Disubstituted 2-Cyclohexen-1-ones 26. General Procedure.[26] A solution of diethyl *N*-benzylidenaminomethylphosphonate (**7**, 3.06 g, 12.0 mmol) in anhydrous THF (5 mL) was added over a 5-min period to a stirred solution of *n*-butyllithium (12.0 mmol, 2.9 N hexane) in anhydrous THF (40 mL) at −78 °C under dry nitrogen. After 1 h, a solution of the carbonyl compound **1** (10.0 mmol) in anhydrous THF (5 mL) was added, and the resulting solution heated at reflux for 2 h. The resulting solution was cooled to −78 °C, *n*-butyllithium (15.0 mmol, 2.9 N hexane) was added (5 min), and the stirring was continued at −78 °C for 1 h. After the addition of freshly distilled hexamethylphosphoramide (HMPA, 20 mL), a solution of pure 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[25] (2.9 g, 15.0 mmol) in anhydrous THF (5 mL) was added. The reaction mixture was then stirred at ambient temperature for 18 h, whereupon 1 N hydrochloric acid (50 mL) was added and the stirring continued at room temperature for 6 h. Saturated brine (50 mL) was added, and the resulting mixture was extracted with hexane (3 × 100 mL). The combined organic layers were washed with saturated sodium bicarbonate (1 × 100 mL) and saturated brine (1 × 100 mL) and dried ($MgSO_4$). The excess solvents were removed under reduced pressure to provide the crude δ-keto aldehyde **25**. This residual oil was dissolved in methanol (30 mL), and 10% aqueous potassium hydroxide (30 mL) was added. The resulting mixture was stirred at room temperature for 1 h, whereupon the methanol was removed under reduced pressure and saturated brine (50 mL) added. The aqueous mixture was extracted with ether (3 × 75 mL), and the combined organic layers were dried ($MgSO_4$). Removal of excess solvents under reduced pressure afforded the crude cyclohexenone **26**, which was purified by preparative LC by using hexane/ethyl acetate (8:1) as the eluting solvent and/or vacuum distillation.

Spiro[5.5]undec-1-en-3-one (26a): 55%; bp 108–110 °C (4.5 mm); mp of 2,4-dinitrophenylhydrazone 134–135 °C (from ethanol/benzene) (lit.[27] mp 135 °C); (film) 1681 cm^{-1}; NMR δ 6.85 (d, 1 H, J = 10 Hz), 5.86 (d, 1 H, J = 10 Hz), 2.42 (d of t, 2 H, J = 1.5, 7 Hz), 1.9 (d of t, 2 H, J = 1, 7 Hz), 1.52 (br s, 10 H); mass spectrum m/e 164, 136, 122 (base).

9-*tert*-Butylspiro[5.5]undec-1-en-3-one (26b): 57%; as ca. 95:5 mixture of diastereomers, bp 134–136 °C (0.65 mm); mp of 2,4-dinitrophenylhydrazone 173–175 °C (from ethanol); IR (film) 1681 cm^{-1}; NMR (major diastereomer) δ 7.17 (d, 0.95, J = 10 Hz), 5.90 (d, 0.95 H, J = 10 Hz), 1.1–2.6 (comp, 13 H), 0.88 (s, 9 H); (minor diastereomer) δ 6.52 (d, 0.05 H, J = 10 Hz), 5.82 (d, 0.05 H, J = 10 Hz); mass spectrum m/e 220.1828 ($C_{15}H_{24}O$ requires 220.1827), 192, 178, 165, 164, 57 (base). Anal. ($C_{15}H_{24}O$) C, H.

8,10,10-Trimethylspiro[5.5]undeca-1,7-dien-3-one (26c): 65%; bp 118–120 °C (1.2 mm); IR (film) 1675 cm^{-1}; NMR δ 6.73 (d, 1 H, J = 10 Hz), 5.80 (d, 1 H, J = 10 Hz), 5.24 (m, 1 H), 1.2–2.6 (comp, 11 H), 0.98 (s, 6 H); mass spectrum m/e 204.1514 ($C_{14}H_{20}O$ requires 204.1514), 176, 162, 133, 91 (base).

4-Methyl-4-phenyl-2-cyclohexen-1-one (26d): 59%; bp 131–133 °C (2.0 mm) [lit.[28] bp 93–94 °C (0.25 mm)]; IR (film) 1681 cm^{-1}; NMR δ 7.27 (m, 5 H), 6.82 (d, 1 H, J = 10 Hz), 6.06 (d, 1 H, J = 10 Hz), 2.23 (m, 4 H), 1.52 (s, 3 H).

Geminal Acylation–Hydroxyalkylation of Carbonyl Compounds 1. General Procedure.[26] To a well-stirred solution of *n*-butyllithium (6.0 mmol, 2.2 N hexane) in anhydrous THF (35 mL) under dry nitrogen at −78 °C was added over about 2 min a solution of the diethyl *N*-benzylidenaminoalkylphosphonate **7** or **8** (6.0 mmol) in anhydrous THF (2 mL), and the resulting solution stirred at −78 °C for 1 h. A solution of the appropriate ketone **1** (5 mmol) in anhydrous THF (2 mL) was added dropwise and the reaction mixture allowed to warm to room temperature over 1 h, whereupon the mixture was heated under reflux for 2 h. After the mixture thus obtained was cooled to −78 °C, *n*-butyllithium (6.0 mmol, 2.2 N hexane) was added (2–3 min) and the resulting solution of metalloenamine **24** or **27** was stirred at −78 °C for 1 h, at which time the appropriate aldehyde (6.0 mmol) in anhydrous THF (1 mL) was added. After 30 min methyl chloroformate or bromomethyl methyl ether (20.0 mmol) was added, and the resulting mixture was

(27) Christol, H.; Plenat, F.; Saloncon, J. *Bull. Soc. Chim. Fr.* **1970**, 4468.
(28) Zimmerman, H. E.; Jones, II, G. *J. Am. Chem. Soc.* **1970**, *92*, 2753.

stirred at −78 °C for 1 h and then allowed to warm to room temperature over 2–3 h. The reaction was quenched by the addition of 1 N HCl (35 mL), and the stirring was continued at room temperature for 5 h, at which time saturated brine (50 mL) was added. The layers were separated, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic fractions were washed with saturated sodium bicarbonate (1 × 50 mL) and dried ($MgSO_4$). The excess solvent was removed under reduced pressure, and the protected aldols **28** were purified by preparative LC by using hexane/ethyl acetate (5:1) as the eluting solvent. Analytical samples were prepared by subsequent bulb-to-bulb distillation (Kügelrohr).

2-(1′-Methoxycarbonyloxybenzyl)-2-(1′-propyl)pentanal (28a): 56%; 120 °C bath (0.05 mm); IR ($CHCl_3$) 1721 cm^{-1}; NMR δ 9.63 (s, 1 H), 7.22 (s, 5 H), 5.80 (s, 1 H), 3.61 (s, 3 H), 2.80–1.67 (comp, 14 H); mass spectrum *m/e* 292, 188, 165, 121 (base). Anal. ($C_{17}H_{24}O_4$) C, H.

1-(1′-Methoxycarbonyloxybutyl)cyclohexanecarboxaldehyde (28b): 45%; 140 °C bath (0.05 mm); IR ($CHCl_3$) 1724 cm^{-1}; NMR δ 9.56 (s, 1 H), 4.95–4.70 (m, 1 H), 3.78 (s, 3 H), 2.28–0.67 (comp, 17 H); mass spectrum *m/e* 242, 138, 112, 81 (base). Anal. ($C_{13}H_{22}O_4$) C, H.

1-(1′-Methoxycarbonyloxybenzyl)cyclohexanecarboxaldehyde (28c): 47%; 180 °C bath (0.05 mm); IR ($CHCl_3$) 1727 cm^{-1}; NMR δ 9.61 (s, 1 H), 7.27 (s, 5 H), 5.58 (s, 1 H), 3.68 (s, 3 H), 2.30–0.70 (comp, 10 H); mass spectrum *m/e* 276, 172, 165, 121 (base). Anal. ($C_{16}H_{20}O_4$) C, H.

1-(1′-Methoxycarbonyloxybenzyl)-3,5,5-trimethylcyclohex-2-enecarboxaldehyde (28d): 59% as 60:40 mixture of diastereomers; 135 °C bath (0.05 mm); IR ($CHCl_3$) 1730 cm^{-1}; NMR δ 9.67 (s, 0.4 H), 9.63 (s, 0.6 H), 7.25 (s, 3.0 H), 7.23 (s, 2.0 H), 5.65 (s, 0.6 H), 5.61 (s, 0.4 H), 3.66 (s, 1.8 H), 3.64 (s, 1.2 H), 2.10–1.18 (comp, 7 H), 0.91 (s, 3 H), 0.68 (s, 3 H); mass spectrum *m/e* 316, 211, 165, 121 (base). Anal. ($C_{19}H_{24}O_4$) C, H.

1-(1′-Methoxymethyloxybenzyl)-3,5,5-trimethylcyclohex-2-enecarboxaldehyde (28e): 42% as 55:45 mixture of diastereomers; 135 °C bath (0.05 mm); IR ($CHCl_3$) 1724 cm^{-1}; NMR δ 9.70 (s, 0.45 H), 9.66 (s, 0.55 H), 7.20 (s, 5 H), 5.82 (br s, 0.45 H), 5.71 (br s, 0.55 H), 4.70 (s, 0.55 H), 4.64 (s, 0.45 H), 4.41 (s, 1.1 H), 4.33 (s, 0.9 H), 3.29 (s, 1.65 H), 3.22 (s, 1.35 H), 2.07–1.14 (comp, 7 H), 0.89 (s, 1.65 H), 0.87 (s, 1.35 H), 0.65 (s, 3 H); mass spectrum *m/e* 212, 196, 105, 45 (base). Anal. ($C_{19}H_{26}O_3$) C, H.

2-Methyl-2-phenyl-3-methoxycarbonyloxyhexanal (28f): 49% as 55:45 mixture of diastereomers; 115 °C bath (0.05 mm); IR ($CHCl_3$) 1721 cm^{-1}; NMR δ 9.46 (s, 0.55 H), 9.44 (s, 0.45 H), 7.30 (s, 2.75 H), 7.27 (s, 2.25 H), 5.65–5.22 (comp, 1 H), 3.68 (s, 1.65 H), 3.50 (s, 1.35 H), 1.49 (s, 3 H), 1.45–0.70 (comp, 7 H); mass spectrum *m/e* 264, 160, 131, 105 (base). Two 2,4-dinitrophenylhydrazones were obtained upon fractional recrystallization (10% aqueous MeOH), mp 139–140 and 146–147 °C. Anal. ($C_{21}H_{24}N_4O_7$) C, H, N.

2-Methyl-3-methoxycarbonyloxy-2,3-diphenylpropanal (28g): 62% as 56:44 mixture of diastereomers; 185 °C bath (0.05 mm); IR ($CHCl_3$) 1730 cm^{-1}; NMR δ 9.59 (s, 1 H), 7.48–6.63 (comp, 10 H), 6.36 (s, 0.56 H), 6.20 (s, 0.44 H), 3.71 (s, 0.56 H), 3.61 (s, 0.44 H), 1.54 (s, 0.56 H), 1.36 (s, 0.44 H); mass spectrum *m/e* 298, 165, 121, 105 (base). Anal. ($C_{18}H_{18}O_4$) C, H.

3-(1′-Methoxycarbonyloxybenzyl)-3-phenyl-2-butanone (28h): 51% as a 55:45 mixture of diastereomers; 200 °C bath (0.05 mm); IR ($CHCl_3$) 1739, 1709 cm^{-1}; NMR δ 7.43–6.58 (comp, 10 H), 6.40 (s, 0.55 H), 6.31 (s, 0.45 H), 3.72 (s, 0.55 H), 3.60 (s, 0.45 H), 2.01 (s, 0.55 H), 1.94 (s, 0.45 H), 1.67 (s, 0.55 H), 1.43 (s, 0.45 H); mass spectrum *m/e* 312, 237, 194 (base), 179, 165. Anal. ($C_{19}H_{20}O_4$) C, H.

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Lewis Acid Induced Conjugate Addition of Alkenes to α,β-Unsaturated Ketones or Aldehydes

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Abstract: α,β-Unsaturated ketones or aldehydes form a 1:2 complex with ethylaluminum dichloride which reacts with alkenes either intermolecularly or intramolecularly to give a zwitterion. The zwitterion collapses reversibly to a cyclobutane in geometrically favorable cases and undergoes hydride and alkyl shifts to generate α,β-unsaturated carbonyl compounds. The intramolecular reactions proceed with high regio- and stereospecificity (e.g., **18** → **20**). The reaction is quite general for a variety of enone and alkene substitution patterns. Other Lewis acids do not give similar reactions. Use of less than 1 equiv of $EtAlCl_2$ in intramolecular reactions gives concerted ene reactions in geometrically favorable cases and complex mixtures of products where an ene reaction cannot occur. In one case, transfer of the β hydrogen of the ethyl group to the carbenium ion of the zwitterion results in reduction to give a saturated ketone.

Introduction

As part of a program designed to explore novel carbon–carbon bond forming reactions of alkenes, we have been exploring the Lewis acid catalyzed reactions of alkynyl and alkenyl esters[2] and alkynyl ketones[3] with alkenes. Ene reaction and stereospecific cycloaddition have been observed. Lewis acid complexes of β-substituted α,β-unsaturated ketones are unreactive toward alkenes. We have found that a complex of these ketones with 2 equiv of $EtAlCl_2$ reacts reversibly with alkenes in a stepwise manner to give a zwitterion. This zwitterion reacts reversibly to give a cyclobutane or undergoes two 1,2-hydride or alkyl shifts to irreversibly generate an α,β-unsaturated carbonyl compound (see Schemes I, II, or III). The intermolecular addition of an enone, as an electrophile, to an alkene has not been observed previously. The specific termination of the reaction by a series of alkyl and hydride shifts is also novel. The absence of polymerization is remarkable.

Complexes of α,β-unsaturated ketones with 2 equiv of $EtAlCl_2$ can also be used as initiators for cation–olefin cyclization, a well-known method for the construction of polycyclic compounds.[4] α,β-Unsaturated ketones have been used as initiators for this reaction, typically by acylation or protonation of the carbonyl group in the presence of a nucleophile.[5] Intramolecular addition

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