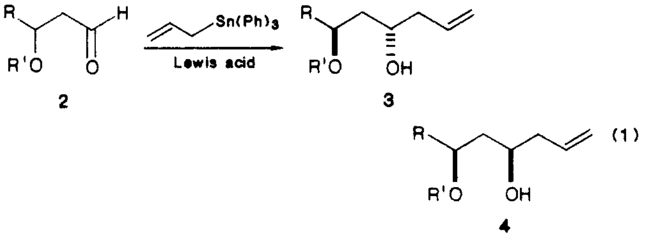
**Table II**

| substrate | R | R′ | Lewis acid; 3:4 ratio |  |  |  |
|---|---|---|---|---|---|---|
|  |  |  | $TiCl_4$ | $MgBr_2$ | $SnCl_4$ | $BF_3$·$OEt_2$ |
| **2a** | $CH_3$ | $PhCH_2$ | 32:1 | 8.1:1 | 3.4:1 | 3.9:1 |
| **2b** | *n*-hexyl | $PhCH_2$ | 96:1 | 9.7:1 | 3.3:1 | 4.9:1 |
| **2c** | *n*-hexyl | $CH_3$ | 3.8:1 | 1.3:1 | 1:3.3 | 3.5:1 |
| **2d** | *n*-hexyl | $CH_3CH_2$ | 61:1 | 3.9:1 | 3.0:1 | 4.4:1 |
| **2e** | *n*-hexyl | *t*-$BuSiMe_2$ | 1:1.1 | 1.7:1 | 1.7:1 | 3.4:1 |

to be high with **2d**, since the *n*-hexyl group is pseudoaxial in the $TiCl_4$ and $MgBr_2$ complexes. (5) Low levels of stereoselectivity are again expected with **2e**, which is not expected to form a bidentate complex with any of the Lewis acids examined.[6]

The chemical results are summarized in eq 1 and Table II.[7] In all cases, the stereochemistry assigned to the products produced was assigned by *chemical correlation* with materials that were independently synthesized by established, unambiguous methods. In particular, the very powerful method of Chamberlin[8] was utilized to secure the anti relationship of oxygenated centers present in the products. Mixtures containing roughly equal amounts of **3** and **4** were prepared via nonselective allyl addition reactions with each of the aldehydes **2a–e**, which then allowed for the development of analytical and/or preparative techniques for the separation of diastereomers. The anti diol (or a simple derivative such as the diacetate) could then be identified via capillary VPC and $^{13}C$ NMR comparison with the independently prepared anti material.



Inspection of the data in Table II reveals that the chemical results anticipated based upon the NMR study are in fact realized. For example, with $TiCl_4$ as Lewis acid, substrate **2b** (R′ = benzyl) affords a 96:1 level of stereoselectivity which falls to 3.8:1 with **2c** (R′ = $CH_3$) and is totally eliminated (1:1.1) in the reaction with **2e** (R′ = *t*-$BuSiMe_2$), situations in which the group R at $C_3$ is equatorial, or in which bidentate chelation is not established. With **2d** (R′ = ethyl), behavior that parallels that observed with **2b** is observed, consistent with the observation that the $C_3$ substituents are pseudoaxial in both cases.[9] In no case are high levels of stereoselectivity observed with the monodentate Lewis acid $BF_3$·$OEt_2$ or with $SnCl_4$ as the Lewis acid. The observed results quite strongly suggest that transmetalation between $SnCl_4$ and allyltriphenylstannane is faster than, or at least competitive with, the addition of allyltriphenylstannane to the chelate in this case, and presumably in other cases as well. In fact, "inverse addition" experiments (reaction of substrate with the reagent resulting from reaction of allyltriphenylstannane with Lewis acid) were performed with substrate **2b** by using both $SnCl_4$ and $TiCl_4$ and gave 3.1:1 and 1.5:1 stereoselectivities, respectively. Comparison with the data in Table II reveals that the transmetalation hypothesis is quite consistent with this result for the case of $SnCl_4$ as Lewis acid, but is clearly an unimportant aspect of the reaction of allyltriphenylstannane with the chelate derived from **2b** and $TiCl_4$. In general, it seems reasonable to expect that transmetalation possibilities should be considered as possible complications in such reactions with β-alkoxy aldehydes that are rather hindered at or around the ether oxygen, particularly with $SnCl_4$ as Lewis acid.[10]

In summary, the present investigation provides additional evidence that the sense of asymmetric induction expected in "chelation controlled" nucleophilic additions of allylstannanes to β-alkoxy aldehydes can be predicted by an examination of the solution structures of such chelates and also reveals that rather dramatic changes in solution conformation can result from rather modest changes in substrate structure. Finally, it is of interest to note that rather weak Lewis acids such as $MgBr_2$ can be much more effective in bidentate chelation than Lewis acids generally regarded as considerably stronger, such as $SnCl_4$. Further studies along these and similar lines are in progress and will be reported in due course.[11]

**Registry No.** **2a**, 86272-40-4; **2b**, 105538-80-5; **2c**, 22418-61-7; **2d**, 91243-26-4; **2e**, 105538-81-6; **3a**, 86272-43-7; **3b**, 105538-82-7; **3c**, 105538-83-8; **3d**, 105538-84-9; **3e**, 105538-85-0; **4a**, 86272-50-6; **4b**, 105538-86-1; **4c**, 105538-87-2; **4d**, 105538-88-3; **4e**, 105538-89-4; $CH_2$=$CHCH_2Sn(Ph)_3$, 76-63-1.

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[6] (a) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.*, in press. (b) Keck, G. E.; Castellino, S. *Tetrahedron Lett.*, in press.

[7] Reactions involving the use of $MgBr_2$·$OEt_2$ as Lewis acid were initiated at −23 °C and allowed to warm slowly to room temperature; those utilizing $TiCl_4$ or $SnCl_4$ were conducted at −78 °C. Isolated yields of the products **3** and **4** are typically greater than 85%.

[8] Chamberlin, A. R.; Mulholland, R. L., Jr. *Tetrahedron* **1984**, *40*, 2297.

[9] Although we are presently able to make *qualitative* predictions as to the stereochemical outcome of such reactions based upon preferred solution conformations of intermediate complexes, quantitative predictions as to the level of stereoselectivity expected are much more difficult. For example, the stereoselectivity observed with **2d** and $MgBr_2$ as Lewis acid is unexpectedly low.

[10] Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927.

[11] Financial support of this research by the National Institutes of Health through Grant GM-28961 is gratefully acknowledged.

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## Formation of Quaternary Centers via the Michael Reaction. Electronic Compensation for Steric Congestion

*Summary:* Compensation for steric bulk at the β-terminus of a Michael acceptor may be provided by the attachment of two electron-withdrawing substituents at the α-terminus. The Michael reaction of ketone and ester enolates is useful for the preparation of contiguous quaternary carbon centers in high yield.

*Sir:* The construction of quaternary carbon centers is one of the more difficult operations in synthetic organic chemistry.[2] We now report methodology that not only provides a simple solution to this problem but is also

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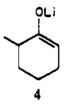
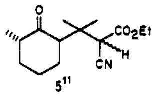
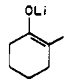
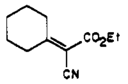
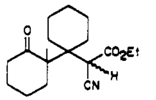
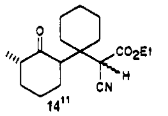
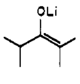
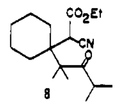
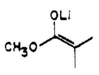
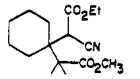
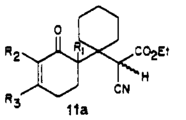
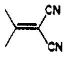
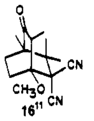
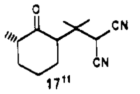
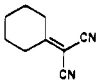
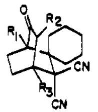
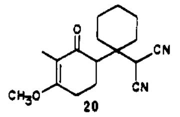
[1] Address correspondence to this author at the Florida State University.

[2] For an excellent review, see: Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

**Table I. Formation of Quaternary Centers via the Michael Reaction[9]**

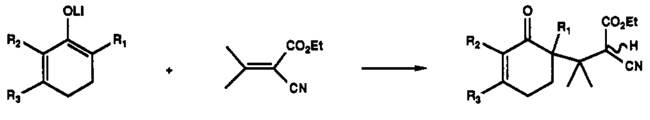
| enolate[6] | acceptor | adduct[7] | yield,[8] % |
|---|---|---|---|
| 1c | 2 | 3c | 83 |
| <br>4 | 2 | <br>5[11] | 64 |
| <br>12 | <br>7 | <br>13 | 56 |
| 4 | 7 | <br>14[11] | 55 |
| <br>6 | 7 | <br>8 | 95 |
| <br>9 | 7 | <br>10 | 90 |
| 1a | 7 | <br>11a | 98 |
| 1b | 7 | 11b | 89 |
| 1c | 7 | 11c | 99 |
| 1d | 7 | 11d | 87 |
| 1a | <br>15 | <br>16[11] | 82 |
| 4 | 15 | <br>17[11] | 45 |
| 1a | <br>18 | <br>19a[11] | 78 |
| 1c | 18 | 19c | 96 |
| 1d | 18 | 19d | 95 |
| 1b | 18 | <br>20 | 91 |

amenable to the preparation of *contiguous* quaternary carbon centers in high yield.

Traditionally, Michael additions have been conducted in protic media under conditions that permit rapid proton transfer.[3] The reaction has earned a reputation for sensitivity to steric encumbrance,[3,4] and it has only recently been found that sterically demanding substrates can be forced to undergo reaction under conditions of extreme pressure.[4]

Elegant pioneering studies conducted by Stork[5a] demonstrated that the Michael addition may be carried out under aprotic conditions, provided that the enolate formed in the addition is more stabilized than that which acts as the nucleophilic addend. These observations have been fully verified in numerous subsequent studies.[5b-x]

We have examined several aprotic Michael additions and have found that compensation for steric bulk at the $\beta$-terminus of the Michael acceptor may be provided by the attachment of two electron-withdrawing substituents. For example, the lithium enolate of 3-methoxy-2,6-dimethylcyclohexenone (**1a**)[6] reacts rapidly with ethyl isopropylidenecyanoacetate (**2**) in THF at -78 °C to form enone **3a**,[7] *having vicinal quaternary centers*, in 82% yield.[8]



1a-d 2 3a-d

a, $R_1 = R_2 = CH_3$, $R_3 = OCH_3$
b, $R_1 = H$, $R_2 = CH_3$, $R_3 = OCH_3$
c, $R_1 = R_2 = R_3 = CH_3$
d, $R_1 = H$, $R_2 = R_3 = CH_3$

The combination of either cyano and carbethoxy groups or two cyano groups is most favorable for the formation of adducts having contiguous quaternary centers. These results are summarized in Table I and demonstrate that both ketone and ester enolates react smoothly. Reactions of dienolates with ethyl cyclohexylidenecyanoacetate (**7**) were found to proceed to completion within 15 min at -78 °C[9a,b] to give products of single Michael addition. Iso-

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(3) (a) Bergman, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* (*N.Y.*) **1959**, *10*, 179. (b) Gawley, R. E. *Synthesis* **1976**, 777. (c) Jung, M. E. *Tetrahedron* **1976**, *32*, 3.

(4) (a) Dauben, W. G.; Gerdes, J. M. *Tetrahedron Lett.* **1983**, *24*, 3841. (b) Matsumoto, K. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 770. (c) Matsumoto, K. *Ibid.* **1980**, *19*, 1013. (d) Matsumoto, K.; Uchida, T. *Chem. Lett.* **1981**, 1673. (e) Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1983**, *48*, 4642 and references contained therein.

(5) (a) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152. (b) Stork, G.; Singh, J. *Ibid.* **1974**, *96*, 6181. (c) Boeckman, R. K., Jr. *Ibid.* **1974**, *96*, 6179. (d) Cregge, R. J.; Herrmann, J. L.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2603. (e) Herrmann, J. L.; Kieczykowski, G. R.; Romanet, R. F.; Wepple, P. J.; Schlessinger, R. H. *Ibid.* **1973**, 4711. (f) Herrmann, J. L.; Kieczykowski, G. R.; Romanet, R. F.; Schlessinger, R. H. *Ibid.* **1973**, 4715. (g) Oppolzer, W.; Pitteloud, R.; Bernardinelli, G.; Baettig, K. *Ibid.* **1983**, *24*, 4975. (h) David, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755. (i) Kende, A. S.; Constantinides, D.; Lee, S. J.; Liebeskind, L. *Tetrahedron Lett.* **1975**, 405. (j) Schultz, A. G.; Yee, Y. K. *J. Org. Chem.* **1976**, 41, 4044. (k) Schultz, A. G.; Godfrey, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 2414. (l) Kido, F.; Noda, Y.; Yoshikoshi, A. *Ibid.* **1982**, *104*, 5509. (m) Tanaka, T.; Toru, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 4103. (n) Suzuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R. *Ibid.* **1982**, *23*, 4057. (o) Suzuki, M.; Kawagishi, T.; Noyori, R. *Ibid.* **1982**, *23*, 5563. (p) Takahashi, T.; Naito, Y.; Tsuti, J. *J. Am. Chem. Soc.* **1981**, *103*, 5261. (q) Cory, R. M.; Anderson, P. C.; McLaren, F. R.; Yamamoto, B. R. *J. Chem. Soc., Chem. Commun.* **1981**, *73*. (r) Takaki, K.; Ohsugi, M.; Okada, M.; Yasumura, M.; Negoro, K. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 741. (s) Takaki, K.; Okada, M.; Yamada, M.; Negoro, K. *J. Org. Chem.* **1982**, *47*, 1200. (t) Takaki, K.; Okada, M.; Yamada, M.; Negoro, K. *J. Chem. Soc., Chem. Commun.* **1980**, 1183. (u) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207. (v) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1977**, 3929. (w) For a review containing examples of 1,4 additions of nitrile anions, see: Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* (*N.Y.*) **1984**, *31*, 1. (x) Trost, B. M.; Schmuff, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 396 and references therein.

(6) Prepared either (a) by addition of the corresponding ketone to a THF solution of LDA at -78 °C or (b) by treatment of the corresponding TMS enol ether with MeLi in THF.

(7) Characterized by IR, NMR, and either combustion analysis or high resolution mass spectral analysis.

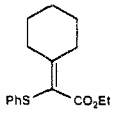
(8) All yields refer to isolated chromatographically and spectrally homogeneous materials.

propylidenemalononitrile (**15**) and cyclohexylidenemalononitrile (**18**) reacted much more slowly (−78 °C, 12 h)[9a] with dienolates to provide, in most cases, the product of double Michael addition.[5q,s,10] The reasons for this difference in reactivity are not clear, but we speculate that coordination of lithium ion may play a role in accelerating additions to cyano esters.

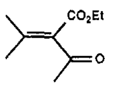
Several other features of this reaction are noteworthy. Double Michael addition products **16**, **19a**, and **19c** contain *four* contiguous quaternary centers. The occurrence of the second Michael addition to form bicyclo[2:2:2] ring systems appears to be limited to those cases where activation is provided by two cyano substituents and depends upon a combination of electronic and steric buttressing factors. The formation of uncyclized **20** from **1b** and **18** may be rationalized on the basis of the absence of methyl buttressing ($R_1$ = H) along with deactivation of the enone ($R_3$ = $OCH_3$).

Although this reaction is remarkably capable of accommodating steric bulk at the reacting centers, we believe that the lower yields of **5**, **13**, **14**, and **17** result from remote steric interference with the cyclohexanone enolate ring. In support of this hypothesis, we have observed that the kinetic lithium enolate of isophorone completely fails to react with **2**.

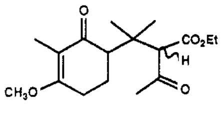
Hindered Michael acceptors bearing other activating groups were generally found to react less readily. For example, sulfide ester **21**[5r–t] failed to react with **1a**.[12] Diethyl cyclohexylidenemalonate and diethyl isopropylidenemalonate were also unreactive. Ethyl isopropylideneacetoacetate (**22**) formed no Michael adduct with **1a** but reacted with **1b** to give **23**[7] in 50% yield.[8]



21



22



23

These results unambiguously demonstrate, for the first time, that contiguous quaternary carbon centers can be formed under very mild conditions via the aprotic Michael addition. We are currently investigating the possibility of diastereoselectivity in these processes[13] as well as their utility in the total synthesis of natural products.

**Acknowledgment.** We thank the National Cancer Institute for generous financial support of our programs.

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[9] (a) In all cases, reactions were quenched at −78 °C by rapid addition to a large excess of saturated sodium bicarbonate solution. (b) Temperatures higher than −78 °C appear to favor either competing proton transfer or retro Michael reaction, or both. (c) In a typical experiment, a solution of 0.154 g (1.0 mmol) of 3-methoxy-2,6-dimethylcyclohexenone in 2 mL of THF was added to a solution of 1.1 mmol of LDA in 7 mL of dry THF at −78 °C. The mixture was stirred at −78 °C for 15 min before addition of a solution of 0.193 g (1.0 mmol) of ethyl cyclohexylidenecyanoacetate in 2 mL of dry THF. After being stirred at −78 °C for 15 min, the mixture was rapidly poured into a mixture of 75 mL of saturated aqueous $NaHCO_3$ and 20 mL of 40% ethyl acetate/hexane. The aqueous layer was extracted with an ethyl acetate/hexane mixture, and the organic layers were combined, dried, and concentrated to yield a light yellow oil. Flash chromatography (20% EtOAc/hexane) afforded 0.338 g (98%) of pure Michael adduct.

[10] (a) White, K. B.; Reusch, W. *Tetrahedron* **1978**, *34*, 2439. (b) Lee, R. A. *Tetrahedron Lett.* **1973**, 3333. (c) Spitzner, D. *Ibid.* **1978**, 3349. (d) Gibbons, E. G. *J. Org. Chem.* **1980**, *45*, 1540. (e) Narula, A. S.; Birch, A. J. *Tetrahedron Lett.* **1981**, *22*, 591. (f) Hagiwara, H.; Nakayama, K.; Uda, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3769. (g) Roberts, M. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 724. (h) Quesada, M. L.; Schlessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968. (i) Ohnuma, T.; Oishi, T.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 301. (j) Cory, R. M.; Chan, D. M. T.; Naguib, Y. M. A.; Rastall, M. H.; Renneboog, R. M. *J. Org. Chem.* **1980**, *45*, 1852 and references cited therein.

[11] The stereochemistry of **5**, **14**, and **16** was determined by $^1H$ NMR decoupling and NOE difference experiments. The stereochemistry of **19a**, **19c**, and **19d** was assigned by analogy with **16**.

[12] The reaction of the corresponding sulfoxide with **1a** has provided interesting preliminary results. Because of their increased complexity, these reactions are still under investigation and will be described in a future communication.

[13] Krafft, M. E.; Kennedy, R. M.; Holton, R. A. *Tetrahedron Lett.* **1986**, *27*, 2087.

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*Received October 14, 1986*

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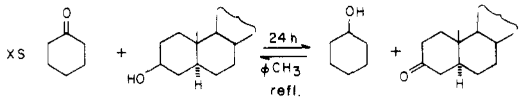
## Oxidation of Secondary Alcohols Using Raney Nickel

*Summary:* A high yield, one-step oxidation procedure has been developed for the selective oxidation of secondary alcohols.

*Sir:* We report that Raney nickel in refluxing benzene can be used to efficiently oxidize secondary alcohols to ketones. Numerous methods exist for the oxidation of alcohols to ketones[1] and for the selective oxidation of primary–secondary diols.[2] The use of Raney nickel provides a mild and inexpensive means of oxidizing secondary alcohols to the corresponding carbonyl compounds.

Oxidation of secondary alcohols to ketones using Raney nickel has been reported. However, the reaction was either carried out at very high temperatures[3] or under equilibrating conditions in the presence of a large excess of a reversible hydrogen acceptor, cyclohexanone, to drive the reaction to completion[4] (eq 1). It would be more desirable if one could use an irreversible hydrogen acceptor and eliminate the need for an excess of cyclohexanone.



(1)

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