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A New Regiospecific Synthesis of Enol Boranes of Methyl Ketones

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1,2-Migrations of organoborates are a cornerstone of numerous organoborane-based syntheses,[1] and a knowledge of relative "migratory aptitudes" for intermediates containing mixed groups should significantly enhance their synthetic utility. Among such "mixed" derivatives containing alkyl groups, the ease of transfer has been established as normal > secondary > tertiary for both the cyanoborate process[2] and the iodination of ethynyltrialkylborates,[3] whereas for rearrangements of α-halo boronates[4] as well as intermediates obtained from reaction of mixed boranes with α-diazo carbonyls,[5] the order is Ar > R > Cl. The latter process provides a route to regio- and stereodefined *internal* enol boranes[6] A (Scheme I, path a), but to date no method exists for the regiospecific construction of *terminal* enol derivatives B from nonketonic precursors (Scheme I, path b, G = H).

Accordingly, we have investigated the efficiency of several boranes for this purpose, including H_3B·THF, dichloroborane, 9-borabicyclo[3.3.1]nonane (9-BBN),[7] thexylborane, dicyclohexylborane, and disiamylborane—using as criteria a combination of nitrogen evolution and, after protolysis, methyl ketone formation. The former represents a rough measure of overall enol borinate formation,[5,8] and the latter indicates regiochemistry (i.e., relative migratory aptitude), as depicted in Scheme I (path b, G = H, $E^+ = H^+$).

In the event, dicyclohexylborane proved most efficient,[9] and the derived enol borinate **3** reacted with various electrophiles (Eschenmoser's reagent,[12] aldehydes, and ketones) to provide good yields of the corresponding Mannich bases and crossed-aldol products, respectively. It should be emphasized that in all cases examined there was no evidence (GLPC, NMR) of product formation derived from either cyclohexyl group migration or the regioisomer due to proton scrambling.

Table I. Formation of Mannich Bases from Reaction of Enol Borinates with Dimethylmethyleneammonium Iodide

$R_2BOC(R^1)=CH_2 + Me_2N^+=CH_2I^- \rightarrow R^1COCH_2CH_2NMe_2$[a]

R	R^1	product yield,[b] %	bp, °C (torr)	picrate mp, °C
C_6H_{11}	$CH_3(CH_2)_4$	80	74–75 (1.5)	87–88
C_6H_{11}	$(CH_3)_2CH(CH_2)_2$	73	57–58 (0.70)	97–98
C_6H_{11}	C_6H_{11}	68	83–84 (0.60)	119–120

[a] All structures were confirmed by IR, ^1H NMR, mass spectral data and satisfactory (±0.3%) elemental analyses. [b] Yields of pure products isolated by distillation.

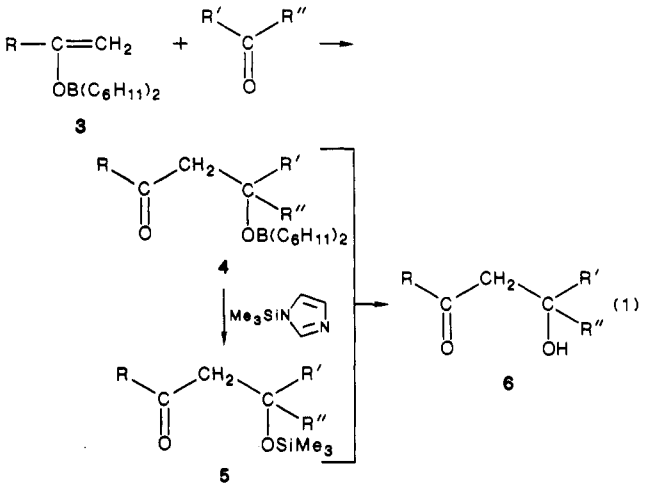
Table II. Cross-Aldol Products from Reaction of Enol Borinates with Aldehydes and Ketones

$R_2BOC(R')=CH_2 + R''COR''' \rightarrow R'COCH_2C(OSiMe_3)R''R'''$

R	R′	R″	R‴	product yield,[a,b] %
C_6H_{11}	n-C_5H_{11}	CH_3	CH_3	74
C_6H_{11}	n-C_5H_{11}	CH_3	H	70
C_6H_{11}	n-C_5H_{11}	CH_3	C_2H_5	72
C_6H_{11}	n-C_5H_{11}	C_6H_{11}	H	(60)
C_6H_{11}	n-C_5H_{11}	C_6H_5	H	70[c]

[a] All structures were verified by compatible IR, ^1H NMR, and mass spectral data. [b] Yield of isolated product. Value in parentheses indicates yield determined by GC analyses. [c] Isolated as 1-phenyl-1-octen-3-one, mp 48–49 °C.

Yields of several Mannich bases prepared in this manner are presented in Table I. Similarly, crossed-aldol products could be readily assembled (eq 1), but isolation of product



6 in pure form from boryloxy derivative **4** was often complicated by the formation of byproducts. This obstacle was circumvented by the discovery of a mild boryloxy → silyloxy exchange (**4** → **5**) upon treating derivative **4** with *N*-trimethylsilylimidazole.[13] The resulting trimethylsilyl aldol-protected derivative **5** could be easily isolated by distillation[14] or hydrolyzed to **6** without complication. Table II summarizes the results. Importantly, the entire

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(13) This reagent also readily exchanges with enol borinates to provide the corresponding enol silyl ethers in excellent yield; Hooz, J.; Oudenes, J. *Tetrahedron Lett.* **1983**, 5695.

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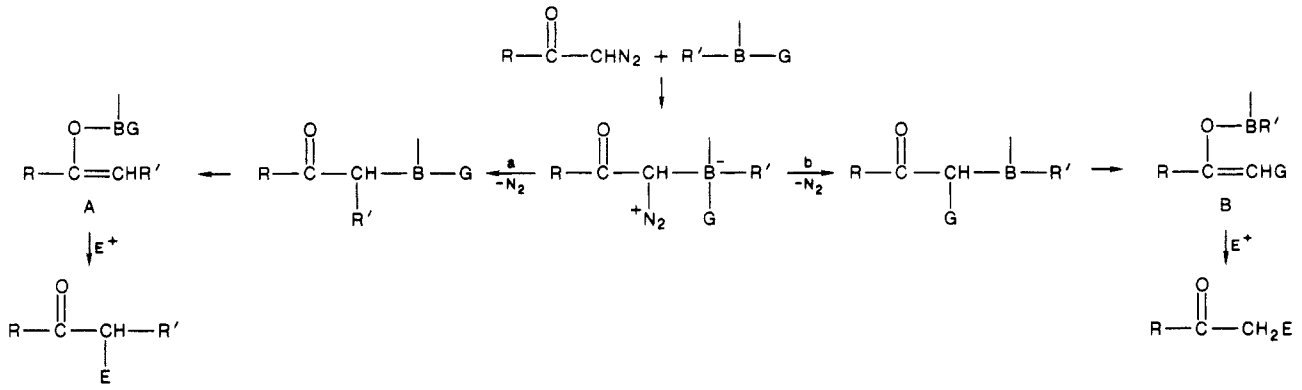
Scheme I



operation is experimentally simplified as a single-flask procedure, by sequential addition of reagents.

An exploratory experiment to alkylate enol derivative **3** (R = n-C_5H_{11}) with $C_6H_5CH_2Br$ by employing lithium dimethylaminoethoxide as "activator"—conditions which are regiospecific for alkylation of *internal* enol boranes[6b]—gave a complex mixture in which the undesired internal regioisomer predominated (ca. 3:1). Thus, toward less reactive electrophiles, terminal enol derivatives **3** exhibit unselective behavior similar to that demonstrated by the corresponding lithium enolates.[15]

In summary, the exclusive hydride migration observed for dicyclohexylborane and the regiospecificity of the reaction of the derived enol borinates toward sufficiently reactive electrophiles expand considerably the range of structures available via the α-diazo organoborane route.

Experimental Section

General Procedures. Infrared (IR) spectra were recorded with a Unicam SP1000 or Perkin-Elmer 421 grating spectrophotometer. The ^1H NMR spectra were determined with a Varian Model A-60 or Bruker Model WH-200 NMR spectrometer. Chemical shifts are expressed as δ values (ppm) with Me_4Si as internal standard. The mass spectra were obtained with an AEI Model MS-2, MS-12, or MS-50 spectrometer. All reactions employing enol borinates were conducted under a nitrogen atmosphere. Commercial nitrogen (Union Carbide) was purified either by passage through a sodium benzophenone ketyl solution in diglyme and a drying train or by passage through a column of reduced BASF Catalyst R3-11 and a drying tower filled with Drierite. All ethereal solvents were successively distilled from lithium aluminum hydride and sodium benzophenone ketyl under nitrogen. Borane–methyl sulfide and BH_3·THF were commercial products (Alfa), used without further purification. Standard techniques were used[1a] in all reactions requiring the exclusion of air and moisture.

General Procedure Used for the Preparation of Mannich Bases. A heterogeneous mixture of dicyclohexylborane was prepared from cyclohexene (1.64 g, 20 mmol) and borane (10 mmol) in tetrahydrofuran (10 mL). The magnetically stirred mixture was cooled to ca. 5 °C (ice bath), and a solution of the diazo ketone (7.5 mmol) in 10 mL of THF was added dropwise over 30 min. After the mixture was stirred an additional 30 min, nitrogen evolution was complete. Then a solution of dimethylmethyleneammonium iodide[12] (1.85 g, 10 mmol) in 10 mL of anhydrous dimethyl sulfoxide was added and the mixture allowed to warm to room temperature. After being stirred at room temperature for 3 h the mixture was cooled to 0 °C, and aqueous sodium hydroxide (15 mL of a 3 N solution) was added. The mixture was stirred vigorously for an additional 20 min, poured into 100 mL of ice–water, and extracted with pentane (5 × 50 mL). After concentration of the extract, the residue was extracted with ice-cold 5 N HCl (5 × 50 mL), and the aqueous layer was made basic with cold sodium hydroxide solution (10 N). The basic mixture was extracted with pentane (5 × 50 mL), and the residue remaining after concentration of the dried (Na_2SO_4) extract was distilled to provide the Mannich base.

1-(Dimethylamino)-6-methyl-3-heptanone: colorless liquid, bp 57–58 °C (0.70 torr); n^{20}_D 1.4363; IR ($CHCl_3$) 2870, 2780, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 5 Hz, 6 H), 1.20–1.73 (br, 3 H), 2.23 (s, 6 H), 2.37 (m, 2 H), 2.59 (s, 4 H); MS, m/e (relative intensity) 172 (0.2), 171 (1.1), 123 (3.0), 111 (12), 58 (100). Anal. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.38; H, 12.51; N, 8.23. Picrate: mp 97–98 °C. Anal. Calcd for $C_{16}H_{24}N_4O_8$: C, 48.00; H, 6.04; N, 13.99. Found: C, 48.10; H, 6.13; N, 14.01.

1-(Dimethylamino)-3-octanone: colorless liquid, bp 74-75 °C (1.5 torr); n^{22}_D 1.4388; IR ($CHCl_3$) 2820, 2780, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84–1.80 (br, 6 H), 0.90 (t, 3 H), 2.23 (s, 6 H), 2.37 (m, 2 H), 2.59 (s, 4 H); MS, m/e (relative intensity) 171.1617 (calcd for $C_{10}H_{21}NO$, 171.1623), 172 (0.4), 171 (3.8), 84 (5.5), 72 (7.1), 60 (5.2), 59 (4.8), 58 (100), 57 (5.7), 55 (5.2). Anal. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.38; H, 12.51; N, 8.23. Picrate: mp 87–88 °C. Anal. Calcd for $C_{16}H_{24}N_4O_8$: C, 48.00; H, 6.04; N, 13.99. Found: C, 48.22; H, 6.12; N, 13.71.

1-Cyclohexyl-3-(*N*,*N*-dimethylamino)-1-propanone: colorless liquid, bp 83–84 °C (0.60 torr); n^{20}_D 1.4674; IR ($CHCl_3$) 2830, 2795, 1705 cm^{-1} ^1H NMR ($CDCl_3$) δ 0.99–2.00 (br, 11 H), 2.2 (s, 6 H), 2.57 (s, 4 H); MS, m/e (relative intensity) 183 (1.6), 182 (1.3), 84 (80), 83 (5), 72 (5), 58 (100), 55 (14), 42 (16), 41 (15). Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.43. Found: C, 72.34; H, 11.56; N, 7.64. Picrate: mp 119–120 °C. Anal. Calcd for $C_{17}H_{24}N_4O_8$: C, 49.51; H, 5.87; N, 13.59. Found: C, 49.65; H, 5.43; N, 13.80.

General Procedure for the Preparation of Silyloxy Ketones 5. A heterogeneous mixture of dicyclohexylborane was prepared by hydroboration of cyclohexene (26 mmol) using borane–methyl sulfide (13 mmol) in 15 mL of anhydrous tetrahydrofuran. The magnetically stirred mixture was cooled (ca. 5 °C), while a solution of the diazo ketone (10 mmol) in THF (10 mL) was added dropwise over 30 min. After the mixture was stirred an additional hour, nitrogen evolution was complete, and a solution of aldehyde or ketone (14 mmol) in 4 mL of THF was added at 5 °C; then the mixture was stirred for an additional 2 h at room temperature. *N*-(Trimethylsilyl)imidazole (14 mmol) was injected, and the resulting mixture was stirred for 1 h. After concentration of the mixture in vacuo, the silyloxy ketone was isolated by distillation.

Data for Silyloxy Ketones 5 (R = n-C_5H_{11}). 5 (R′ = R″ = CH_3): Kugelrohr bp 75–80 °C/(0.01 torr); IR (neat) 1710, 1250, 1040, 840 cm^{-1}; ^1H NMR (CCl_4) δ −0.22 (s, 9 H), 0.56 (t, J = 7 Hz, 3 H), 0.98 (s, 6 H), 0.8–1.6 (m, 6 H), 2.09 (t, J = 7 Hz, 2 H), 2.11 (s, 2 H); MS m/e (relative intensity) 229 (79), 171 (91), 131 (100), 115 (24), 99 (41), 75 (45), 73 (65), 71 (14); calcd for $C_{12}H_{25}SiO_2$ (M−CH_3) 229.1623, found 229.1623.

The free hydroxy ketone was obtained by heating 1.5 mmol of derivative **5** in 20 mL of ethanol–water (3:1) at 50 °C for 5 min with several drops of dilute aqueous hydrochloric acid. After

(14) The byproduct, $(C_6H_{11})_2B$–imidazole, is a waxy solid which softens at temperatures above ca. 200 °C and appears completely inert in the reaction medium.

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extraction (hexane), drying (Na_2SO_4), and concentration of the resulting solution in vacuo, the residue was distilled to provide 2-hydroxy-2-methyl-4-nonanone (92%); Kugelrohr bp 80 °C (0.01 torr); IR (neat) 3450, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3 H), 1.25 (s, 6 H), 1.0–1.8 (m, 6 H), 2.43 (t, J = 7 Hz, 2 H), 2.60 (s, 2 H); MS m/e (relative intensity) 172 (0.5), 157 (22), 154 (9), 116 (5), 114 (8), 101 (6), 99 (100), 71 (39); calcd for $C_{10}H_{20}O_2$ 172.1487, found 172.1475.

5 (R′ = CH_3, R″ = C_2H_5): Kugelrohr bp 80–85 °C (0.01 torr); IR (neat) 1710, 1260, 1040, 840 cm^{-1}; ^1H NMR (CCl_4) δ −0.15 (s, 9 H), 0.5–0.8 (m, 6 H), 1.03 (s, 3 H), 0.8–1.5 (m, 8 H), 2.0–2.4 (m, 4 H); MS, m/e (relative intensity) 243 (19), 229 (75), 171 (33), 145 (44), 129 (17), 99 (100), 75 (74), 73 (60), 71 (30); calcd for $C_{13}H_{27}SiO_2$ (M − CH_3) 243.1779, found 243.1772.

5 (R′ = CH_3, R″ = H): Kugelrohr bp 75–80 °C (0.01 torr); IR (neat) 1710, 1250, 1040, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.03 (s, 9 H), 0.87 (t, J = 7 Hz, 3 H), 1.10 (d, J = 6 Hz, 3 H), 0.9–1.8 (m, 6 H), 2.1–2.6 (m, 4 H), 4.0–4.1 (m, 1 H); MS, m/e (relative intensity) 230 (1), 215 (100), 171 (99), 159 (43), 143 (14), 117 (77), 101 (15), 99 (28), 75 (86), 73 (86); calcd for $C_{12}H_{28}SiO_2$ 230.1700, found 230.1681.

5 (R′ = C_6H_{11}, R″ = H): Kugelrohr bp 105–110 °C (0.01 torr); IR (neat) 1715, 1250, 1044, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.05 (s, 9 H), 0.8–1.0 (m, 20 H), 2.1–2.5 (m, 4 H), 3.9–4.2 (m, 1 H); MS, m/e (relative intensity) 298 (0.6), 283 (58), 227 (15), 215 (71), 185 (13), 171 (19), 152 (31), 137 (42), 99 (100), 72 (25), 73 (23), 71 (21).

5 (R′ = C_6H_5, R″ = H): microdistillation [Kugelrohr bp 90–95 °C (0.01 torr)] provided a solid, which upon recrystallization (pentane) had mp 48–49 °C and identical spectroscopic properties with those reported in the literature.[15b]

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Synthesis of High-Specific Activity Hydroprene: Use of an Iron Carbonyl Adduct To Protect an (*E*,*E*)-Dienoate during Homogeneous Tritiation

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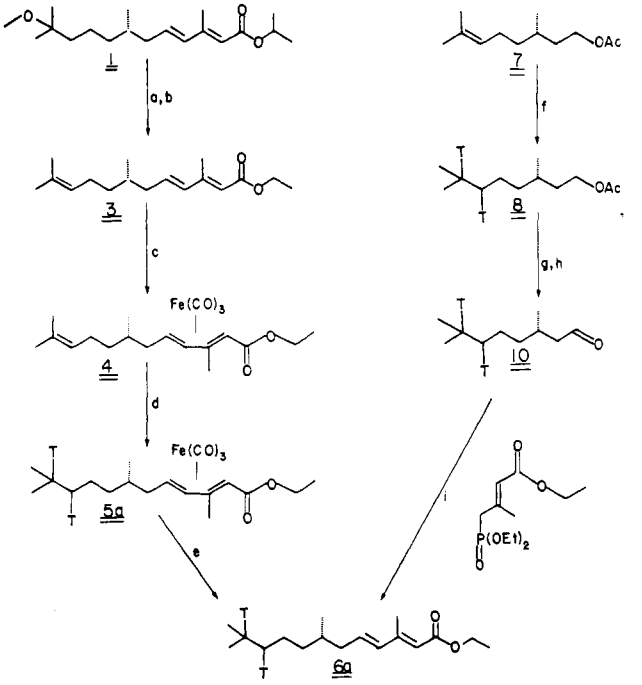
The dodecadienoates, e.g., methoprene (1) and hydroprene (6), are important commercial insect growth regulators related to insect juvenile hormones (JH).[1] Despite the abundant literature on the preparation and testing of over 5000 JH analogues (JHA),[1,2] little is known of the molecular action of these analogues. In order to study macromolecular binding components, synthetic methods are needed for preparing high specific activity radiolabeled juvenile hormones (JH) and juvenile hormone analogues (JHA).[3-5] Following the preparation of the chiral JH homologues[6] and an iodinated (7*S*)-methoprene analogue[7] we turned our attention to the synthesis of high specific activity tritium-labeled (7*S*)-hydroprene, a potent insect growth regulator currently being developed for domestic cockroach control.[8]

Scheme I. Synthesis for (7*S*)-[$^3H_2$]Hydroprene[a]



[a] Reagents: (a) NaOEt, EtOH, 20 °C, 15 h (87%); (b) concentrated H_2SO_4, hexane, 20 °C, 18 h (89%); (c) $Fe_3(CO)_{12}$, benzene, 85 °C, 6.5 h, (85%); (d) $Rh[(C_6H_5)_3P]_3Cl$, $^3H_2$, benzene, 20 °C, 15 h, (93%); (e) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, 0 °C, 4 h; (f) 10% Pd/C, EtOAc, $^3H_2$, 20 °C, 1 h; (g) 3 N NaOH, MeOH, 20 °C, 4 h; (h) PDC CH_2Cl_2, 20 °C, 4 h; (i) $EtOC(O)CH{=}C(CH_3)CH_2P(O)(OEt)_2$, NaOEt, DMF, 20 °C, 1.5 h.

Selective hydrogenation of one double bond in a polyene is crucial for preparing stoichiometrically and specifically tritium-(or deuterium-)labeled substances. When trienoates containing the (2*E*,4*E*)-dienoate unit and a third olefinic bond in the terminal 10,11- or the internal 8,9-position were hydrogenated with tris(triphenylphosphine)rhodium chloride, 5% Pt/C, or 10% Pd/C catalysts, however, hydrogenation of the Δ^4 bond of the dienoate was competitive with reduction of the nonconjugated olefinic bond.[17] In order to hydrogenate (or tritiate) an isolated olefinic bond selectively in the presence of a dienoate, a protecting group for the dienoate was needed that could be easily attached and removed without alteration of the 2*E*,4*E* stereochemistry of the dienoate. Iron tricarbonyl is one such protecting group and has been used previously to protect a B ring $\Delta^{5,7}$ diene during the hydrogenation of a side chain Δ^{22} double bond in a steroid.[9] We report the application of this methodology to protect a (2*E*,4*E*)-dienoate during a remote hydrogenation or tritiation using a homogeneous catalyst. The iron tricarbonyl complex also prevented isomerization of the dienoate. We also report that a more traditional route to the tritiated dienoate is inferior in yield and stereochemical purity to the dienoate protection procedure.

The iron carbonyl complex was synthesized in two steps from (7*S*)-methoprene. Methoprene was converted to the ethyl ester 2 (87%) with sodium ethoxide in ethanol, and sulfuric acid mediated elimination of methanol in a bi-

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