3-o-Carboranylcarbenes[1,2]

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Abstract: An investigation of the reactions of three boron-substituted carbenes with alkenes and alkanes uncovers substantial triplet reactivity. The triplet reveals itself not through addition or insertion reactions, but by abstraction to give a radical that abstracts again to give, ultimately, methyl-o-carboranes.

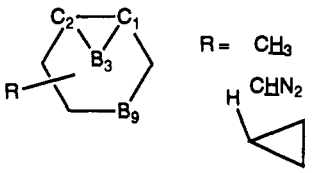
One theme in the exploration of carbene chemistry over the last three decades has been the differentiation of singlet and triplet reactions. Singlets add stereospecifically to alkenes in a concerted, if not symmetrical, process, insert into carbon–hydrogen bonds in a single step, and are little affected by added oxygen. Triplet chemistry is characterized by two-step reactions in which an intermediate separates starting material and products. Formation of the second bond follows creation of the first. In addition reactions this is revealed by loss of the stereochemical relationships present in the starting alkene. In formal insertion reactions the presence of radical intermediates can often be detected. Radical scavengers such as oxygen and, sometimes, dienes are effective at removing triplets.[3] Mechanistic analysis is often complicated by interconversion of singlets and triplets. In order to understand any carbene reaction, even qualitatively, it is necessary to take account of the potential interconversion of singlets and triplets (k_1 and k_{-1}) as well as the relative rate constants of singlet and triplet reactions (k_s and k_t). Often, reactions of ground-state triplets are not detectable because of the generally far greater rates of singlet reactions.

A second theme in carbene chemistry has been the effect of substituents on the mix of singlet and triplet reactions. Most attention has been paid to the rich chemistry of singlet and triplet arylcarbenes[4] and to the effects of halogen substitution. In the arylcarbenes, reactions of both singlets and triplets have been uncovered. Indeed, it was almost 30 years ago that fluorenylidene was used to reveal for the first time the reactions of well-characterized singlet and triplet states of the *same* carbene.[5]

Generally, halogen, oxygen, or nitrogen substitution preferentially stabilizes singlets, as electrons are shared between a filled p orbital on the heteroatom and the empty 2p orbital on carbon.[6] For example, the chemistry of the dihalocarbenes is completely dominated by the singlet state.[3]

Almost no experimental attention has been paid to the other side of the periodic table where relatively electropositive elements dwell and where empty orbitals tend to be more prominent than filled ones. However, theoretical work gives us an idea of what to expect. For an atom such as boron, the presence of an empty p orbital should stabilize the singlet state through overlap with the filled orbital of the divalent carbon. In this case, however, there is a compensating effect stabilizing the triplet state. This operates through the σ system and depends upon the electronegativity difference between the two atoms. The effect is to donate electrons through the σ system, and for atoms less electronegative than carbon[7] it favors the triplet state. Thus, for a simple boron-substituted carbene such as $HCBH_2$, there should be compensating effects stabilizing both the singlet and triplet states. Calculations bear this out, with the most recent efforts (MP4/6-311G** at the geometry of 6/31G*) predicting the two spin states to be close in energy, with the singlet state the ground state by about 6 kcal/mol.[8]

Table I. Some ^{1}H NMR Chemical Shifts (δ, $CHCl_3$)



R position		
C_1	B_3	B_9
2.04	0.56	0.30
4.38	3.15	
1.36	ca. −0.7	

We have developed a route to boron-substituted carbenes through manipulations of substituted o-carboranes. Although this does yield a carbene adjacent to a boron atom, it must be emphasized that this is no ordinary boron. In particular, the empty 2p orbital, so influential in the chemistry of "normal" trisubstituted boranes, is largely absent as it is occupied in the web of three-center, two-electron bonding making up the icosahedral cage. Although the singlet-stabilizing π effect seems likely to be largely absent in a carboranylcarbene, the triplet-stabilizing σ effect remains. In addition, there appears to be substantial electron density at the B_3 position, and this should especially favor the triplet. A variety of ^{1}H NMR chemical shift comparisons demonstrates the extra shielding provided by B_3 (Table I). The B_9 position is especially shielded and should be even more effective at triplet stabilization.

Thus, our preliminary expectation was that a boron-substituted carboranylcarbene might show enhanced triplet reactivity, as the triplet should be especially favored. We report here addition and insertion reactions of the first boron-substituted carbenes, 3-o-carboranylcarbene (**2**), (1,2-dimethyl-3-o-carboranyl)carbene (**3**), and (1-methyl-3-o-carboranyl)carbene (**4**), as well as newly analyzed reactions of 1-o-carboranylcarbene (**1**).[2,9]

The new carbenes are generated by the traditional route: photolysis of a diazo compound. The diazo compounds are made from the tosylhydrazone salts, themselves available through the route shown. A set of 3-vinyl-o-carboranes **6a–c** was made by insertion of a vinyl-substituted boron into $Li_2B_9C_2H_{11}$ or a methylated derivative.[10] Further methylation (if needed) and

(1) Support for this work by the National Science Foundation through Grant CHE-9024996 is gratefully acknowledged.

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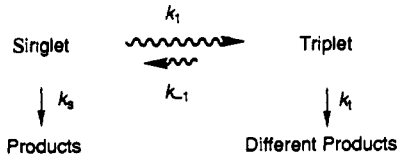

Figure 1.

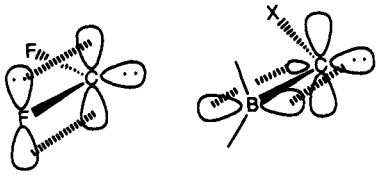

Figure 2.

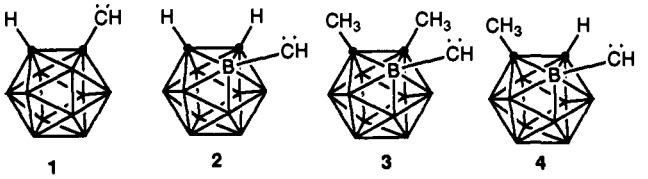

Figure 3. In this and all following drawings the dots represent carbon atoms. All other vertices are borons, and there is a hydrogen on every unencumbered vertex. The labeled boron is the 3 position.

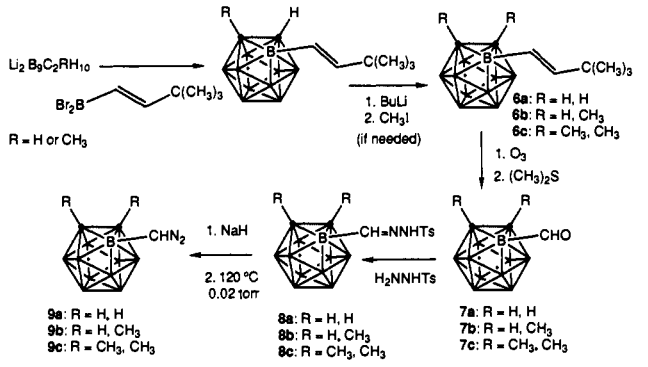

Figure 4.

ozonolysis led to **7**, and reaction with tosylhydrazine gave **8**. Heating the sodium salts of the tosylhydrazones under vacuum (120 °C/0.02 Torr) gave the diazo compounds **9** in about 80% yield. The diazo compounds appear stable, but should be treated with caution in view of the possible explosion hazard.

A traditional test of singlet vs triplet reactivity has been the stereochemistry of additions to alkenes.[3] Singlets add in a single step to preserve the stereochemical relationships present in the starting alkenes in the product cyclopropanes. Triplets also give cyclopropane products, but only after the formation of intermediate diradicals in which the stereochemical relationships present in the starting alkene are lost through rotations about carbon–carbon single bonds. Table II compares the stereochemistry of addition of **1**,[9] **2**, and **3** to *cis*- and *trans*-2-butene. The identity of the trans adduct can be determined by the appearance of two methyl signals in the ^{1}H NMR spectrum. As in the earlier reactions of **1**, the *cis,syn*-cyclopropane was distinguished from the cis,anti compound by its larger coupling constant J_{ab} (Table II). All cis,syn compounds had coupling constants of 10–11 Hz, whereas the coupling constants for the cis,anti compounds were much smaller, J_{ab} = 5–6 Hz.[11]

It is the results of addition to *cis*-2-butene that are the most revealing. *trans*-2-Butene is likely to give overwhelming amounts of trans adduct no matter what the mechanism, but a stepwise addition to the cis isomer should lead to substantial amounts of

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Table II. Cyclopropanes Formed in the Reactions of **1–3** with Alkenes

	R = carborane			% triplet reaction
2 +	–	–	100	0
2 +	74	24	2	3
3 +	9	–	91	22
3 +	63	25	12	18
1 +	4	–	96	10
1 +	84	16	0	0

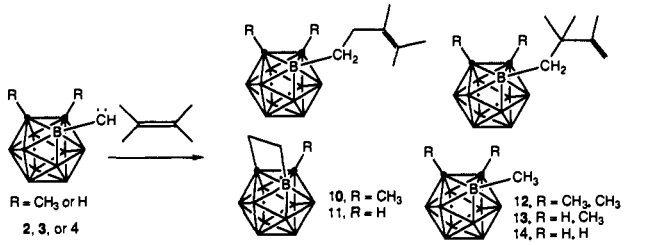

Figure 5.

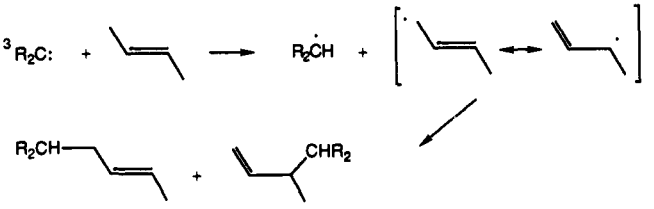

Figure 6.

the more stable trans adduct. The mechanistic importance of the relatively small amounts of *trans*-cyclopropanes formed is magnified by the "invisible" cis components formed by closure of the putative diradical involved in the reaction. For every molecule of trans adduct formed from the triplet there must be some cis as well, lost in the sea of *cis*-cyclopropane formed from stereospecific addition of the singlet. The last column of Table II is only approximate and is calculated on the assumption that the thermodynamic preference for trans adduct over cis is about 60/40, as it is for other known examples.[5] Although only small amounts of triplet are involved in any of the cycloaddition reactions, there seems to be more reactive triplet **3** than **2**. This is surely reasonable given the additional interference in two-bond-forming reactions (singlets) of the pair of methyl groups. One-bond-forming reactions (triplets), taking place at the periphery of the molecule, will have an advantage for sterically congested carbenes, and this seems to be expressed here.

The reactions of carbenes **2–4** with alkenes lead to products other than cyclopropanes. Intermolecular carbon–hydrogen insertions lead to alkenes and intramolecular insertion to the "cyclobutanes" **10** or **11**. Substantial amounts of 3-methyl-*o*-carboranes (**12–14**) are formed as well.

One might hope to evaluate the contribution of triplet carbene in the insertion reaction by determining the amount of isomerized products in the intermolecular insertion reaction. Triplet carbene should react by hydrogen atom abstraction, and this should lead to the isolation of isomerized insertion product.

Table III. Products from Carbenes 1–4

	Alkene	Total allylic insertion	Total cyclopropanes	10 or 11	B_3-methyl- (12, 13, or 14) or *C-methyl-*o*-carboranes
R = R = CH_3 **3**		36	44	4	15
		40	33	4	23
		38	25	8	29
R = R = H **2**		28	50	–	19
		41	36	–	23
		48	16	–	36
R = H, R = CH_3 **4**		49	18	3	31
1		8	84	–	8
		7	87	–	6
		27	67	–	6

Unfortunately, the compounds formed by allylic insertion are not stable, and they isomerize to give the products of allylic rearrangement. Even though the amounts of observed isomerized materials correlate rather well with the small amounts of the "wrong" stereoisomer obtained in cycloaddition reactions, these data are not reliable. Table III gives the relative amounts of total intermolecular insertion products, products of intramolecular insertion, (**10** or **11**), and methyl compounds **12–14** for B-substituted carbenes **2–4** as well as for the C-substituted carbene **1**.

It appears as though cyclopropane formation is favored by easy access to the alkene. That is, *cis*-2-butene, in which one side of the alkene is unguarded by methyl groups, gives the most cyclopropane, and tetramethylethylene, in which the maximum methyl shielding exists, gives the least.

As we could not use the products of allylic rearrangement as a diagnostic for triplet carbene reaction, we undertook a labeling experiment. We appropriated, with neither permission nor apology, the classic experiment of Doering and Prinzbach, who in 1962 had the daring to irradiate diazomethane in ^{14}C-labeled isobutene in the absence of solvent.[12] From this work they determined that allylic insertion took place without rearrangement, in a direct process involving no intermediates. Today, we would take this to be diagnostic for the singlet nature of reacting methylene.

Deuterium-labeled isobutylene was used as a substrate for carbene **2**. The triplet should reveal itself through the appearance of protons in the terminal methylene position of the "insertion products" **15** and **16**. Analysis of the crude products by ^1H NMR spectroscopy showed only small amounts of protium in the position of absorption of the terminal methylenes of **16** (δ 4.74 ppm, 5–10% formation of **16**). Provided that a radical recombination mechanism would give equal amounts of **15** and **16**, this corresponds to 10–20% triplet activity and is consistent with our estimates of the amount of triplet in the cyclopropane-forming addition reaction (Table II). Although it was not possible to make an accurate quantitative determination of the amount of triplet participation in allylic insertion, clearly the insertion product was overwhelmingly **15**, the isomer derived from the singlet, not **16**, the isomer

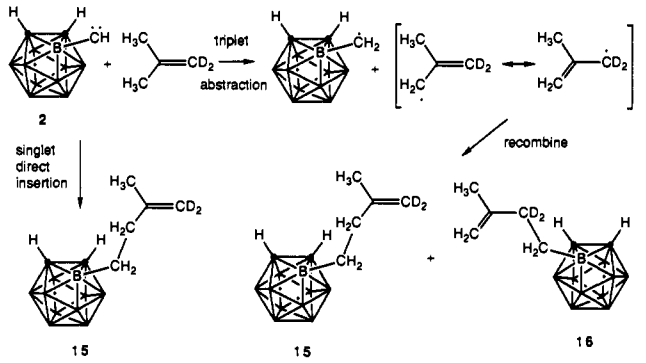

Figure 7.

Table IV. Effect of Oxygen on the Product Ratio from Carbene 3[a]

	10	12					
no oxygen	11	25	28	11	5	4	15
in oxygen	7	32	37	21	<1	2	trace

[a] R = carborane.

Table V. Singlet and Triplet Reactivity for Carbenes 1–4

carbene	alkene	% triplet[a]	% singlet[b]
1	*cis*-2-butene	8	92
	trans-2-butene	16	84
	2,3-dimethyl-2-butene	>6	
2	*cis*-2-butene	22	78
	trans-2-butene	23	77
	2,3-dimethyl-2-butene	>36	<64
3	*cis*-2-butene	33	67
	trans-2-butene	38	62
	2,3-dimethyl-2-butene	>29	<71
4	2,3-dimethyl-2-butene	>31	<69

[a] "Wrong" cyclopropane plus some "right" cyclopropane, plus methyl compound. [b] "Right" cyclopropane plus allylic insertion, plus self-insertion.

diagnostic for the triplet. The reason seems to be that carboranyl radicals prefer abstraction of a second hydrogen to recombination. Methyl compounds **12–14** are substantial products of the reactions of carboranylcarbenes with alkenes (Table III). Compound **14** also appears in 15% yield in the reaction of isobutylene with **2**. It seems safe to assign the origin of most of the insertion products to the singlet.

To summarize what we know at this point: It appears that the boron-substituted carbenes **2–4** give cyclopropanes and insertion products largely through their singlet states. Table III reveals no great difference between these intermediates and **1**, the carbon-attached carbene. What, then, of our expectation of increased triplet reaction? Where is the triplet? The answer seems to be, "In the methyl groups of **12–14**." These compounds must arise by a double abstraction reaction and are most reasonably attributed to the triplet. In order to test this notion and to verify our mental separation of products into those formed from singlet (cyclopropanes of retained stereochemistry and most insertion products) and triplet products ("wrong" cyclopropanes, plus an estimated portion of the other cyclopropanes, and methyl compounds), we have repeated the reaction of **3** with *cis*-2-butene in an atmosphere of oxygen. Oxygen is a known trap for triplets[13] and should reduce or eliminate compounds that owe their origin to a triplet reaction. Table IV shows the products of the reaction of **3** with *cis*-2-butene in the absence and presence of oxygen.

As predicted, the products attributed to triplet carbene, the *trans*-cyclopropane and methyl compound **12**, are greatly diminished. In their place are found *o*-carborane-3-carboxaldehyde,

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(13) Morgan, S.; Platz, M. S.; Jones, M., Jr.; Myers, D. R. *J. Org. Chem.* **1991**, *56*, 1351.

Table VI. Carbon–Hydrogen Insertion into Alkanes

Alkane	Primary 1°	Secondary 2°	Tertiary 3°	2°/1° per H	3°/1° per H	10 or 11	12, 13, or 14
R = R = CH_3 (3)	43	40	–	1.5	–	4	10
	64	–	15	–	1.5	3	9
R = R = H (2)	43	41	–	1.5	–	–	11
	68	–	16	–	1.4	–	10
R = H, R = CH_3 (4)	58	–	16	–	1.5	3	13
(1)				3.0[9a]			

o-carborane-3-carboxylic acid, and 3-*o*-carboranyl formate (not shown in Table IV). The 3-aldehyde is the expected product of oxidation of the triplet carbene, and the other two compounds are known to derive from overoxidation of the aldehyde.[14] We now feel it justified to provide a new estimate of the amount of triplet reactivity present in the reactions of carbenes **1–4** with *cis*- and *trans*-2-butenes (Table V). The remaining uncertainties are the amount of triplet reactivity to assign to the allylic insertion reaction and the amount (if any) to which triplet participates in the self-insertion reaction to give **10** and **11**. These will add only very small corrections to the numbers of Table V, which assumes that the insertion products, like the cyclopropanes, are mainly derived from the singlet carbene. Carbenes **2–4** show substantially more triplet reactivity than does **1**.

Alkanes also react with **2–4** through intermolecular carbon–hydrogen insertion. Table VI shows the products of insertion of the three carbenes into the various carbon–hydrogen bonds of butane and 2,3-dimethylbutane, the other products formed, and the secondary/primary (2°/1°) and tertiary/primary (3°/1°) ratios. The relative rates of insertion seem unremarkable. They are consistent with a predominately singlet process, as occurs in allylic insertion. Note, however, that there must be some incursion of triplet reaction contributing to the numbers of Table VI. The boron-substituted carbenes are less selective than the carbon-substituted carbene **1** and simple arylcarbenes. For example, phenylcarbene show a secondary/primary ratio of about 8.3.[15]

We have used an analysis of the reaction of **2** with cyclohexane and dodecadeuteriocyclohexane[16] to verify the notion that most, but not all, insertion product comes from singlet carbene and to provide an estimate for the isotope effect for the singlet insertion reaction. Carbene **2** was first generated from irradiation of the diazo compound in both pure cyclohexane and dodecadeuteriocyclohexane to produce insertion products **17** and **18** in about 45% yield. In a third experiment, **2** was allowed to react with a 1/1 mixture of cyclohexane and dodecadeuteriocyclohexane. The presumption in this experiment was that triplet **2** would be revealed through formation of "cross products" **19** and **20** formed from recombination of radicals produced by hydrogen and deuterium

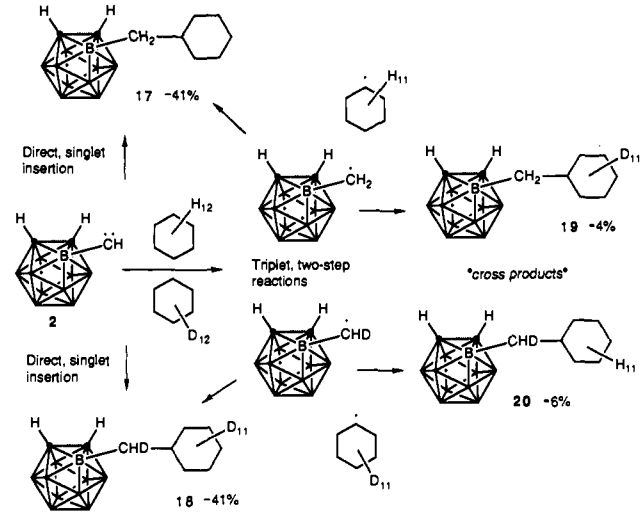

Figure 8.

abstraction. In all of these experiments about 8% of the 3-methyl-*o*-carborane was formed in addition to the insertion products. This is somewhat less than appears in the reactions with alkenes (Table III). Presumably, this reflects the relative difficulty of abstraction from a non-allylic methylene group.

Adducts **17** and **18** were well separated by gas chromatography, but the cross products **19** and **20** differ by only a single deuterium from **17** and **18** and could not be separated. Analysis of mass spectra showed that within the peak for **17** there was about 5% of a product with an extra deuterium (presumably **20**) and that within the peak for **18** was 5% of a compound with one less deuterium (presumably **19**). This analysis shows that triplet abstraction can account for only about 10% of the overall insertion reaction.

When the reaction with the mixture of cyclohexanes was run in the presence of oxygen, a scavenger likely to remove all, or almost all, of the radicals formed by triplet reactions, the ratio of **17** and **18** changed from 1/1 to 1.2/1. This provides a measure of the isotope effect ($k_H/k_D \approx 1.2$) for the singlet insertion reaction of **2** with cyclohexane. Isotope effects for the insertion reactions of singlet phenylcarbene, 1-naphthylcarbene, and fluorenylidene are higher than this value, clustering close to 2.[16] Both the isotope effect data and the selectivity data of Table VI show **2** to be more reactive (less selective) than "normal" two-dimensional arylcarbenes.

To summarize, addition of boron-substituted carbenes **2** and **3** to alkenes is largely stereospecific, showing that the singlet state is more reactive than the triplet in the cyclopropanation reaction. Similarly, the carbon–hydrogen insertion reactions with alkenes and alkanes are shown to be largely the result of a singlet carbene reaction. The substantial amount of triplet **2** and **3** is revealed through the formation of methyl-*o*-carboranes, produced through abstraction by the triplet to give a radical that does not recombine with its partner radical, but instead abstracts again. It is not yet clear why these radicals behave in this way. We hope to investigate their properties directly, but suggest for the moment that, as they are not likely to be stabilized by delocalization, they are relatively reactive species, likely to abstract hydrogen from solvent quite rapidly.

Experimental Section

General Remarks. ^1H and ^{13}C NMR spectra were recorded on a General Electric QE 300 spectrometer at 300 and 75.0 MHz, respectively, with signals referenced to Me_4Si, using $CDCl_3$ as solvent. Infrared spectra were recorded on a Nicolet 730 FT-IR spectrometer. Precise masses were measured on a KRATOS MS 50 RFA high-resolution mass spectrometer. Analytical gas chromatography (AGC) was performed on a Hewlett-Packard 5890A gas chromatograph (60 m × 0.75 mm × 1.0 mm SPB-1 glass capillary column; carrier gas, helium). GC/MS was performed on a Hewlett-Packard GC-5890/MSD-5971 instrument (12 m OV-101 capillary column; carrier gas, helium). Preparative gas chromatography (PGC) was performed on a GOW-MAC GC 580 in-

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(15) For a summary, see: Moss, R. A.; Jones, M., Jr. *Carbenes*; Wiley: New York, 1973; Vol. 1, pp 65–66.
(16) Barcus, R. L.; Hadel, L. M.; Johnston, L. J.; Platz, M. S.; Savino, T. G.; Scaiano, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3928. Baer, T. A.; Gutsche, C. D. *J. Am. Chem. Soc.* **1971**, *93*, 954. Savino, T. G.; Kanakarajan, K.; Platz, M. S. *J. Org. Chem.* **1986**, *51*, 1305.

strument (6 ft × 1/4 in. stainless steel column packed with 10% OV-101 on Chromosorb W-HP 80-100; carrier gas, helium). Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and were not corrected. Elemental analyses were performed by Robertson Laboratories, Inc., Madison, NJ.

In general, reactions were run under an argon atmosphere. The reaction systems were kept as dry as possible, and all solvents were purified and dried by standard procedures.

(1*E*)-(3,3-Dimethyl-1-buten-1-yl)dibromoborane Dimethyl Sulfide. Brown's procedure[17] was followed exactly. To a solution of 4.2 g (51 mmol) of 3,3-dimethylbutyne in 15 mL of CH_2Cl_2 maintained at 10–15 °C was added dropwise a solution containing 6.4 mL (50 mmol) of $HBBr_2{\cdot}SMe_2$ in 10 mL of CH_2Cl_2. After completion of the addition of the $HBBr_2{\cdot}SMe_2$ solution, the cold bath was removed, and the reaction was warmed to room temperature and then stirred for 1 h. The solvent was removed under vacuum to give the crude product, which was used for the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 6.21 (d, 1H), 5.53 (d, 1 H), 2.35 (s, 6 H), 1.05 (s, 9 H).

3-(3′,3′-Dimethylbutenyl)-*o*-carborane (6a). To the flask containing ether and $(B_9C_2H_{11})^{2-}$, made from 8.7 g (45 mmol) of $[Me_3NH][B_9C_2H_{12}]$,[10] was added dropwise the borane made above in 80 mL of dimethyl sulfide. The reaction was kept at 0 °C during the addition. After the addition was finished, the reaction mixture was stirred at 40 °C for an additional 12 h. Then the reaction mixture was cooled to room temperature and quenched with 10 mL of water. The organic layer was then washed with 5% aqueous NaOH (3 × 10 mL) followed by water (2 × 10 mL) and dried over $MgSO_4$. After filtration the solvent was removed under vacuum. The crude product was chromatographed (silica gel/hexanes) to produce 8.3 g of a waxy solid (81% yield): mp 35–40 °C; ^{1}H NMR ($CDCl_3$) δ 6.23 (d, 1 H), 5.46 (d, 1 H), 3.48 (br s, 2 H), 1.01 (s, 9 H), 3.10–1.10 (m, 9 cage H); ^{13}C NMR ($CDCl_3$) δ 159.9 (d), 57.2 (d, 2C), 35.5 (s), 29.6 (q, 3C); IR ($CHCl_3$) 3088 (w), 2961 (m), 2594 (s), 1631 (w) cm^{-1}; MS 228 (46), 227 (95), 226 (M^+, 97), 210 (100), 209 (99), 194 (56), 180 (32); HRMS calcd for $^{11}B_8{}^{10}B_2C_8H_{22}$ 226.2725, found 226.2743. Anal. Calcd for $B_{10}C_8H_{22}$: C, 42.48; H, 9.73. Found: C, 42.57; H, 9.61.

1-Methyl-3-(3′,3′-dimethylbutenyl)-*o*-carborane (6b) was made from the treatment of $(B_9C_3H_{13})^{2-}$ (itself made from $[Me_3NH][B_9C_3H_{14}]$ generated from 1-methyl-*o*-carborane) with the borane made above in 87.7% yield (75% overall yield from 1-methyl-*o*-carborane): ^{1}H NMR ($CDCl_3$) δ 6.29 (d, 1 H), 5.42 (d, 1 H), 3.33 (br s, 1 H), 1.87 (s, 3 H), 1.05 (s, 9 H), 3.10–1.10 (m, 9 cage H); IR ($CHCl_3$) 3090 (w), 2958 (m), 2590 (s), 1635 (w) cm^{-1}; MS 242 (41), 241 (91), 240 (M^+, 100), 223 (87), 208 (50). Anal. Calcd for $B_{10}C_9H_{24}$: C, 46.96; H, 10.43. Found: C, 47.02; H, 10.34.

1,2-Dimethyl-3-(3′,3′-dimethylbutenyl)-*o*-carborane (6c). To a solution of 5.6 g (50 mmol) of **6b** in 15 mL of anhydrous ether at 0 °C was added 42 mL (105 mmol) of 2.5 M BuLi in hexane. When the addition was complete, the reaction mixture was stirred at 40 °C for 1 h and then cooled to room temperature. A solution of 15.0 g (105 mmol) of MeI in 15 mL of ether was added dropwise. The reaction mixture was then stirred at 40 °C for an additional 2 h. The reaction mixture was washed with 3 × 10 mL of 3% aqueous HCl followed by water (2 × 10 mL) and dried over $MgSO_4$. Analytically pure product was obtained in almost 100% yield after the solvent was removed under vacuum: ^{1}H NMR ($CDCl_3$) δ 6.36 (d, 1 H), 5.24 (d, 1 H), 3.10–1.10 (m, 9 cage H), 1.81 (s, 6 H), 1.06 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 162.5 (d), 73.0 (s, 2 C), 35.8 (s), 29.7 (q, 3 C), 21.3 (q, 2 C); IR ($CHCl_3$) 2960 (m), 2582 (s), 1626 (w) cm^{-1}; MS 256 (52), 255 (97), 254 (M^+, 100), 238 (85), 237 (87), 222 (41); HRMS calcd for $^{11}B_8{}^{10}B_2C_{10}H_{26}$ 254.3038, found 254.3051.

1,2-Dimethyl-3-formyl-*o*-carborane (7c).[18] A solution of 5.1 g (20 mmol) of **6c** in 100 mL of dry CH_2Cl_2 was placed in a three-necked flask equipped with a gas inlet and outlet. The solution was stirred at −78 °C in a dry ice–ethanol bath during the whole reaction period. Ozonized oxygen (0.5 L/min), generated with a Welsbach ozonizer operated at 100 W with an inlet pressure of 5 psi, was bubbled in for 5 min. The reaction mixture was purged with nitrogen and treated with 10 mL of dimethyl sulfide, added all at once. The mixture was warmed to room temperature and was allowed to stand for 1 h. The solvent was removed under vacuum, and the residue was extracted with 3 × 15 mL of ether, washed with brine (3 × 10 mL), and dried over $MgSO_4$. GC/MS showed a mixture of the aldehyde and the corresponding acid (17/1). The acid was removed by washing the ether solution with 5% NaOH (3 × 10 mL). The ether layer was dried over $MgSO_4$ and the solvent removed under vacuum to yield 3.4 g (86%) of **7c**: ^{1}H NMR (acetone-d_6) δ 3.18 (q, 1 H), 3.05–0.98 (m, 9 cage H), 2.10 (s, 6 H); IR ($CHCl_3$) 2961 (w), 2567 (s), 1679 (m) cm^{-1}; MS 202 (16), 201 (48), 200 (M^+, 94), 199 (100), 198 (61), 172 (41), 171 (50).

1-Methyl-3-formyl-*o*-carborane (7b)[18] was made from **6b** in 82% yield through the same procedure as was used for **7c**: ^{1}H NMR (acetone-d_6) δ 3.51 (s, 1 H), 3.18 (q, 1 H, J = 2–3 Hz), 3.05–0.98 (m, 9 cage H), 2.05 (s, 3 H); IR ($CHCl_3$) 3056 (m), 2961 (w), 2575 (s), 1680 (m) cm^{-1}; MS 188 (9), 187 (44), 186 (M^+, 95), 185 (100), 159 (16), 158 (34), 157 (44).

3-Formyl-*o*-carborane (7a)[18,19] was made from **6a** in 77% yield through the same procedure as was used for **7b** and **7c**: ^{1}H NMR (acetone-d_6) δ 3.46 (s, 2 H), 3.20 (q, 1 H, J = 2–3 Hz), 3.05–0.98 (m, 9 cage H); IR ($CHCl_3$) 3070 (s), 2961 (w), 2597 (s), 1700 (m) cm^{-1}; MS 174 (8), 173 (48), 172 (M^+, 95), 171 (100), 143 (42), 142 (38).

1,2-Dimethyl-3-formyl-*o*-carborane Tosylhydrazone (8c). To a solution of 3.0 g (15 mmol) of **7c** in 75 mL of methanol was added *p*-toluenesulfonohydrazide (3.0 g, 16 mmol). Two drops of concentrated HCl were added, and the reaction mixture was refluxed overnight. Most of the solvent was removed under vacuum. The tosylhydrazone **8c** precipitated (5.0 g, 77%) and was recrystallized from methanol to yield an analytical sample: mp 184–5 °C; ^{1}H NMR (acetone-d_6) δ 10.31 (s, 1 H), 7.53 (q, 4 H), 7.43 (s, 1 H), 3.30–1.05 (m, 9 cage H), 2.40 (s, 3 H), 1.87 (s, 6 H); ^{13}C NMR (acetone-d_6) δ 144.9 (s), 137.1 (s), 130.4 (d, 2 C), 128.6 (d, 2 C), 75.7 (s, 2 C), 21.3 (q), 20.7 (q); IR ($CHCl_3$) 3192 (m), 2582 (s), 1184 (s) cm^{-1}. Anal. Calcd for $B_{10}C_{12}H_{24}O_2N_2S$: C, 39.13; H, 6.52. Found: C, 39.38; H, 6.31.

1-Methyl-3-formyl-*o*-carborane tosylhydrazone (8b) was made in a similar fashion in 78% yield from **7b**: ^{1}H NMR (acetone-d_6) δ 10.34 (s, 1 H), 7.78 (d, 2 H), 7.49 (s, 1 H), 7.39 (d, 2 H), 4.60 (s, 1 H), 3.12–1.03 (m, 9 cage H), 2.40 (s, 3 H), 1.77 (s, 3 H); ^{13}C NMR (acetone-d_6) δ 144.7 (s), 137.1 (s), 130.2 (d, 2 C), 128.5 (d, 2 C), 73.2 (s), 63.5 (d), 23.5 (q), 21.4 (q); IR ($CHCl_3$) 3192 (m), 3070 (m), 2577 (s), 1184 (s) cm^{-1}. Anal. Calcd for $B_{10}C_{11}H_{22}O_2N_2S$: C, 37.29; H, 6.21. Found: C, 37.17; H, 6.16.

3-Formyl-*o*-carborane tosylhydrazone (8a) was made in a similar fashion in 72% yield from **7a**: ^{1}H NMR (acetone-d_6) δ 10.27 (s, 1 H), 7.76 (d, 2 H), 7.46 (s, 1 H), 7.38 (d, 2 H), 4.57 (s, 2 H), 3.09–1.08 (m, 9 cage H), 2.41 (s, 3 H); ^{13}C NMR (acetone-d_6) δ 144.6 (s), 137.1 (s), 129.9 (d, 2 C), 128.1 (d, 2 C), 64.7 (d, 2 C), 21.4 (q); IR ($CHCl_3$) 3192 (m), 3066 (s), 2577 (s), 1184 (s) cm^{-1}. Anal. Calcd for $B_{10}C_{10}H_{20}O_2N_2S$: C, 35.29; H, 5.88. Found: C, 35.33; H, 5.81.

1,2-Dimethyl-3-(diazomethyl)-*o*-carborane (9c). Under an argon atmosphere, sodium hydride, 80% dispersion in oil (16 mg, 0.53 mmol), was placed in a 50-mL flask, washed with dry pentane (2 × 5 mL), and slurried with 5 mL of dry THF. The mixture was then stirred at −78 °C for 5 min before the solution of **8c** (184 mg, 0.5 mmol) in 8 mL of dry THF was added. The cooling bath was removed right after the addition was complete, and the reaction temperature was slowly raised to room temperature over 30 min. The reaction mixture was stirred for an additional 4 h at this temperature. The THF was removed, and the resulting gummy mass was triturated with dry pentane to remove the residual THF. The sodium salt of the tosylhydrazone so obtained was placed in a vacuum dessicator and pumped dry overnight. The crude sodium salt thus obtained was pyrolyzed in the same flask which was attached to a series of bulbs surrounded by dry ice and connected to a vacuum and inert gas source by a valve. The flask was placed in a Kugelrohr oven and evacuated to 0.02 Torr. The oven temperature was raised slowly to 110–120 °C, when decomposition occurred to yield the bright yellow diazo compound **9c** (90 mg, 84%), which condensed in the bulbs and was used in further reactions immediately: ^{1}H NMR ($CDCl_3$) δ 3.02 (s, 1 H), 1.86 (s, 6 H), 3.05–0.85 (m, 9 cage H); IR ($CHCl_3$) 2581 (s), 2082 (s), 1340 (m) cm^{-1}; MS 214 (7), 213 (13), 212 (M^+, 14), 184 (74), 182 (95), 181 (100), 180 (96), 179 (77), 178 (51).

1-Methyl-3-(diazomethyl)-*o*-carborane (9b) was made in the same way from **8b**: ^{1}H NMR ($CDCl_3$) δ 3.31 (s, 1 H), 3.16 (s, 1 H), 2.00 (s, 3 H), 3.05–0.85 (m, 9 cage H); IR ($CHCl_3$) 3057 (s), 2586 (vs), 2080 (vs), 1340 (s) cm^{-1}; MS 200 (7), 199 (15), 198 (M^+, 11), 170 (42), 169 (77), 168 (100), 167 (94), 166 (68).

3-(Diazomethyl)-*o*-carborane (9a) was made in the same way from **8a**: ^{1}H NMR ($CDCl_3$) δ 3.56 (s, 1 H), 3.15 (s, 1 H), 3.05–0.85 (m, 9 cage H); IR ($CHCl_3$) 3067 (s), 2592 (s), 2080 (vs), 1343 (s) cm^{-1}; MS 186 (5), 185 (11), 184 (M^+, 13), 156 (48), 155 (78), 154 (100), 153 (84), 152 (55).

General Procedure for All Photolyses of the Diazo Compounds. The still-frozen diazo compound was washed by the liquid reactants or by condensation of gaseous reactants (butenes) into a Pyrex tube equipped with a T-joint closed by a high-vacuum Teflon stopcock. The reaction mixture containing a large excess of the reactant was degassed by the

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freeze-thaw method and the stopcock closed. The Pyrex tube was now irradiated by a 450-W medium-pressure Hanovia lamp through Pyrex in a water-cooled bath. The diazo compound was completely decomposed in 6 h as seen by the discharge of the yellow color. The tube was cooled and opened, and the excess reactant was removed. The crude products were well separated by the Hewlett-Packard GC/MS, and the data were processed on HP-ChemStation software. Finally, the crude products were chromatographed and collected by using a 6-ft 10% OV-101/Gas-chrom W-HP 80-100 column on the GOW-MAC GC 580 instrument.

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Supplementary Material Available: Table of ^1H NMR, ^{13}C NMR, and IR spectral data and MS and HRMS data for compounds **10-14** and **17**, as well as for all of the addition and insertion products formed from carbenes **2-4** (7 pages). Ordering information is given on any current masthead page.

Synthesis of 3-Deoxy-D-*manno*-2-octulosonic Acid (KDO) and Its Analogs Based on KDO Aldolase-Catalyzed Reactions[1]

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Abstract: 3-Deoxy-D-*manno*-2-octulosonic acid (D-KDO) was synthesized from D-arabinose and pyruvate in 67% yield by using KDO aldolase (EC 4.1.2.23) from *Aureobacterium barkerei* strain KDO-37-2 (ATCC 49977). Studies on the substrate specificity of the enzyme with more than 20 natural and unnatural sugars indicate that this enzyme widely accepts trioses, tetroses, pentoses, and hexoses as substrates, especially the ones with the *R* configuration at the 3 position. The substituent on the 2 position had little effect on the aldol reaction. Nine substrates were submitted to the aldol reaction to prepare the products, including D-KDO, 3-deoxy-D-*arabino*-2-heptulosonic acid (D-DAH), 2-keto-3-deoxy-L-gluconic acid (L-KDG), and 3-deoxy-L-*glycero*-L-*galacto*-nonulosonic acid (L-KDN). It appears that the attack of pyruvate took place on the *re* face of the carbonyl group of acceptor substrates, a facial selection complementary to sialic acid aldolase (*si* face attack) reactions. The aldolase products can be converted to aldoses via radical-mediated decarboxylation. For example, decarboxylation of pentaacetyl-KDO and hexaacetylneuraminic acid gave penta-*O*-acetyl-2-deoxy-β-D-*manno*-heptose and penta-*O*-acetyl-4-acetamido-2,4-dideoxy-β-D-*glycero*-D-*galacto*-octose, respectively.

Introduction

3-Deoxy-D-*manno*-2-octulosonic acid (KDO, **1**) is a vital component of the outer membrane lipopolysaccharide of Gram-negative bacteria.[2] Of many chemical[3] and enzymatic (based on KDO-8 phosphate synthase[4a] or sialic acid aldolase[4b]) syntheses developed so far, the Cornforth's method[3a,b] of chemical aldol reaction of D-arabinose and oxalacetic acid has been considered the most practical. The yield, stereoselectivity, and reproducibility of the reaction, however, are not satisfactory although several improved procedures have been reported.[3e,k] Thus, the enzymatic aldol reaction[5] of pyruvate and D-arabinose and analogs catalyzed by KDO aldolase under nearly neutral and mild conditions may be useful for the synthesis of KDO and analogs.

In lipopolysaccharide biosynthesis, the incorporation of KDO[6] consists of two steps: the formation of CMP-KDO by CMP-KDO synthetase[7] (EC 2.7.7.38) and the subsequent coupling with lipid-A precursor.[8] Since the rate-limiting step is the activation of the KDO moiety,[9] inhibitors of CMP-KDO synthetase are potentially

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