Studies Directed toward the Synthesis of Prostaglandins.
Useful Boron-Mediated Olefin Syntheses

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The reactions of bis(2-ethylcyclopentyl)borane, dicyclopentylborane, with 3-(tert-butyldimethylsiloxy)-1-octyne and subsequent iodine-promoted rearrangement to Z olefins or unsymmetrical acetylenes are reported. Mixed dialkylboranes are also examined in this olefin—acetylene cross process. Significant amounts of thexyl-migrated acetylenic by-products are observed in several instances. The synthesis of either E- or Z-1,2-disubstituted olefins by reaction of boronic esters with both (E)- and (Z)-alkenyllithium reagents is examined. This study demonstrates that 50–70% yields of either E- or Z-1,2-disubstituted olefins are obtainable from the aforementioned reagents. The overall objectives in this investigation are to assess the potential of employing organoborane intermediates in the coupling of the C13–C20 prostaglandin olefinic side chain to cyclopentenoid precursors.

As part of our program directed toward the total synthesis of prostaglandin hormones we recently reported a general stereospecific approach to the synthesis of cis-2-alkyl-2-cyclopentene-1,4-diols (1) via the three-step sequence illustrated below.2 This expeditious synthetic scheme readily affords a variety of functionalized cyclopentene derivatives which should be amenable to further elaboration to various prostanooids and known intermediates in published prostaglandin syntheses.3 Based upon the multitude of cross-coupling reactions that have been developed in recent years which have employed organoboranes,4 we have initiated studies aimed at transforming olefins such as 1 to organoborane intermediates (cf. 2). These intermediates could serve as versatile precursors to elaborated prostanoid intermediates such as 3–5.

Recently, an elegant approach to the synthesis of both E- and Z-1,2-disubstituted olefins from common intermediates has been reported by Zweifel (Scheme I).7 Dialkyloborane–

Scheme I

At the present time it is a rare occurrence when boron-mediated carbon–carbon bond constructions are employed in a multistage organic synthesis. This underutilization of a potentially powerful class of reactions generally is due to the relative inefficiency with which a single carbon ligand on a given boron atom can be coupled to other carbon substrates. Partial solutions to this shortcoming have been provided via the design of boron-bound carbon ligands such as 9-BBN5 and thexyl6 which generally exhibit low migratory aptitudes in organoborane transformations; however, in specific cases even these ligands lead to unwanted side reactions (vide infra). The purpose of this study has been to survey those organoborane cross-coupling processes which could be ultimately applicable to coupling the C13–C20 prostaglandin side chain (cf. 3, 4) to cyclopentene precursors in high efficiency with respect to the cyclopentene moiety.

Boron-Mediated Olefin Synthesis. The application of organoboranes to carbon–carbon bond construction has been extensively studied, and a wide variety of processes are becoming available for carbon skeletal assembly.4 Of particular interest in the present study were those processes which assemble cyclic olefinic and acetylenic moieties to E olefins and internal acetylenes as schematically represented below (cf. 6 and 7).

Stereochemistry
acetylene hydroboration has been shown to readily produce vinylborane intermediates.\(^8\) In situ electrophile-induced (El\(^{+}\)) rearrangements of these species have been postulated to proceed via 11 to either the Z olefin 9 by base-induced trans fragmentation or to the E olefin 10 by thermal cis elimination of the boron and electrophile functions.\(^7\) Both processes have been shown to be highly stereoselective and afford olefins of high (92-99\%) stereochemical purity. Recently Negishi has employed this olefination sequence in the synthesis of the \(\alpha,\beta\)-unsaturated esters 13 and 14 in 91–95\% isomeric purity.\(^8\)

\[
\text{RL} + \text{R} = \text{CIC-R} \rightarrow \text{RL} \rightarrow \text{R-CIC-R}
\]

with the realization that only one of the three carbon ligands on boron can be effectively utilized in the cross-coupling process. Studies directed toward defining practical "nonmigrating" carbon ligands have met with mixed success in the above process.\(^13\)\(^{b,14}\)

In an effort to ascertain whether any or all of the above olefination sequences could be efficiently applied to the elaboration of the C\(_{13}\)–C\(_{20}\) olefinic prostanoid side chain onto cycloalkene derivatives (cf. 1 → 3), the following general studies were undertaken.

**Synthesis of Internal Acetylenes.** The reaction sequence chosen for initial study was the acetylene synthesis illustrated in eq 1.\(^{12,15}\) Following the procedure of Brown and co-workers,\(^20\) reaction of tricyclohexylborane (20) with the lithium acetylide 21 followed by iodine-promoted decomposition of the ate complex 22 afforded acetylene 23 in greater than 65\% yield. The corresponding cyclopentyl acetylene 24 was also produced in comparable yield from tricyclopentylborane.\(^{15}\) These preliminary experiments firmly establish that the tert-butyldimethylsilyloxy function does not interfere with the desired coupling reaction. Extension of this acetylene–olefin cross-coupling to trisubstituted olefins was next examined. Reaction of ethylcyclopentene (3 equiv) with BH\(_3\)-THF (1 equiv)\(^{16}\) followed by successive addition of lithium acetylide 21 (R = SiMe\(_2\)-t-Bu) and iodine afforded the desired acetylene 25 in only 31\% yield. The lower yields encountered in this instance could have been associated with difficulties in the formation of the trialkylborane with this olefin,\(^7\) or due to possible steric factors associated with either formation or rearrangement of the intermediate ate complex.\(^{16}\) Since the penultimate intermediate in the acetylene coupling reaction is the presumed ate complex 27 (X = C-H\(_2\)_3) (Scheme III), various alternate approaches to 27 from the dialkylborane 26a\(^7\) were investi-
In order to avoid competitive ligand migration in the rearrangement of 27, an alkoxyl group was chosen as the nonmigrating ligand in the ate complex. In situ generation of dialkylborane 26a followed by the successive addition of 1-butanol (1 equiv) and lithium acetylide 21 afforded the presumed complex 27b (X = OC₂H₅). Subsequent rearrangement afforded acetylene 25 in only 20% yield (procedure A). An alternate procedure was examined within 27a, produced via the addition of 21 to 26a, was transformed into the alkoxy ate complex 27b (X = OC₂H₅) by reaction with heptanal. However, after stirring the borohydride complex in the presence of 1-heptanal (1 equiv, 0 °C, 1 h), the addition of iodine gave only a 25% yield of acetylene 25 (procedure B). A successful variant of this latter procedure involving initial generation of a borinate ester 26b via reduction of heptanal with 26a followed by the successive addition of 21 and iodine was found to afford the desired coupled acetylene in 72% yield (procedure C). This latter experiment demonstrates that dialkylborinic esters (cf. 26b) can serve as valuable substrates in such acetylene coupling reactions. In addition, the olefin: acetylene stoichiometry has been improved by this modification from 2:1 (Scheme II) to 1:1 (Scheme III) while comparable yields have been maintained. In an effort to achieve cross-coupling stoichiometry of unity for olefinic and acetylene moieties, the mixed dialkylborinic ester 28 was prepared in analogous fashion (cf. Scheme III, procedure C). Reaction of 28 with acetylide 21 and subsequent iodine-induced rearrangement afforded acetylene 25 (34%) and 29 (6%), the latter having been formed as a result of thexyl ligand migration.

**Stereoselective Olefin Synthesis.** Attention was next turned to the application of the Zweifel olefin synthesis (Scheme I) to the construction of the prostanoïd olefin models 30 and 31 (R = H). Hydroboration of acetylene 33 with the dialkylborane derived from 1-ethylcyclopentene (32, R = C₂H₅) afforded the presumed vinyl borane 34 which was rearranged to the Z olefin 31 in 70% yield (Scheme IV). However, the use of thexyl-2-ethylcyclopentylborane (32, R = C₂H₅) in the same reaction sequence resulted in only a 30% yield of olefin 31 which was accompanied by 14% of the olefin obtained via alkyl or alkylboronic ester precursors, might be expected to undergo stereospecific rearrangement to olefinic products in the presence of iodine—base. In this overall olefin construction the final olefin geometry may be defined by the stereochemistry of either the alkenyllithium or vinylboronic ester moieties chosen for the synthesis of the ate complex 36. An important feature of this process is the absence of ligands in the ate complex which can compete with the illustrated boron extrusion process. To test the viability of the illustrated olefin synthesis, vinyl lithium reagents 37b and 38b were prepared from the corresponding iodides 37a and 38a by metal—halogen exchange, and boronic ester 39.

**Stereoselective Olefin Synthesis.** Attention was next turned to the application of the Zweifel olefin synthesis to the specific types of olefin syntheses under discussion, we turned to a study of the potential olefin synthesis illustrated below. Based upon analogy, the boronic ester-derived ate complex 36, readily
the olefination reaction were made when the ate complex
latter explanation. Brown and co-workers have reported a
tion of ate complex
gested that, under the reaction conditions, either the forma-
was treated with iodine in the presence of sodium hydroxide.
vinylborane 34 or its ate complex was
of the alkenyl-boron bond was competing
was noted worthly that "direct iodination" of
significant side reaction, although we have observed 37a as
as well
as vinyl iodide 37a (22%) and olefin 37c (11%). Although these results were encouraging, the presence of vinyl iodide sugges-
ted that, under the reaction conditions, either the forma-
tion of ate complex 40 was not complete or “direct iodination”
of the alkenyl-boron bond was competing directly with the
desired rearrangement. Control experiments implicated the
latter explanation. Brown and co-workers have reported a
related process in the reaction of vinylboronic acids with io-
dine and base.26 It is noteworthy that “direct iodination” of
vinylborane 34 or its ate complex was not observed to be a
significant side reaction, although we have observed 37a as
a minor by-product in this reaction. Minor improvements in
the olefination reaction were made when the ate complex 40
was treated with iodine in the presence of sodium hydroxide.
After a careful study of the iodine-promoted rearrangement
of both 40 and 41, we have found the overall process to be
dramatically solvent dependent. Rearrangement of 40 with
iodine in a methoxide–methanol medium afforded a 75% yield
of desired olefin 31a, accompanied by only 15% of the “direct
iodination” product 37a. GLC analysis of the Z olefin 31a
indicated that the Z:E isomer ratio was greater than 96:4,
indicating that olefins of high geometric purity are accessible
via this route.24
Mechanistically, it was predicted that the E olefin would
result from the iodine-promoted rearrangement of ate com-
plex 41. Indeed, the addition of 1 equiv of boronic ester 39 to
Z vinylolithium reagent 38b generated in ether,26 followed by
iodine-promoted rearrangement in methanol–methoxide
solution, afforded the desired E olefin 30a in 58% yield. The
E:Z olefinic isomer ratio was greater than 99:1 in this instance.
The successful synthesis of 30a via this route, as contrasted
by the failure to obtain the same compound via the cyanogen
bromide rearrangement of vinylborane 34 (Scheme IV), is

![Scheme V](image)

was prepared by analogy to the procedure of Brown (Scheme
V).26 Addition of 1 equiv of boronic ester 39 to a tetrahydro-
furan (THF) solution of E vinylolithium reagent 37b (0 °C)
followed by the addition of iodine (1 equiv) and subsequent
stirring at 25 °C (3 h) afforded the Z olefin 31a (22%) as well

![Scheme V](image)

noteworthy. Other mechanistic points in the olefination se-
quence illustrated in Scheme V are worthy of discussion. Heteroatom-substituted boronate complexes are known to be labile intermediates.26 The potentially serious ligand ex-
change reaction shown below (eq 2) could complicate these
and related boronic ester cross-coupling reactions. Ligand
exchange on 36 which can occur via tricoordinate borane in-

![Scheme V](image)

termediates could lead to alternate ate complex 42. Based
upon the known migratory aptitudes of alkyl and alkynyl li-
gands,7b the presence of 42 would be implicated by the ob-
servation of dienes subsequent to iodine-promoted rear-
rangement. Careful examination of the products of the boronic
ester mediated olefination sequence (Scheme V) revealed that
diene by-products are not significant contaminants. Hence,
the ate complexes 40 and 41 do not undergo ligand exchange
under the stated reaction conditions. With simple procedures
now available for the synthesis of both alkyl and alkynylbo-
ronic esters,27 the results of this study indicate that such or-
ganoboranes will be useful substrates for olefin synthesis.

Conclusion

Over the last several years boron-mediated cross-coupling
reactions which result in the stereospecific synthesis of olefin-
s and acetylenes have been developed by numerous investiga-
tors. The major limitations of these synthetic methods relate
to the overall cross-coupling stoichiometry. The present study
has sought to solve some of the inherent problems associated
with these highly useful bond construction reactions. In par-
ticular, the use of boronic esters in hydrocarbon coupling re-
actions shows considerable promise. The application of the
chemistry detailed herein to the synthesis of prostaglandin
hormones will be detailed elsewhere.

Experimental Section

Materials. THF and ether were dried by distillation under nitrogen
from lithium aluminum hydride or benzophenone ketyl. Dry methanol
was anhydrous reagent or spectral grade and was stored over 3
molecular sieves. Alkylolithium reagents were purchased from Ventron
as solutions in n-hexane or cyclohexane, and were standardized by
the procedure of Gilman.28

Procedure. GLC analyses were run on a Varian Aerograph Model
1400 gas chromatograph equipped with a flame ionization detector
using a 6 ft by 0.125 in. stainless steel column of 10% SE-52 or Carboxax
20M on 60–80 mesh acid-washed dimethyldichlorosilanized Chro-
mosorb W. Preparative GLC was carried out using a Varian Aerograph
Model 90-F gas chromatograph. Detector response calibrations were
determined by comparison of the peak areas (measured by triangu-
lation) of the compound and standard at a variety of weight ratios.
Infrared spectra were recorded using a Perkin-Elmer Model 700 or
a Beckman IR 4210 spectrophotometer. Proton magnetic resonance
spectra were recorded on a Varian Associates Model T-60, A-80, or
A-90D spectrometer. Chemical shifts are reported in parts per million
on the δ scale relative to tetramethylsiline internal standard or
chloroform internal standard for silicon-containing compounds. Data
are reported as follows: chemical shift, multiplicity (s = singlet, d =
doublet, t = triplet, q = quartet, m = multiplet), integration, coupling
constants, and interpretation.
Synthesis of Prostaglandins


3-[(trans-Butylidimethylsiloxy)-1-octyne (33). To a dry 100-ml flask containing 15 ml of dry DMF was added 0.69 g (55.5 mmol) of 1-octyn-3-01, 8.2 g (61 mmol) of tert-butylidimethylchlorosilane, and 9.4 g (139 mmol) of imidazole (freshly sublimed). The reaction mixture was stirred under nitrogen for 36 h. Hexane (150 ml) was added, and the mixture was stirred for five times of octyne (Na2SO4). Removal of the solvent and molecular distillation of the remaining liquid at 45 °C (12 mmHg) afforded 12.34 g (61.4 mmol, 92%) of acetylene 33. Analytically pure material was obtained by a second molecular distillation of the above liquid: ir (neat) 3280 cm⁻¹; NMR (CDCl₃) 0.13 (d, 6, CH₃Si), 0.93 (s, 12, -CH₃), 1.12–1.92 (m, 8), 2.35 (d, 1, -CH₂), 4.34 (m, 1, -CHO-).

Anal. Caled for C₁₀H₂₀O: C, 62.01; H, 12.03.

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Calcd for C₁₀H₂₀O: C, 62.01; H, 12.03.
1-(trans-2-Ethylcyclopentenyl)-3-(tert-butyl(dimethyl)silyloxy)-(Z)-1-octene (31) from Boronic Ester 39. To a solution of 388 mg (1.05 mmol) of (E)-1-iodo-3-(tert-butyl(dimethyl)silyloxy)-1-octene (37a) in 6 ml of dry THF, cooled to −78 °C under argon in a 25-ml pear-shaped flask, was added 3.13 ml (21.0 mmol) of a 0.66 M solution of sodium in hexane. The reaction mixture was stirred for 1 h at −78 °C and then brought to 0 °C. Boronic ester 39 (0.204 ml, 1.08 mmol) was added to 37b and the solution stirred for 10 min at 0 °C. To the reaction mixture was added a solution of 3.15 mmol of sodium methoxide in 1 ml of methanol, and a solution of 1.53 g (5.25 mmol) of triethylamine was added over 20 min. The reaction mixture was stirred for 3 h at room temperature and diluted with 200 ml of ether. The mixture was washed with 5% sodium thiosulfate solution, H2O, 5% sodium hydroxide solution with −10% hydrogen peroxide, and brine. The ether layer was dried (Na2SO4) and filtered, and solvent removed in vacuo to yield 100 mg (0.34 mmol, 45%) of alcohol 30b. Molecular distillation at 100 °C for 3 h at room temperature and the bulk of the methanol was removed in vacuo.

Analysis by GLC (5% SE-52, 100-250 °C at 6 °C/min) showed the presence of olefin 30a (51%) and vinyl iodide 38a (-15%). The product was chromatographed on 100 g of silica gel with petroleum ether cooled to −78 °C under argon in a 25-ml pear-shaped flask was added 3.18 ml (2.10 mmol) of a 0.66 M solution of 1.2 M borane in THF solution. The reaction mixture was stirred for 1 h at −78 °C and 0.096 mmol (0.15%) of 1-(trans-2-Ethylcyclopentyl)-(E)-1-octen-3-ol (31b) was added, and analysis by GLC (5% SE-52, 100-250 °C at 6 °C/min) showed the presence of olefin 30a (51%) and vinyl iodide 38a (-15%). The product was chromatographed on 100 g of silica gel with petroleum ether to give 73.5 mg of colorless oil. A portion of this material was purified by medium-pressure liquid chromatography on 100 g of preparative TLC grade silica gel, eluting with petroleum ether, to give pure olefin 31.

1-(trans-2-Ethylcyclopentenyl)-(tetrahydropyran-2-yl)oxo)-(E)-1-octene (30a). To a solution of 168 mg (0.497 mmol) of (Z)-1-iodo-3-(tetrahydropyran-2-yl)oxo)-1-octene (38a)20 in 5 ml of ether cooled to −78 °C under argon in a 25-ml pear-shaped flask was added 0.89 ml (0.984 mmol) of a 1.2 M solution of sodium in hexane. The reaction mixture was stirred for 1 h at −78 °C and then 0.60 ml (0.497 mmol) of boronic ester 39 was added. The reaction mixture was stirred for 10 min at −78 °C and 10 min at 0 °C. To the reaction mixture was added a solution of 1.49 mmol of sodium methoxide in 1 ml of methanol and a solution of 630 mg (2.48 mmol) of iodine in 15 ml of methanol. The reaction mixture was stirred for 3 h at room temperature and the bulk of the methanol was removed in vacuo. Ether (150 ml) was added and the solution was washed with 5% sodium thiosulfate, 5% sodium hydroxide solution, 5% sodium hydrogen peroxide, 5% sodium thiosulfate, and brine. The ether layer was dried (Na2SO4) and filtered, and solvent removed in vacuo to yield 236 mg of product. Tetracosane (55.3 mg) was added, and analysis by GLC (5% SE-52, 100-250 °C at 6 °C/min) showed the presence of olefin 30a (51%) and vinyl iodide 38a (21%). Fractional molecular distillation at 120 °C (0.001 mm) gave an analytical sample: (δ) (neat) 1660, 1020, 970 cm−1; NMR (CDCl3) δ 5.35-5.60 (m, 2, vinyl), 4.00 (m, 1, −CHOH−), 0.70-2.20 (m, 25). Analysis by GLC indicated the product to be a diastereoisomer mixture containing less than 1% of the isomeric alcohol 31b. Analysis by NMR indicated the product to be a diastereoisomer mixture containing less than 1% of the isomeric alcohol 31b.

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**References and Notes**

14. The following workers have also synthesized the (Z)-1-iodo-3-(tert-butyldimethylsiloxy)-1-octene. (15) The following workers have also synthesized 1-(trans-2-Ethylcyclopentylborane, 60134-96-5; 26a, 60134-86-3; 26b, 60134-57-4; 26c, 60134-86-3; 26d, 60134-87-4; 30, 60134-87-4; 30 (RI=trans-2-Ethylcyclopentenyl)borane, 60134-95-4; 1-octyn-3-ol, 818-72-4; tetrahydropyran-2-ylborane, 23985-40-2; triis-(trans-2-ethyldclopentyl)borane, 60134-95-4; (trans-2-ethyldclopentyl)borane, 60134-95-6; (trans-2-ethyldclopentyl)thexyborane, 60134-94-7; ethyloctane, 3688-24-2; 1-ethyldclopentene, 933-06-2.

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Total Synthesis of (±)-cis-Sativenediol

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A total synthesis of the plant growth promoter cis-sativenediol (2) is reported. The key step involves internal alkylation to cyclopropane 7 followed by thermal rearrangement to tricyclic enone 6. Cis hydroxylation of the double bond, followed by transformation of the carbonyl into a methylene group, completes the synthesis.

Some years ago we reported a stereospecific total synthesis of the tricyclic sesquiterpene hydrocarbon sativene (1). More recently, our continuing interest in this skeletal class has also led to syntheses of copacamphene and of longifolene. When, therefore, Marumo and Arigoni independently assigned the cis-sativenediol structure (2) to a metabolite isolated from the fungus Helminthosporium sativum, we were drawn to attempt a synthesis of the molecule. The Marumo report is particularly interesting because it appears that cis-sativenediol possesses gibberellin-like plant growth promoter activity.

The key step in our sativene synthesis was the intramolecular alkylation of bicyclic keto tosylate 3b to tricyclic ketone 4. If one imagines that the cis diol functionality in the target 2 arises by less hindered exo hydroxylation of the proper olefinic ketone 6, then this requires that we synthesize and cyclize the enone tosylate 5b. One conceivable difficulty with this route is that 5b might choose an alternate mode of cyclization leading to cyclopropane 7, but only experiment can show which cyclization path is more favorable.

Enone 5b was therefore synthesized in straightforward manner from 3a whose synthesis we have previously reported. One modification made in the present work, however, is the use of aqueous titanous ion to cleave 2,4-DNP 14 to the corresponding ketone 3a. The transformation occurred in 97% yield vs. the 70% reported earlier when ozonolytic cleavage was used. Ketone 3a was readily transformed into enone 5a in 82% yield by the Reich-Sharpless procedure, and after tosylation, we were ready to attempt intramolecular alkylation.

Treatment of keto tosylate 5b with 1.2 equiv of dimsyl sodium in Me2SO for 5 min at room temperature led to a nearly quantitative yield of pure cyclization product. IR and NMR spectroscopy clearly showed, however, that the product was exclusively the undesired cyclopropane, 7 (ir 1870 cm⁻¹).