Consequences of α-Bromo Substitution on the Course of Allylmetal Additions to 1-Oxaspiro[4.5]dec-7-en-6-one

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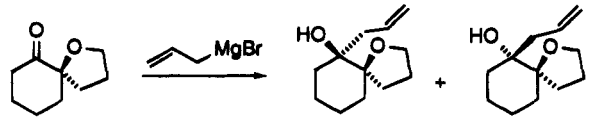
Although reactions involving the addition of organometallics to ketones play a key role in modern synthesis, the consequences of structural effects on stereoselectivity and regioselectivity continue to elicit considerable attention. We have recently reported a three-step capping sequence by which carbonyl groups can be readily transformed into spirocyclic tetrahydrofuranyl building blocks.[1] The first step, consisting for example in the addition of allylmagnesium bromide to **1**, proceeded to give alcohols **2** and **3** in a 5:1 ratio.



1 **2** **3**

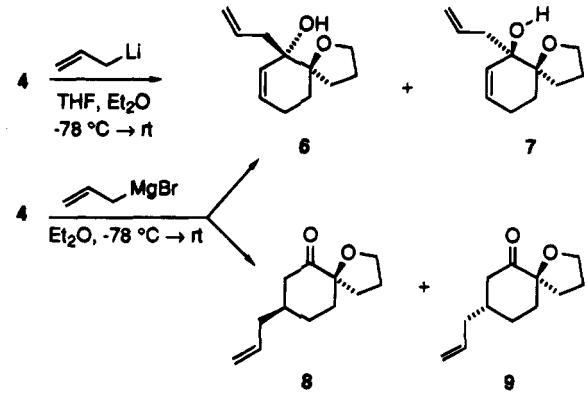
Extensions of this investigation have required that we subject the α,β-unsaturated analog of **1**, viz. **4**, as well as the corresponding α-bromo enone **5** to the same capping protocol. Although a great deal of information is available concerning the reaction of conjugated enones with organolithium and Grignard reagents, studies relating to α-bromo enones are rare indeed. In actuality, the few available reports detail chemistry involving cuprates as co-reagents.[2] In this paper, we detail how **4** and **5** differ in their role as electrophilic acceptors of allyllithium and allylmagnesium bromide.

4 **5**

Results

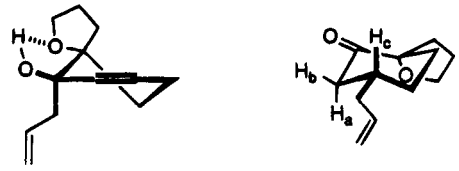
Introduction of the double bond into **1** was accomplished by conversion to the α-bromo ketone with pyridine hydrobromide perbromide[3] and dehydrobromination with lithium carbonate and lithium bromide in hot dimethylacetamide.[4] Bromination of **4** in the presence of triethylamine[5] furnished **5**.

The addition of allyllithium[6] to **4** in cold THF solution proved to be chemoselective in that only the 1,2-addition products **6** and **7** were formed. However, the 1:1 distribution of these alcohols revealed a lack of stereoselectivity. The stereochemical assignments to **6** and **7** are based



on the internal hydrogen bonding[7] present in **7** as evidenced by the sharp, concentration-independent hydroxyl absorption exhibited by this alcohol in its ^{1}H NMR spectra. The three-dimensional arrangement uniquely capable of accommodating this feature is **A**. Under essentially identical circumstances, the hydroxyl proton of **6** is not observed.

When **4** was treated with ethereal allylmagnesium bromide[8] at −78 °C, two differing features of this process were made immediately obvious. The significant new products were now the ketones **8** (38%) and **9** (8%), which unlike **6** (14%) and **7** (16%) were formed with a kinetic bias in favor of addition cis to the ethereal oxygen atom. For stereoelectronic[9] and steric reasons, the conformation of **8** is expected to be that depicted as **B**. Examination



A **B**

of this ketone by 300 MHz ^{1}H NMR spectroscopy revealed the appearance of H_a as a multiplet centered at δ 2.59, the principal coupling partners to which were H_b ($J_{a,b}$ = 11.5 Hz) and H_c ($J_{a,c}$ = 11.5 Hz).

The bromo enone **5** proved to be a more extraordinary electrophile toward allylation. No 1,2-addition was observed with either organometallic. When **5** was admixed with allyllithium as before, the four possible diastereomeric 1,4-adducts **10**–**13** were isolated as pure entities in a combined yield of 74%. Since the stereogenicity of the bromine-substituted carbon originates during protonation of the intermediate enolate, a more relevant feature of these products is the stereochemical disposition of their allyl group relative to the spirocyclic ether

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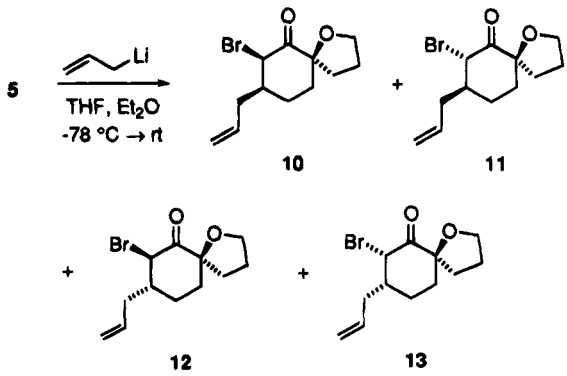
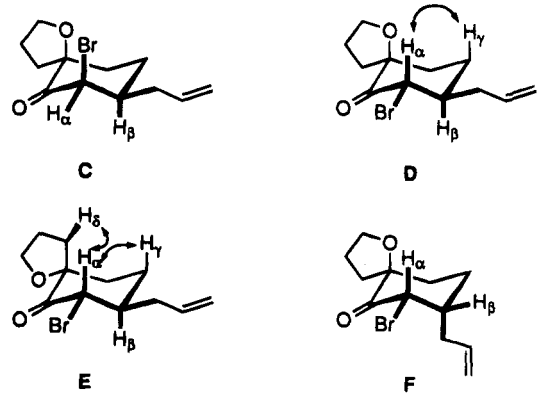


oxygen. In this connection, it is noteworthy that the combined total of **12** (36%) and **13** (12%) is approximately double that realized for **10** (9%) and **11** (17%). This distribution is not in keeping with the observations made earlier for allylmagnesium bromide capture by **4**.

The ^{1}H NMR spectra of **10**–**13** are sufficiently distinctive below δ 3.0 in C_6D_6 solution to permit unequivocal assignment to their individual chair conformations. In the final analysis, structural elucidation was based on the chemical shift of H_α (the proton vicinal to Br), the magnitude of its coupling to H_β, and the presence or absence of diagnostic NOE interactions. Key stereochemical information was also derived from the realization that the dual axial projection of H_α and the spirocyclic ether oxygen gives rise to a downfield shift of 0.7–0.9 ppm as a direct consequence of anisotropic deshielding.

In line with these considerations, **10** was identified as adopting conformation **C** on the basis of the lack of an anisotropic field effect of H_α (δ 4.32), the magnitude of $J_{\alpha,\beta}$ (4.3 Hz), and the absence of an NOE interaction with H_γ. For comparison, H_α in **11** appears at δ 5.05, exhibits



strong diaxial coupling (J = 12 Hz) to H_β, and produces a respectable 3% NOE effect at H_γ. These data require orientation of the relevant protons as shown in **D**. The dispositions of the key protons in **12** were defined to be as in **E** on the strength of the appearance of H_α at δ 4.12, strong diaxial coupling (J = 12 Hz) to H_β, and NOE interactions with both H_γ (2%) and H_δ (3.4%). For **13**, the results were: H_α at δ 5.05 and $J_{\alpha,\beta}$ = 4.5 Hz.

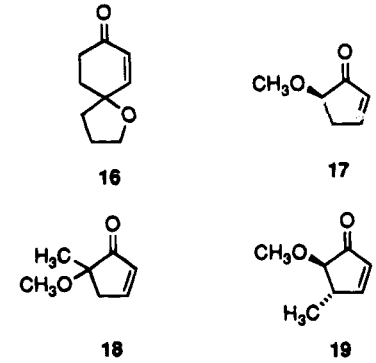
In further confirmation of these geometries, reliance was placed on the fact that equatorial α-alkoxy ketones are more polar than their axial counterparts.[9] For example, **14** (X = OCH_3) exhibits an R_f of 0.13 in 4:1 hexanes-ether while the R_f for **15** (X = OCH_3) is 0.39.[10] For the subset, **10**–**13**, the polarity ordering in ether–

petroleum ether (3:1) was determined to be 0.50, 0.75, 0.25, and 0.63, respectively. The most polar diastereomer **12** has both neighboring hetero atoms projected equatorially as in **E**. The finding that **10** is the third least polar member of this series is in agreement with the axial nature of its spirocyclic oxygen atom.

Finally, the ^{13}C NMR shifts of the bromine-substituted carbons in **10**–**13** correlate very well with those exhibited by model compounds for which the axial and equatorial orientations of the α-bromine atom have been unambiguously defined.[11] A particularly diagnostic example is that reported for **14** (X = Br) and **15** (X = Br) where the equatorial substituent (56.4 ppm) is seen to exert a downfield shift relative to that resident in the axial epimer (51.8 ppm).[12] This general trend is manifested as well by **D** (61.6 ppm), **E** (60.9 ppm), and **F** (58.3 ppm) when these data are compared with **C** (57.0 ppm).

When **5** was treated with allylmagnesium bromide, only **10** (35%), **11** (18%), and **12** (21%) were produced. No evidence was obtained for the possible coformation of **13**.[13] This product distribution reveals a predominance of attack from that surface of the bromo enone π-bond syn to that occupied by the ether oxygen. A parallel therefore exists in the stereoselectivity responses of **4** and **5** to 1,4-addition by the allyl Grignard reagent.

Although the present investigation is the first to address explicitly the contrasting behavior of α′-alkoxy cyclic enones substituted by both H and Br at C_α, conjugate additions to the related compounds **16**–**19** have been reported earlier.[14,15] Lithium dimethylcuprate



adds 1,4 to these substrates in THF at −78 °C to rt to give predominantly cis product in the case of **16** (92%) and **19** (78%), and trans adducts in the other two examples (98% and 97%, respectively). When trimethylsilyl chloride (TMSCl) is present as a co-reactant, the corresponding cis/trans ratios are reversed for **16** (<1:99) and **19** (1:4.8), but not for **17** (1:34) or **18** (1:5.5). The TMSCl is believed to suppress equilibration in advance

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(11) Duddeck, H. *Topics in Stereochemistry* **1986**, *16*, 279.

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(13) Workup in this instance was modified to involve quenching with a saturated $NaHCO_3$ solution instead of aqueous NH_4Cl. As shown by independent experimenta-tion, these conditions are adequate to epimerize **13** to **12** during the course of several hours.

(14) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

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of C-C bond formation, the accompanying rate acceleration being influenced more by stereoelectronic than by steric factors.[14]

As in **16**–**19**, the lone pair of electrons associated with the spirocyclic ether oxygen in **4** and **5** is available for chelation to a lithium or magnesium center. Attack from the syn face would be expected[16] as a consequence of intramolecular delivery. Indeed, this stereochemical course is the more dominant for the allyl Grignard additions. The structural features of allyllithium[17] appear equally conducive to precoordination to the same heteroatom. The experimental data for **5** do not agree with this conclusion. The possibility exists that electrostatic repulsion,[18] stereoelectronic contributions,[19,20] and steric effects singly or in combination override the reversible complexation phenomenon.

Whatever the actual situation, our findings indicate that further investigation of the regio- and diastereoselectivity aspects of α-bromo enone reactions with various types of organometallics is warranted.

Experimental Section[21]

1-Oxaspiro[4.5]dec-7-en-6-one (4). A cold (0 °C), magnetically stirred solution of **1** (4.38 g, 28.4 mmol) in dry THF (50 mL) was treated with pyridine hydrobromide tribromide (11.00 g, 34.4 mmol), stirred at rt for 1 h, poured into a separatory funnel, treated with saturated sodium thiosulfate solution (50 mL), and extracted with ethyl acetate (5×). The combined organic phases were washed twice with brine, dried, and evaporated. Chromatography of the residue (8.72 g) on silica gel afforded 2.84 g (43%) of the sensitive α-bromo ketone which was directly added to a slurry of lithium bromide (2.70 g, 30.5 mmol) and lithium carbonate (2.80 g,m 36.6 mmol) in dimethylacetamide (20 mL) and heated to 170 °C for 2 h. After being cooled to rt, the mixture was directly applied to a column of silica gel. Elution with 1:1 ether–petroleum ether gave 480 mg (26%) of **4** as a colorless oil; IR (film, cm^{-1}) 1683, 1430, 1388, 1222, 1088, 803; ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (ddd, J = 10, 1, 1 Hz, 1 H), 5.94 (d, J = 10 Hz, 1 H), 3.92 (m, 2 H), 2.53 (dddd, J = 14, 6, 4,1 Hz, 1 H), 2.34 (dddd, J = 14, 6, 4, 1 Hz, 1 H), 2.21–1.62 (series of m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.0, 149.6, 128.0, 84.0, 69.0, 34.4, 32.1, 25.5, 24.9; MS m/z (M^+) calcd 152.0837, obsd 152.0835.

7-Bromo-1-oxaspiro[4.5]dec-7-en-6-one (5). A 304 mg (2.0 mmol) sample of **4** was dissolved in dry CH_2Cl_2 (2 mL), cooled to 0 °C, and treated dropwise with a 10% solution of bromine in CCl_4 (1.1 mL, 2.1 mmol). The reaction mixture was allowed to warm to rt during 1 h, treated with triethylamine (0.3 mL, 4.0 mmol), and stirred for an additional hour before being poured into 15% sodium thiosulfate solution and extracted with ethyl acetate (5×). The combined organic layers were dried and evaporated to afford 410 mg (90%) of **5** as a clear oil; IR (neat, cm^{-1}) 1695, 1603, 1420, 1322, 1098, 1016; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (dd, J = 4.5, 4.5 Hz, 1 H), 3.92 (m, 2 H), 2.63 (dddd, J = 19, 10, 4.5, 1.5 Hz, 1 H), 2.38 (dddd, J = 19, 10, 4.5, 1.5 Hz, 1 H), 2.21–1.63 (series of m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 191.0, 150.2, 121.8, 84.7, 69.2, 34.3, 32.5, 26.3, 25.6; MS m/z (M^+) calcd 229.9942, obsd 229.9903.

Reaction of 4 with Allyllithium. A solution of allyltri-*n*-butyltin (0.31 mL, 1.0 mmol) in dry THF (2 mL) was treated dropwise via syringe with a solution of *n*-butyllithium in hexanes (0.6 mL of 1.6 M, 0.96 mmol) and stirred for 45 min. Ketone **4** (29 mg, 0.19 mmol) dissolved in anhydrous ether (2 mL) was added to the cold (−78 °C) allyllithium solution, stirred at this temperature for 1 h, allowed to warm to rt, and poured into saturated NH_4Cl solution. The mixture was twice extracted with ethyl acetate and the combined extracts were dried and concentrated. Chromatography of the residue on silica gel (elution with 25% ether in petroleum ether) afforded 10.3 mg (28%) of **6** and 10.3 mg (28%) of **7**.

For **6**: colorless oil; IR (neat, cm^{-1}) 1458, 1058; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (m, 1 H), 5.75 (m, 1 H), 5.60 (d, J = 12 Hz, 1 H), 5.20 (m, 2 H), 4.90 (m, 2 H), 2.35–1.30 (series of m, 10 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.3, 131.7, 128.4, 118.7, 85.9, 73.7, 68.4, 41.5, 31.7, 30.6, 26.3, 23.8; MS m/z (M^+) calcd 194.1307, obsd 194.1311.

For **7**: colorless oil; IR (neat, cm^{-1}) 1052, 911; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (m, 1 H), 5.70 (m, 1 H), 5.59 (d, J = 11 Hz, 1 H), 5.05 (m, 2 H), 3.90 (m, 2 H), 2.75 (br s, 1 H), 2.30–1.30 (series of m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.3, 132.6, 127.6, 117.2, 85.9, 72.8, 68.2, 43.1, 30.6, 29.7, 25.5, 22.4; MS m/z (M^+) calcd 194.1307, obsd 194.1297.

Reaction of 4 with Allylmagnesium Bromide. A magnetically stirred solution of **4** (29 mg, 0.19 mmol) in anhydrous ether (2 mL) was cooled to −78 °C and treated dropwise with a solution of allylmagnesium bromide in ether (1.0 mL of 0.5 M, 0.50 mmol). After 1 h, the reaction mixture was allowed to warm to rt, poured into 1 M $NaHCO_3$ solution, and extracted with ethyl acetate (2×). The combined organic phases were dried and concentrated prior to chromatography of the products on silica gel. Gradient elution with 20–50% ether in petroleum ether furnished 14.0 mg (38%) of **8**, 3.3 mg (9%) of **9**, 5.2 mg (14%) of **6**, and 6.3 mg (17%) of **7**.

For **8**: colorless oil; IR (neat, cm^{-1}) 1719, 1458, 1438, 1128, 1036, 994, 914; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 1 H), 5.00 (m, 2 H), 3.85 (m, 1 H), 3.65 (m, 1 H), 2.59 (m, 1 H), 2.55 (m, 1 H), 2.30 (m, 1 H), 2.10 (ABm, 2 H), 2.1–0.8 (series of m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.1, 135.8, 116.7, 86.5, 68.1, 44.4, 40.8, 39.4, 37.5, 30.3, 27.9, 25.7; MS m/z (M^+) calcd 194.1307, obsd 194.1304.

For **9**: colorless oil; IR (neat, cm^{-1}) 1718, 1458, 1438, 1099; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 1 H), 5.05 (m, 2 H), 3.90 (m, 1 H), 2.55 (m, 1 H), 2.10–0.80 (series of m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.5, 135.6, 117.0, 87.8, 68.5, 45.4, 40.3, 38.6, 37.4, 34.1, 30.3, 25.3; MS m/z (M^+) calcd 194.1307, obsd 194.1303.

Reaction of 5 with Allyllithium. Reaction of **5** (208 mg, 0.90 mmol) with allyllithium in the predescribed manner afforded 22.1 mg (9%) of **10**, 41.8 mg (17%) of **11**, 88.5 mg (36%) of **12**, and 29.5 mg (12%) of **13**.

For **10**: colorless oil; IR (neat, cm^{-1}) 1737; ^1H NMR (300 MHz, C_6D_6) δ 5.40 (m, 1 H), 4.85 (m, 2 H), 4.32 (d, J = 4.3 Hz, 1 H), 3.45 (m, 2 H), 2.30 (m, 2 H), 1.60 (m, 2 H), 1.48 (m, 2 H), 1.45 (m, 2 H), 1.28 (m, 1 H), 1.15 (m, 1 H), 1.05 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 201.6, 134.9, 117.5, 87.3, 68.3, 57.0, 43.3, 35.1, 34.0, 33.9, 25.5, 24.4; MS m/z (M^+) calcd 272.0393, obsd 272.0402.

For **11**: colorless oil; IR (neat, cm^{-1}) 1736; ^1H NMR (300 MHz, C_6D_6) δ 5.58 (m, 1 H), 5.05 (d, J = 12 Hz, 1 H), 4.98 (m, 2 H), 3.42 (m, 1 H), 3.38 (m, 1 H), 2.60 (m, 1 H), 2.45 (m, 1 H), 2.08 (m, 1 H), 1.70 (m, 1 H), 1.65 (m, 1 H), 1.55 (m, 1 H), 1.50 (m, 2 H), 1.38 (m, 1 H), 1.12 (m, 1 H), 1.05 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 201.2, 134.0, 118.3, 87.7, 68.5, 61.6, 47.5, 39.5, 37.0, 31.2, 27.0, 25.6; MS m/z (M^+) calcd 272.0393, obsd 272.0394.

For **12**: colorless oil; IR (neat, cm^{-1}) 1735; ^1H NMR (300 MHz, C_6D_6) δ 5.49 (m, 1 H), 5.02 (m, 2 H), 4.12 (d, J = 12 Hz, 1 H), 3.88 (m, 1 H), 3.70 (m, 1 H), 2.35 (m, 1 H), 1.95 (m, 1 H), 1.60 (m, 2 H), 1.48 (m, 2 H), 1.45 (m, 2 H), 1.28 (m, 1 H), 1.15 (m, 1 H), 0.85 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 201.3, 133.6, 118.8, 88.3, 68.5, 60.9, 46.5, 39.1, 36.9, 34.6, 27.9, 25.1; MS m/z (M^+) calcd 272.0393, obsd 272.0410.

For **13**: colorless oil; IR (neat, cm^{-1}) 1738; ^1H NMR (300 MHz, C_6D_6) δ 5.35 (m, 1 H), 5.05 (d, J = 4.5 Hz, 1 H), 4.85 (m, 2 H),

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3.53 (m, 2 H), 2.51 (ddd, J = 5.7, 8.1, 12.1 Hz, 1 H), 2.35 (m, 1 H), 1.65 (m, 2 H), 1.48 (m, 2 H), 1.45 (m, 2 H), 1.28 (m, 1 H), 1.20 (m, 1 H), 1.15 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.2, 135.1, 117.4, 87.7, 68.7, 58.3, 43.4, 35.3, 34.9, 34.1, 25.8, 24.5; MS m/z (M^+) calcd 272.0393, obsd 272.0371.

Reaction of 5 with Allylmagnesium Bromide. Reaction of **5** (208 mg, 0.90 mmol) with allylmagnesium bromide in the predescribed manner except for workup with saturated $NaHCO_3$ solution afforded 85 mg (35%) of **10**, 45 mg (18%) of **11**, and 51 mg (21%) of **12**.

Acknowledgment. We thank the National Science Foundation for financial support.

Supplementary Material Available: Copies of the ^{1}H and ^{13}C NMR spectra of **4**–**13** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.