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Documentation of a rare example of an intramolecular 1,2-addition of a trialkylborane to a carbonyl group

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Abstract

In the course of synthetic studies aimed at the elaboration of highly funtionalized ketone **1**, we observed what appeared to be an extremely rare example of the addition of a trialkylborane to a carbonyl group. We were able to confirm the initial spectroscopic structural assignment by X-ray crystallography. Some preliminary mechanistic experiments suggest that the addition occurs directly in the absence of oxygen prior to oxidation of the trialkylborane during workup.

Simple trialkylboranes do not normally undergo 1,2-addition to the carbonyl groups of aldehydes and ketones.[1] There are numerous examples of hydroboration–oxidation sequences of γ,δ-unsaturated and other unsaturated ketones and aldehydes to afford the expected hydroxycarbonyl derivatives or the related hemiketals or acetals.[2] Thus, it seems well-documented that such ketone and aldehyde functionality is usually compatible with reaction conditions employing even excess of hindered hydroborating agents such as 9-borabicyclo[3.3.1]nonane (9-BBN).[1–3]

We were, therefore, surprised to isolate one major product in good yield (77%) from hydroboration of γ,δ-unsaturated ketone **1** with excess 9-BBN in THF at reflux followed by oxidation with aq. basic peroxide. This material was clearly not the expected hydroxyketone **2** based upon its spectral characteristics (Scheme 1).[4] Further spectroscopic analysis of this material (^{1}H and ^{13}C NMR) was consistent with structure **3** in which a new bond had been formed between the carbonyl and the terminal end of the olefin followed by intramolecular δ lactone formation. Similarly, when hydroboration was carried out with an acidic oxidation step, the analogous crystalline cyclization product **4** was obtained in good yield (82%) rather than the expected carboxylic acid **5**.[5] Identical products were obtained with thexylborane or disiamylborane and when other oxidizing agents such as NMMO and $NaBO_3$ were employed.

Since such an addition was unprecedented in our experience, we sought to verify the structure unequivocally. Single crystal X-ray analysis of alcohol **4** verified the initial spectroscopic structure

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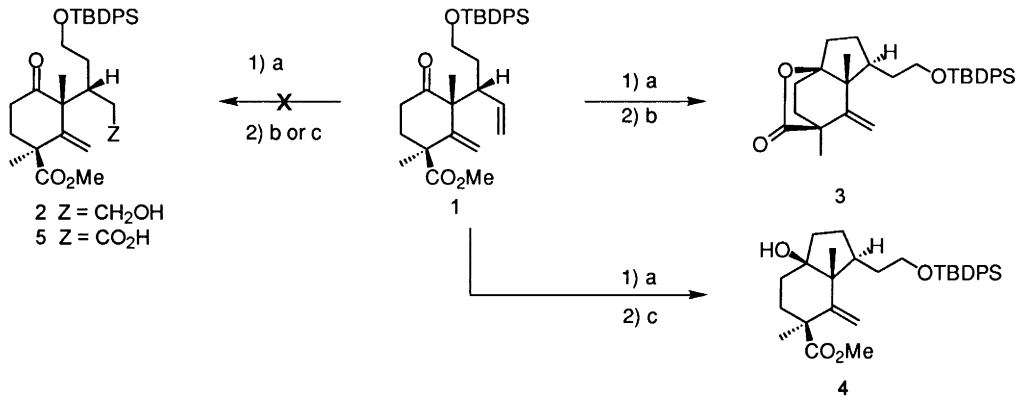


Scheme 1. (a) 9-BBN (xs), THF 66°C; (b) H_2O_2 (xs), NaOH, 50°C; (c) CrO_3/HOAc (xs)

assignment for **4** (and **3**) and clearly confirmed the presence of a cyclopentane ring. An ORTEP drawing of the final crystallographic model is shown in Fig. 1.[6]

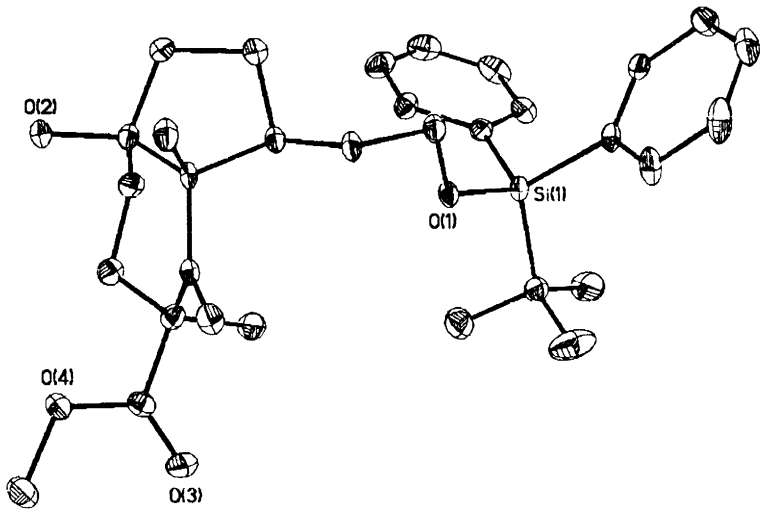
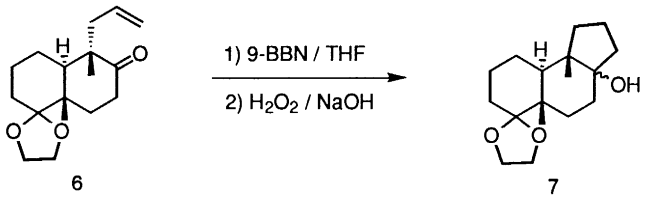


Fig. 1.

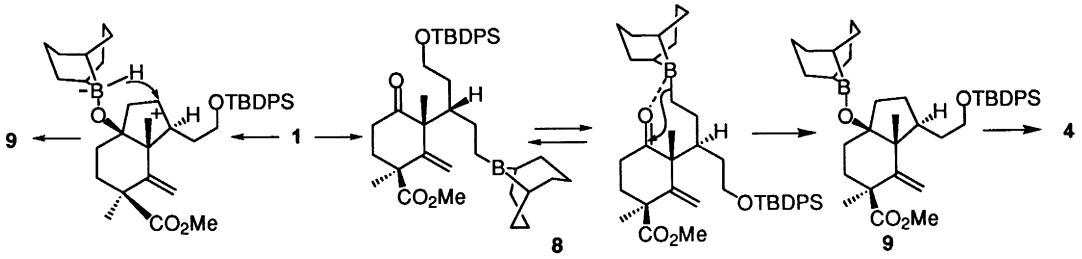
Although our initial survey did not identify any prior reports of such an observation, a more exhaustive search of the literature identified one prior report of such an addition. In the course of synthetic studies toward labdane class terpenes, Ardon-Jimenez and Halsall had occasion to hydroborate **6** (Eq. (1)).[7] They, also, did not obtain the expected primary alcohol, but obtained a product tentatively assigned structure **7** based on ^{1}H NMR spectroscopic data. However, the structure of **7** was not confirmed unequivocally. Interestingly, at the time of its initial report or upon subsequent review, little note was taken of the fact that this transformation was unusual and apparently unprecedented.[1,7]



(1)

It is tempting to ascribe the unusual behavior in these cases to the spatial proximity of the ketone and olefin. However, the plethora of examples in the literature, in which superficially similar substrates undergo hydroboration–oxidation with 9-BBN or other hindered boranes to afford the expected primary alcohol products (or derivatives thereof), suggests that this explanation may be too simplistic.[2,3] Thus, we became interested in investigating the origin of this unusual reactivity and the mechanism by which the addition of the carbon–boron bond to the ketone carbonyl occurs.

At least two general types of mechanisms are conceivable. As shown in Eq. (2), if we assume that initial hydroboration of the terminal olefin takes place normally to afford **8**, then the observed product could result from ring closure by addition of the C–B bond to the carbonyl group in a nominal 1,2-addition process (either radical or ionic). This addition could take place either directly or via a borate formed during the oxidation of **8** by attack of base or peroxide at boron. Alternatively, the reaction pathway could involve boron (9-BBN) acting as a Lewis acid which mediates a reductive cyclization process in which the boron coordinates to the carbonyl oxygen followed by attack of the sidechain olefin and delivery of hydride to the incipient 2° carbenium ion either intramolecularly or from a second molecule of 9-BBN to afford the observed product via borate **9**.



The gross features of these mechanisms are readily distinguished. The latter does not involve the intermediacy of the expected normal borane addition product **8** which may be observable. To test the hypotheses, we monitored the reaction by ^{11}B NMR in d_6 benzene and d_8 THF. The ^{11}B experiments were particularly revealing since direct observation of changes occurring at boron was possible. These experiments demonstrated that, in carefully deoxygenated d_6 benzene: (1) no detectable amounts of the intermediate trialkyborane (δ ~80 ppm from model boranes) were observed; (2) the observed product borate **9** (δ ~50 ppm by comparison to authentic borate) was formed smoothly at 60°C without added base or oxidizing agent; and (3) product formation was not accelerated by the presence or admission of oxygen.[8] No evidence of complexation of the carbonyl in **1** by 9-BBN was observed by ^{11}B NMR. The results were qualitatively the same in d_8 THF, although the reaction was less clean. The ^{1}H NMR of this mixture indicated the presence of a minor amount of second species in addition to **9** which we have tentatively assigned as borane **8**. We also conducted the hydroboration–oxidation of **1** in the presence of radical inhibitors such as 2,6-di-*t*-butyl-4-methylphenol. The conversion of **1** to **4** still proceeded smoothly.

Furthermore, we monitored the hydroboration in d_8 THF by ^{13}C NMR. After reflux in the presence of excess 9-BBN, the ^{13}C NMR spectra of the reaction mixture showed the absence of resonances ascribable to the terminal double bond in **1**. Most diagnostically, the ^{13}C NMR spectrum of the reaction mixture exhibited four signals at δ 175 (2), 208, and 214. By comparison, the ^{13}C NMR spectrum of **1** in $CDCl_3$ exhibited signals at δ 176 and 211, assigned to the ester and ketone carbonyl carbons, respectively. Thus, the ^{13}C NMR data also appear consistent with the intermediacy of **8** (and possibly the intramolecular Lewis acid complex of **8**) since the ester carbonyl group is present and the ketone carbonyl group is also still present, at least in part, after addition of the borane to the terminal olefin is complete.

These experiments exclude base and/or oxidizing agents as requirements for conversion to the carbocyclic products. However, the details of the mechanism by which the putative intermediate borane **8** is converted to the carbocyclic borate **9** remain unresolved except that the intermediacy of a radical would appear less likely, especially in view of the lack of acceleration by oxygen and the reported intermolecular addition of vinylboranes to aldehydes with retention of olefin geometry.[1,9]

Surprisingly, such cyclizations have not been commonly observed in structurally similar substrates.[2,3] As shown in Fig. 2, molecular modeling of the substrates **1** and **6** does suggest that specific steric interactions appear present in the intermediate trialkylboranes derived from **1** and **6** resulting in a thermodynamic preference for proximity of the sidechain bearing the terminal trialkylborane and the ketone carbonyl. Other cases appear to lack such specific interactions which favor proximity, principally because of greater conformational mobility.[2,3] Thus, for the trialkylboranes derived from **1** and **6**, addition to the carbonyl group is more favorable whether it be via an ionic or a radical pathway.[1,9]

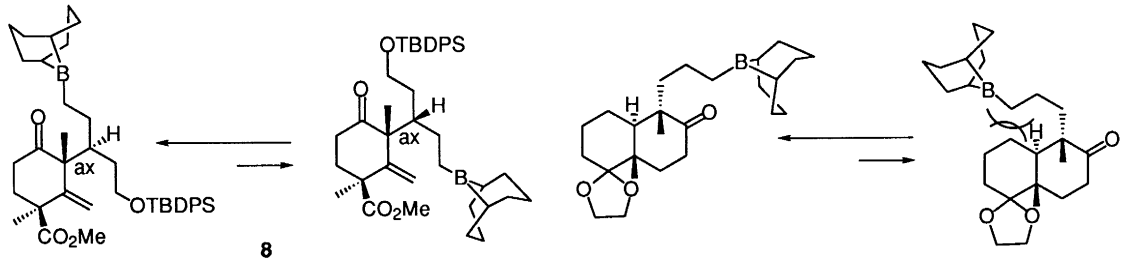


Fig. 2.

Acknowledgements

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References

1. Only vinylboranes add to simple aldehydes: Jacob III, P.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 579–580.
2. (a) Sutherland, A. J.; Sutherland, J. K.; Crowley, P. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 349–354; (b) Snowden, R. L.; Brauchli, R.; Sonnay, P. *Helv. Chim. Acta* **1989**, *72*, 570–593; (c) Zablocki, J. A.; Katzenellenbogen, J. A.; Carlson, K. E.; Norman, M. J.; Katzenellenbogen, B. S. *J. Med. Chem.* **1987**, *30*, 829–838; (d) Snowden, R. L.; Sonnay, P. *J. Org. Chem.* **1984**, *49*, 1464–1465.
3. (a) Jung, M. E.; Siedem, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 3822–3823; (b) Ziegler, F. E.; Mencel, J. J. *Tetrahedron Lett.* **1983**, *24*, 1859–1862; (c) Schultz, A. G.; Dittami, J. P.; Myong, S. O.; Sha, C. K. *J. Am. Chem. Soc.* **1983**, *105*, 3273–3279.
4. NMR spectral data for lactone **3** is as follows: ^{1}H (400 MHz, $CDCl_3$) 7.68–7.65 (m, 4H), 7.47–7.37 (m, 6H), 5.01 (s, 1H), 4.96 (s, 1H), 3.78–3.62 (m, 2H), 2.13–1.34 (m, 9H), 1.33 (s, 3H), 1.32–1.25 (m, 2H), 1.06 (s, 9H), 0.84 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) 177.4, 156.6, 135.6 (4 signals), 133.8 (2 signals), 129.7 (2 signals), 127.4 (4 signals), 105.7, 89.3, 62.5, 50.3, 46.1, 40.0, 35.8, 33.5, 29.5, 28.4, 27.2, 26.9 (3 signals).
5. NMR spectral data for hydroxy ester **4** is as follows: ^{1}H (400 MHz, $CDCl_3$) 7.67–7.65 (m, 4H), 7.45–7.37 (m, 6H), 5.05 (s, 1H), 4.96 (s, 1H), 4.38 (s (br), 1H), 3.70 (s, 3H), 3.73–3.67 (m, 2H), 3.60–3.53 (m, 2H), 2.45 (ddd, 1H, J_1=12.7, J_2=4.1, J_3=4.1 Hz), 2.22 (m, 1H),1.94–1.42 (m, 5H), 1.39 (s, 3H), 1.32–1.23 (m, 2H), 1.04 (s, 9H), 0.98 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) 178.1, 152.9, 135.6 (4 signals), 133.9 (2 signals), 129.5 (2 signals), 127.6 (4 signals), 114.2, 81.3, 62.7, 52.1, 51.8, 48.6, 42.4, 37.8, 33.1, 32.0, 30.2, 27.4, 26.9 (3 signals), 26.2, 19.1, 16.0.
6. For a single crystal ($0.22\times0.20\times0.16$ mm^3) of **4**, grown from ether/hexane, X-ray intensity data were collected at -80°C on a Siemans SMART system with a CCD area detector. A total of 3002 independent reflections were judged observed ($>2\sigma(I)$)

after correction for absorption. Laue symmetry revealed an orthorombic crystal system with unit cell dimensions: a=15.4843 (2), b=7.65020 (10), and c=23.7760 (2) Å^3. The space group was assigned as $Pca2_1$ with Z=4. The structure was solved by direct methods, and refined employing full matrix least-squares on F^2. All non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms were included in idealized positions. The final model refined to a goodness of fit of 1.041, with an absolute structure parameter of 0.0 (2), and final residuals of R_1=4.38% ($I>2\sigma$) and wR_2=9.99% ($I>2\sigma$). Coordinates have been deposited with the Cambridge Crystallographic Data Centre.

7. (a) Ardon-Jimenez, A.; Halsall, T. G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1461–1470; (b) Matteson, D. S. *J. Organomet. Chem.* **1981**, *207*, 13–65.
8. The ^{11}B NMR signals are broad (peak width (half height) ~160 Hz) resulting in an estimated detection limit of ~10%.
9. Miyaura, N.; Itoh, M.; Suzuki, A.; Brown, H. C.; Midland, M. M.; Jacob III, P. *J. Amer. Chem. Soc.* **1972**, *94*, 6549–6550.