Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 3291–3294

The stereochemistry of 1,2-additions of allylmagnesium, allylindium, and allylbismuth to cyclohexenones

Liang Zhao and D. Jean Burnell*

Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J3

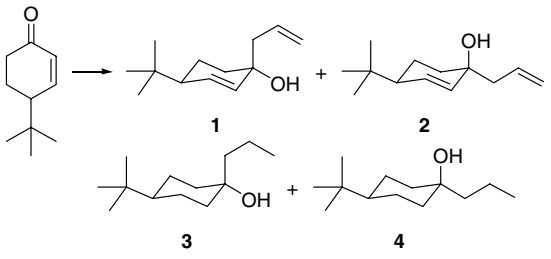
Received 25 January 2006; revised 1 March 2006; accepted 6 March 2006
Available online 29 March 2006

Abstract—Allylmagnesium, allylindium, and allylbismuth generally showed a preference for axial addition to cyclohexenones. Allylmagnesium was the most stereoselective. Reactions with an α-methylated enone (carvone) were the most selective, except that allylbismuth was unreactive with this substrate.

The transition structure for the axial 1,2-addition of a metalated nucleophile to a cyclohexenone is inherently lower in energy than the transition structure for the equatorial addition. Houk and co-workers[1] ascribed this difference to both torsional strain in the equatorial transition structure and maintenance of a nearly coplanar geometry of the enone moiety in the axial transition structure. However, the nature of the metal has been shown to be important with simple cyclohexenones[2] and with α-heterosubstituted cyclohexenones.[3,4] The former might be explained by differences in the geometries about the metals;[1] the latter might be complicated by electrostatic, chelation[3] and additional steric considerations. Also, significant differences in the mechanism have been discovered, depending on a number of parameters including the metal.[5]

In connection with ongoing synthetic efforts, we wished to assess the stereoselectivity of additions of allylindium to cyclohexenones. This is because allylindium species were reported to add to a conformationally restricted ketone, such as 4-*tert*-butylcyclohexanone, to give epimeric alcohols in a ratio of better than 1:4, favoring the equatorial-addition product, whereas allylmagnesium chloride added to the same, saturated ketone to give the epimeric alcohols in a 1.2:1 ratio, very slightly favoring the axial-addition product.[6,7] In addition, allylindium is tolerant of alcohol functions in the substrate. Indeed, allylindium reactions can be conducted in an aqueous medium,[8,9] but the diastereoselectivity of allylindium additions was reported to be better in THF than in water, although reaction times in THF were very much longer than in water.[9]

The reaction of allylmagnesium bromide with 4-*tert*-butylcyclohex-2-enone in ether at room temperature gave a 5:1 mixture of the epimers **1** and **2**,[10] respectively, in a combined yield of 83%. The Grignard reaction in THF gave the same ratio of epimers.



The stereochemistry at the carbinol center was initially assigned based on the relative chemical shifts of the carbinol centers in the ^{13}C NMR spectra. The carbinol signal further downfield should belong to the axial-addition product.[2,4,11] Attempts to corroborate this assignment by measurement of NOE enhancements led to inconclusive results, so each epimer was hydrogenated catalytically. The ^{13}C NMR data and melting point of the saturated tertiary alcohol derived from the minor epimer matched the data for **4** in the literature.[10,12] Thus, the saturated tertiary alcohol derived from the major epimer was **3**.

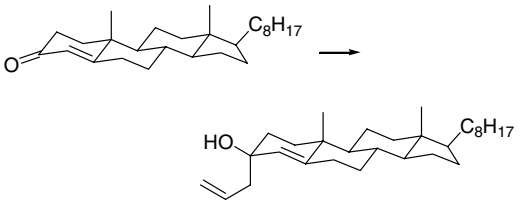
* Corresponding author. Tel.: +1 (902) 494 1664; fax: +1 (902) 494 1310; e-mail: Jean.Burnell@dal.ca

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.034

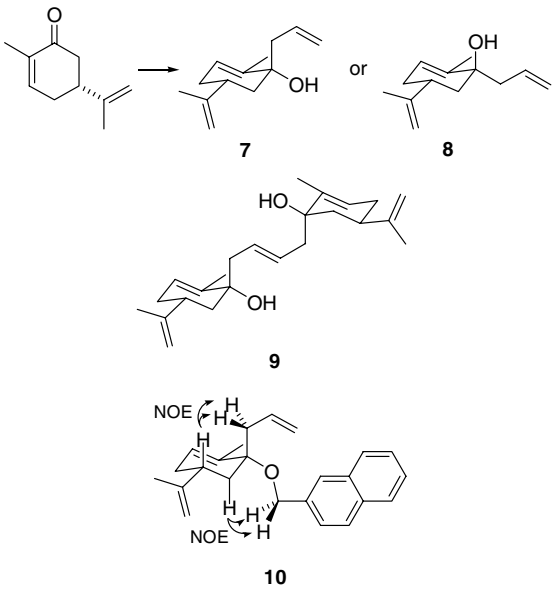
An allylindium reagent was prepared in DMF,[13] and this was reacted with 4-*tert*-butylcyclohex-2-enone at room temperature for 6 h. A 1:1 mixture of **1** and **2** was obtained in a combined yield of 85%. No change in the ratio of the epimers was seen when allylindium reagents were prepared in different solvents, although the reaction rate was affected: DMF/H_2O 1:1 (1 day), H_2O (2 days), and dry THF (incomplete after 7 days). Paquette and Lobben[9] had seen the same trend in the rates. That the ratio of epimers did not change was unexpected, as it is known that the nature of the indium reagent is not the same in aqueous[7] and non-aqueous solutions,[6,14] and some changes in stereoselectivity had been observed in different solvents with 4-*tert*-butylcyclohexanone.[7]

Allylbismuth[15,16] is a nucleophile that has received only scant attention. The stereoselectivity of its additions to enones was unknown. Allylbismuth reacted with 4-*tert*-butylcyclohex-2-enone in THF under reflux to provide a mixture of **1** and **2** in a ratio of 2.2:1, respectively.

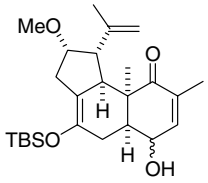
Cholest-4-en-3-one presents facial alternatives that are very similar to those of 4-*tert*-butylcyclohex-2-enone. Allylmagnesium bromide reacted with this enone to give a 6.3:1 mixture of the epimeric alcohols **5** and **6**.[17] The relative positions of the carbinol signals in their ^{13}C NMR spectra indicated that the major isomer was **5**, the product of axial addition. The allylindium reagent in DMF provided a 4.5:1 ratio of **5** and **6**, respectively. The allylbismuth reagent in THF under reflux gave **5** and **6** in a ratio of 4.2:1, respectively.



Carvone is a cyclohex-2-enone with a significant conformational bias but with additional steric bulk in the plane of the carbonyl by virtue of the methyl group. This feature was expected to hinder equatorial addition more than axial addition. Addition of allylmagnesium bromide to (*R*)-carvone in ether produced only one product. In DMF, the allylindium reagent reacted with (*R*)-carvone to give the same product[18] exclusively. On the other hand, the allylbismuth reagent in THF showed no sign of reaction with (*R*)-carvone, even after many days under reflux. The stereochemistry of the single product could not be assigned by comparison of ^{13}C NMR shifts, and overlap in the ^{1}H NMR spectrum led to ambiguous NOE data. In an initial attempt to determine the structure chemically, a solution of the



product in CH_2Cl_2 was stirred with a catalytic amount of Grubbs' 'second generation' ruthenium catalyst.[19] The idea was that the relative stereochemistry of **8**, but not **7**, might make the molecule amenable to ring-closing metathesis. However, the only product (93%) was the result of intermolecular, cross-metathesis (**9**).[20] A survey of derivatives of the addition product led to the (β-naphthyl)methyl ether (**10**),[20] which had a fortuitously dispersed ^{1}H NMR spectrum that allowed unambiguous assignment of the relative stereochemistry by measurement of the NOE enhancements shown above. Therefore, the structure of the addition product was **7**,[20] the result of axial addition to the carbonyl. This result was consistent with a significant attenuation of the rate of equatorial attack by the sterically hindering methyl group. The allylindium reagent in DMF would not react with the even more hindered enone **11**, to which allylmagnesium added with reluctance.[21]



At the moment, any interpretation of these results can only be simplistic as the structures of the allylindium reagent (in DMF) and of allylbismuth are not well understood, and the mechanisms by which all three organometallics react may not be similar. Cyclohexanone has an inherent tendency to be attacked by nucleophiles axially, but other considerations, including steric effects, may disfavor axial attack. In the reaction of cyclohexanone with allylmagnesium, any axial-addition tendency must be almost exactly balanced by other forces because the axial:equatorial ratio was reported to be almost 1:1.[6,7] The inherent tendency for axial

addition with cyclohexanone must be overcome by the other considerations with the allylindium reagent, because the equatorial-addition product was reported to predominate.[7] The inherent tendency for axial attack is greater for cyclohexenone than for cyclohexanone.[1] In our hands, in the reactions with the cyclohexenones, allylmagnesium gave highest proportion of the axial-addition products, whereas in additions of the allylindium reagent and allylbismuth, the proportions of axial-addition products were less. Indeed, with the simplest case, 4-*tert*-butylcyclohex-2-enone, the allylindium reagent returned a 1:1 mixture of the axial- and equatorial-addition products.

Acknowledgements

Support from the Natural Sciences and Engineering Research Council of Canada and the Killam Trust is gratefully acknowledged.

References and notes

1. Wu, Y.-D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* **1991**, *56*, 3656–3664.
2. (a) Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613–615; (b) Trost, B. M.; Florez, J.; Haller, K. J. *J. Org. Chem.* **1988**, *53*, 2396–2398.
3. Klemeyer, H. J.; Paquette, L. A. *J Org. Chem.* **1994**, *59*, 7924–7927.
4. Lindsay, H. A.; Salisbury, C. L.; Cordes, W.; McIntosh, M. C. *Org. Lett.* **2001**, *3*, 4007–4010.
5. Gajewski, J. J.; Bocian, W.; Harris, N. J.; Olson, L. P.; Gajewski, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 326–334.
6. Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1833–1835.
7. Reetz, M. T.; Haning, H. *J. Organomet. Chem.* **1997**, *541*, 117–120.
8. (a) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *21*, 3228–3229; (b) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633–655; (c) Lucas, P.; Gajewski, J. J.; Chan, T. H. *Can. J. Anal. Sci. Spect.* **2003**, *48*, 1–6.
9. Paquette, L. A.; Lobben, P. C. *J. Org. Chem.* **1998**, *63*, 5604–5616.
10. All NMR spectra were run in $CDCl_3$ on a 500 MHz instrument.
For **1**: IR (neat): 3375 cm^{-1}; ^1H NMR: δ 5.90 (1H, m), 5.74 (1H, dt, $J = 10.2$, 1.8 Hz), 5.61 (1H, dt, $J = 10.2$, 2.2 Hz), 5.10–5.17 (2H, m), 2.34 (1H, dd, $J = 7.2$, 13.6 Hz), 2.26 (1H, dd, $J = 7.5$, 13.6 Hz), 1.95 (1H, complex d, $J = 13$ Hz), 1.90 (1H, m), 1.76 (1H, m), 1.56 (1H, m), 1.38 (1H, m), 0.88 (9H, s); ^{13}C NMR: δ 134.4 (1), 133.9 (1), 130.4 (1), 118.9 (2), 70.8 (0), 46.0 (2), 45.6 (1), 36.2 (2), 33.0 (0), 27.4 (3), 22.4 (2).
For **2**: IR (neat): 3416 cm^{-1}; ^1H NMR: δ 5.83–5.89 (2H, m), 5.68 (1H, dt, $J = 10.5$, 2.1 Hz), 5.09–5.14 (2H, m), 2.28 (2H, symmetrical m), 1.76–1.80 (2H, m), 1.69 (1H, m), 1.45–1.56 (2H, m), 0.90 (9H, s); ^{13}C NMR: δ 134.0 (1), 133.2 (1), 132.5 (1), 118.5 (2), 68.7 (0), 47.3 (2), 46.7 (1), 35.7 (2), 32.7 (0), 27.5 (3), 20.2 (2).
For **3**: mp 77–78 °C; IR (cast): 3293 cm^{-1}; ^1H NMR: δ 1.80 (2H, br d, $J = 12.5$ Hz), 1.67 (2H, m), 1.47 (2H, m), 1.32–1.39 (4H, m), 1.01–1.11 (3H, m), 0.95 (3H, t, $J = 7.2$ Hz), 0.86 (9H, s); ^{13}C NMR: δ 72.5 (0), 47.8 (1), 39.1 (2), 39.0 (2), 32.5 (0), 27.9 (3), 24.7 (2), 16.1 (2), 15.0 (3).
For **4**: mp 71–73 °C, lit.[12] 73–74 °C; IR (cast): 3380 cm^{-1}; ^1H NMR: δ 1.66 (2H, m), 1.57 (2H, m), 1.39 (4H, m), 1.26–1.35 (5H, m), 0.91 (3H, m), 0.86 (9H, s); ^{13}C NMR: δ 70.9 (0), 48.2 (1), 46.9 (2), 37.6 (2), 32.6 (0), 27.8 (3), 22.7 (2), 16.6 (2), 15.0 (3); lit.[12] ($CDCl_3$, 80 MHz instrument): δ 70.7, 48.1, 46.8, 37.5, 32.4, 27.6, 22.6, 16.4, 14.8.
11. (a) Buckwalter, B. L.; Burfitt, I. R.; Felkin, H.; Joly-Goudket, M.; Maemura, K.; Salomon, M. F.; Wenkert, E.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 6445–6450; (b) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396–10415.
12. Welch, S. C.; Prakasa Rao, A. S. C.; Lyon, J. T.; Assercq, J.-M. *J. Am. Chem. Soc.* **1983**, *105*, 252–257.
13. *Allylindium procedure*: Indium metal (0.50 mmol) and allyl iodide (0.75 mmol) in DMF (2.0 mL) were stirred under argon for 1 h during which time most of the indium dissolved giving a grey solution. The enone (0.50 mmol) in DMF (1.0 mL) was introduced dropwise, and the solution was stirred at room temperature. Reaction progress was monitored by TLC. Aqueous workup provided the product(s). The ratio of products was determined by NMR.
14. Gynane, M. J. S.; Worrall, I. J. J. *J. Organomet. Chem.* **1974**, *81*, 329–334.
15. (a) Makoto, W.; Hidenori, O.; Kinya, A. *Tetrahedron Lett.* **1986**, *27*, 4771–4774; (b) Makoto, W.; Munekazu, H.; Yoshihiro, K.; Norikazu, M. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2265–2267; (c) Xu, X.; Zha, Z.; Wang, Z. *Synlett* **2004**, 1171–1174.
16. *Allylbismuth procedure*:[15] The enone (0.6 mmol), allyl bromide (1.3 mmol), $BiCl_3$ (0.85 mmol), and zinc powder (1.3 mmol) in THF (10 mL) were heated to reflux under argon. Reaction progress was monitored by TLC. A solid was removed by filtration, and the THF was evaporated under vacuum. Ether was added, and this solution was washed with 0.5 M HCl, H_2O, and saturated $NaHCO_3$. The solution was dried ($MgSO_4$), and the ether was evaporated under vacuum. The ratio of products was determined by NMR.
17. For **5**: IR (cast): 3348 cm^{-1}; ^1H NMR: δ 5.89 (1H, m), 5.10–5.19 (3H, m), 2.33 (1H, dd, $J = 13.7$, 6.9 Hz), 2.25 (1H, dd, $J = 13.7$, 8.0 Hz), 2.20 (1H, dt, $J = 5.5$, 14.0 Hz), 1.99 (2H, m), 1.70–1.89 (3H, m), 1.04 (3H, s), 0.90 (3H, d, $J = 7.1$ Hz), 0.865 (3H, d, $J = 6.5$ Hz), 0.860 (3H, d, $J = 6.5$ Hz), 0.68 (3H, s), and other signals unresolved 0.70–1.68; ^{13}C NMR: δ 147.1 (0), 134.2 (1), 125.6 (1), 118.7 (2), 71.1 (0), 56.5 (1), 56.4 (1), 54.4 (1), 45.7 (2), 42.7 (0), 40.1 (2), 39.7 (2), 37.7 (0), 36.4 (2), 36.2 (1), 36.0 (1), 34.9 (2), 33.5 (2), 32.6 (2), 32.5 (2), 28.4 (2), 28.2 (1), 24.4 (2), 24.1 (2), 23.0 (3), 22.8 (3), 21.4 (2), 19.2 (3), 18.9 (3), 12.2 (3).
For **6**: IR (cast): 3422 cm^{-1}; ^1H NMR: δ 5.85 (1H, m), 5.24 (1H, s), 5.09–5.14 (2H, m), 2.21–2.30 (2H, m), 2.20 (1H, m), 1.97–2.03 (2H, m), 1.80 (1H, m), 1.72 (1H, m), 0.94 (3H, s), 0.90 (3H, d, $J = 6.8$ Hz), 0.87 (3H, d, $J = 6.4$ Hz), 0.86 (3H, d, $J = 6.1$ Hz), 0.66 (3H, s), and other signals unresolved 0.77–1.68; ^{13}C NMR: δ 149.6 (0), 134.3 (1), 124.1 (1), 118.4 (2), 69.3 (0), 56.4 (1), 56.3 (1), 54.5 (1), 47.6 (2), 42.7 (0), 40.1 (2), 39.7 (2), 37.8 (0), 36.4 (2), 36.1 (1), 36.0 (1), 33.5 (2), 32.9 (2), 32.7 (2), 32.2 (2), 28.4 (2), 28.2 (1), 24.5 (2), 24.1 (2), 23.0 (3), 22.8 (3), 21.7 (2), 18.9 (3), 18.1 (3), 12.2 (3).
18. 1,2-Addition of an allylindium reagent to carvone was reported previously: Kim, H. Y.; Choi, K. I.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Cho, Y. S. *Synth. Commun.* **2003**, *33*, 1899–1904, but the stereochemistry of the product was not determined.
19. Scholl, S.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
20. For **7**: IR (neat): 3403, 1644 cm^{-1}; ^1H NMR: δ 5.87 (1H, m), 5.47 (1H, narrow m), 5.16 (1H, br d, $J = 11.0$ Hz), 5.13 (1H, br d, $J = 18.5$ Hz).4.73 (2H, br s), 2.47 (1H, dd,

$J = 13.8$, 7.2 Hz), 2.32–2.37 (2H, m), 2.05–2.14 (2H, m), 1.96 (1H, m), 1.74 (3H, br s), 1.73 (3H, s), 1.50 (1H, t, $J = 12.2$ Hz); ^{13}C NMR: δ 149.2 (0), 138.3 (0), 133.9 (1), 124.1 (1), 118.8 (2), 109.3 (2), 74.0 (0), 43.1 (2), 40.7 (2), 39.4 (1), 31.0 (2), 21.0 (3), 17.2 (3).

For **9**: IR (neat): 3415 cm^{-1}; ^{1}H NMR: δ 5.63 (2H, narrow m), 5.30 (2H, narrow m), 4.80 (2H, s), 4.77 (2H, s), 2.46 (2H, dd, $J = 14.3$, 4.0 Hz), 2.21–2.32 (4H, m), 2.07 (2H, br d, $J = 12.5$ Hz), 1.97 (2H, m), 1.87 (2H, m), 1.77 (6H, s), 1.64 (6H, s), 1.40 (2H, t, $J = 12.5$ Hz); ^{13}C NMR: δ 149.0 (0), 138.2 (0), 129.3 (1), 123.8 (1), 109.2 (2), 73.7 (0), 41.7 (2), 40.4 (2), 39.3 (1), 30.9 (2), 20.7 (3), 17.1 (3).

For **10**: IR (neat): 1640, 1602 cm^{-1}; ^{1}H NMR: δ 7.81 (4H, m), 7.43 (3H, m), 6.03 (1H, m), 5.74 (1H, narrow m), 5.11 (1H, d, $J = 9.5$ Hz), 5.10 (1H, d, $J = 17.5$ Hz), 4.72 (1H, s), 4.71 (1H, s), 4.61 (1H, d, $J = 12.5$ Hz), 4.37 (1H, d, $J = 12.5$ Hz), 2.67 (1H, ddd, $J = 14.3$, 6.1, 1.2 Hz), 2.44 (1H, dd, $J = 14.3$, 8.2 Hz), 2.38 (1H, m), 2.10 (1H, br d, $J = 10$ Hz), 1.95–2.08 (2H, m), 1.82 (1H, t, $J = 13.0$ Hz), 1.72 (6H, s); ^{13}C NMR: δ 149.3, 137.7, 136.6, 135.2, 133.7, 132.9, 128.1, 128.0, 127.9, 127.8, 126.1, 125.7, 125.5, 125.4, 117.4 (2), 109.0 (2), 80.5 (0), 64.1 (2), 43.9 (2), 39.7 (1), 34.7 (2), 31.2 (2), 21.1 (3), 17.6 (3).

21. Zhao, L.; Burnell, D. J. *Org. Lett.* **2006**, *8*, 155–157.