188–9 °C, $[\alpha]^{25}_D$ +135.6° (c 0.84, $CHCl_3$), which was N-protected as the Boc derivative, $[\alpha]^{25}_D$ +104.2° (c 1.43, $CHCl_3$). At this stage, minor quantities of the cis-fused isomer derived from 7 could be easily separated by column chromatography. Acid hydrolysis of the glycosidic linkage followed by oxidation with PCC gave the lactone 10 (72%, two steps), $[\alpha]^{25}_D$ +63° (c 1.12, $CHCl_3$). We were now ready to effect the crucial Bischler–Napieralski reaction, which would give us the desired pentacyclic skeleton and the last stereogenic center at C-3 after catalytic reduction. The two-step sequence proceeded in excellent yield to give the desired product 11 (77% overall), mp 165–170 °C dec, $[\alpha]^{25}_D$ −144.5° (c 1.21, $CHCl_3$).[25]

Having assembled the immediate precursor to 19-epiajamalicine, we were faced with a number of choices for the methoxycarbonylation and functional adjustment of the lactone carbonyl group. Previously, van Tamelen and co-workers[8] had achieved this transformation via acylation of the lactone with methyl formate followed by an acid-catalyzed acyl–lactone rearrangement. More recently Uskokovic and co-workers[12] have used the Bredereck reagent in a bicyclic model lactone to obtain the α-(dimethylamino)methylidene derivative, which was then subjected to strong acid conditions in order to mediate the rearrangement. Although α-branching was successfully achieved in 11 under the same conditions, the subsequent acyl–lactone rearrangement failed and we resorted to an alterative approach. Thus, treatment of the 11 with LDA and Mander's reagent ($CNCO_2Me$)[26] as described by Leonard for a model lactone[16b] effected smooth methoxycarbonylation to give 12 as a single isomer, $[\alpha]^{25}_D$ −62.9° (c 0.7, $CHCl_3$). Treatment with DiBALH, followed by acid-catalyzed dehydration of the resulting lactol, gave crystalline 19-epiajmalicine (2), mp 205–206 °C dec, $[\alpha]^{25}_D$ +58.8° (c 0.17, $CHCl_3$); hydrochloride, mp 255–260 °C dec, $[\alpha]^{25}_D$ +84.5° (c 0.5, MeOH), identical in all respects with published data[15,17d] (^1H NMR, ^{13}C NMR, high-resolution mass, microanalysis).

Ajmalicine (1) was obtained from 10 via a ring-opening and inversion sequence through the intermediacy of the hydroxy acid. Thus, hydrolysis of 10 with barium hydroxide and careful acidification followed by intramolecular inversion of the resulting δ-hydroxy acid under Mitsunobu reaction conditions[27–29] gave the C-19 inverted lactone 13 $[\alpha]^{25}_D$ +12.3° (c 0.47, $CHCl_3$) and 10 (4:1). Application of the same sequence of reactions to 13 as for 10 gave the C-19 epimeric lactone corresponding to 13, $[\alpha]^{25}_D$ −130.4° (c 0.78, $CHCl_3$). Methoxycarbonylation with Mander's reagent followed by reduction with DiBALH gave *N*-Boc-ajmalicinine 14[30] as a 13:1 mixture of anomers. Dehydration of 14 led to ajmalicine isolated as the hydrochloride (21% overall from 10), mp and mixed mp 270–275 °C dec, $[\alpha]^{25}_D$ −12° (c 0.05, MeOH) (lit.[31] $[\alpha]^{25}_D$ −12.9° (c 0.24, MeOH).

We have described a strategy for the total synthesis of (−)-ajmalicine (1), (+)-19-epiajmalicine (2), and *N*-Boc-ajmalicinine (14) from a common progenitor. The general approach can be easily extended to tetrahydroalstonine (3) and rauniticine (4) as well as other 3-α-heteroyohimibines starting with the readily available chiron 7.[32,33]

Acknowledgment. We thank NSERCC for a predoctoral fellowship to A.-M.F. and for generous financial assistance. We acknowledge the assistance of the mass spectrometry and NMR laboratories of the University of Montreal in recording spectra.

Supplementary Material Available: Selected spectra and physical constants of key compounds (37 pages). Ordering information is given on any current masthead page.

(24) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. Borch, R. F. *Org. Syn.* **1972**, *54*, 124. Lane, C. F. *Synthesis* **1975**, 135.

(25) A portion of the product in which the *N*-Boc group was partially hydrolyzed during the reaction was transformed into 11 by treatment with Boc anhydride in CH_2Cl_2/DMAP.

(26) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 3425. *Aldrichimica Acta* **1987**, *20*, 53.

(27) A similar strategy was independently utilized by Leonard et al.[16b] to elaborate a synthesis of methyl elenolate.

(28) Mitsunobu, O. *Synthesis* **1981**, 1.

(29) For the conversion of ajmalicine to 19-epiajmalicine via an intermolecular Mitsunobu reaction, see ref 17d.

(30) Bombardelli, E.; Gabetta, B.; Mustich, G.; Martinelli, E. M. *Fitoterapia* **1974**, *45*, 183.

(31) Obtained from Fluka, A. G. See also: Höfle, G.; Heinstein, P.; Stöckigt, J.; Zenk, M. H. *Planta Medica* **1986**, *40*, 120.

(32) For example, 7 was easily converted to the corresponding lactone and lactam via reduction of aldehyde and lactonization, etc. (see supplementary material).

(33) All new compounds were satisfactorily characterized by chemical, physical, spectroscopic and microanalytical methods (see supplementary material).

On Deuterium-Labeling Studies for Probing Rhodium-Catalyzed Hydroboration Reactions

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Summary: Reactions of deuteriocatecholborane ($C_6H_4O_2BD$) with alkenes in the presence of rhodium(+1) complexes have been reinvestigated. Distributions of label in the products differ significantly from those reported previously, and alternative rationales for these observations are provided.

Deuterium-labeling studies were recently reported[1] to elucidate the mechanism of rhodium-catalyzed hydroborations (Scheme I). Our interest was aroused because the authors implied their results, particularly those depicted in eq 1, cast doubt upon a postulate one of us had used to explain substrate-controlled diastereoselectivities in catalyzed hydroborations of chiral, 1,1-disubstituted, acyclic alkenes.[2,3]

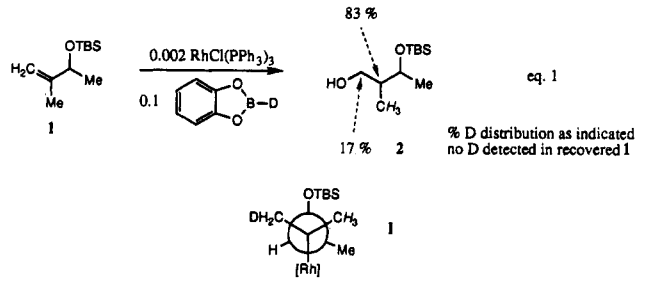
To explain the observed distribution of deuterium in the alcohol 2, the authors proposed,[1] "*The incorporation of deuterium α to the hydroxyl group of the product alcohol*

(1) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 2280.

(2) Burgess, K.; Ohlmeyer, M. J. *Tetrahedron Lett.* **1989**, *30*, 5861.

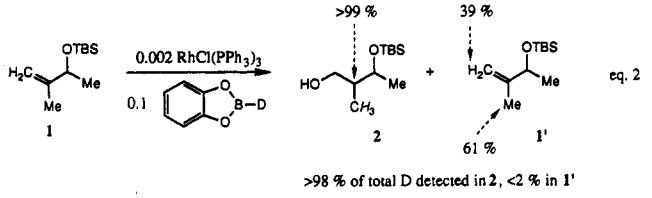
(3) Burgess, K.; Cassidy, J.; Ohlmeyer, M. J. *J. Org. Chem.* **1991**, *56*, 1020.

0022-3263/91/1956-2949$02.50/0



indicates that hydride migration to form the tertiary rhodium alkyl occurs reversibly under the reaction conditions". One might expect such reversible addition of rhodium hydride to deposit label into the 2-methyl group (CH_3); however, the authors explained the absence of deuterium here in terms of preferential β-hydride elimination from one of the two diastereotopic methyl groups of a tertiary rhodium alkyl (we have illustrated this intermediate as projection I), a situation we thought improbable. Furthermore, none of the tertiary alcohol corresponding to reductive elimination of alkyl and boryl ligands from intermediate I was formed, an observation that implies formation of significant amounts of tertiary alkyl complex is unlikely. In view of the significance of this study to our research, we decided to reinvestigate these labeling experiments.

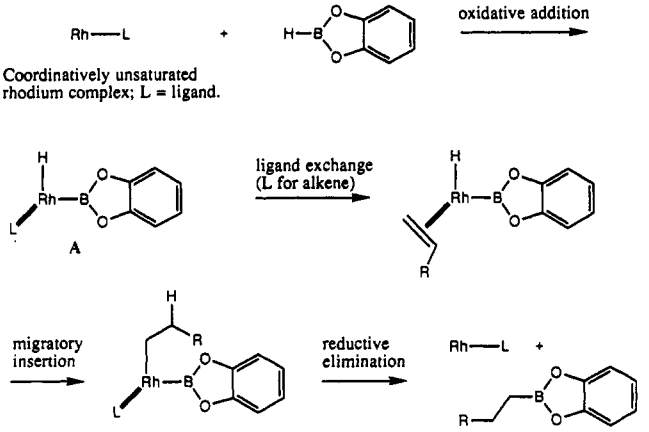
2-Methyl-3-((*tert*-butyldimethylsilyl)oxy)but-1-ene (1). This substrate was deuteroborated under five different sets of conditions (see supplementary), including those we typically use in our studies of substrate-controlled diastereoselectivity [2 equiv of deuteriocatecholborane,[4,5] 1 mol % $[Rh(COD)Cl]_2$, 4 mol % PPh_3, THF, −78 °C to 20 °C, 12 h], and the conditions used by others (i.e. cat. $RhCl(PPh_3)_3$, 2 equiv of deuteriocatecholborane). In all these experiments *less than 1 % of deuterium label in product 2 is situated in the hydroxymethylene group* (by ^2H NMR of isolated 2); the results shown in eq 2 are typical.



Samples of alcohol 2 were also prepared by reducing the corresponding (unlabeled) aldehyde with BD_4^- and by hydroboration/oxidation of 1 using BD_3; consequently our assignments were confirmed by comparison of the ^2H NMR spectra of these materials with spectra from the experiment described by eq 2 (Figure 1).

Alcohol 2 formed via catalyzed deuteroboration consists of two diastereomers; this is evident from ^1H NMR, and ^2H NMR which shows $HOCH_2CDCH_3$ resonances at 1.92 and 1.60 (Figure 1). The ratio of these two ^2H NMR signals is 86:14, *very close to that previously reported for α:β deuteration* (i.e. 83:17, eq 1). The very small amounts of deuterium label observed in the recovered starting material 1'[6] was detected in the $DHC{=}CMe$ and $H_2C{=}C(CDH_2)$ groups in a ratio of 39:61;[7] this is almost exactly the statistical distribution one would expect from *diastereorandom* β-elimination from a tertiary alkyl intermediate of type I (i.e. 40:60).

Scheme I. Generalized Postulate for the Mechanism(s) of Rhodium-Mediated Hydroboration Reactions



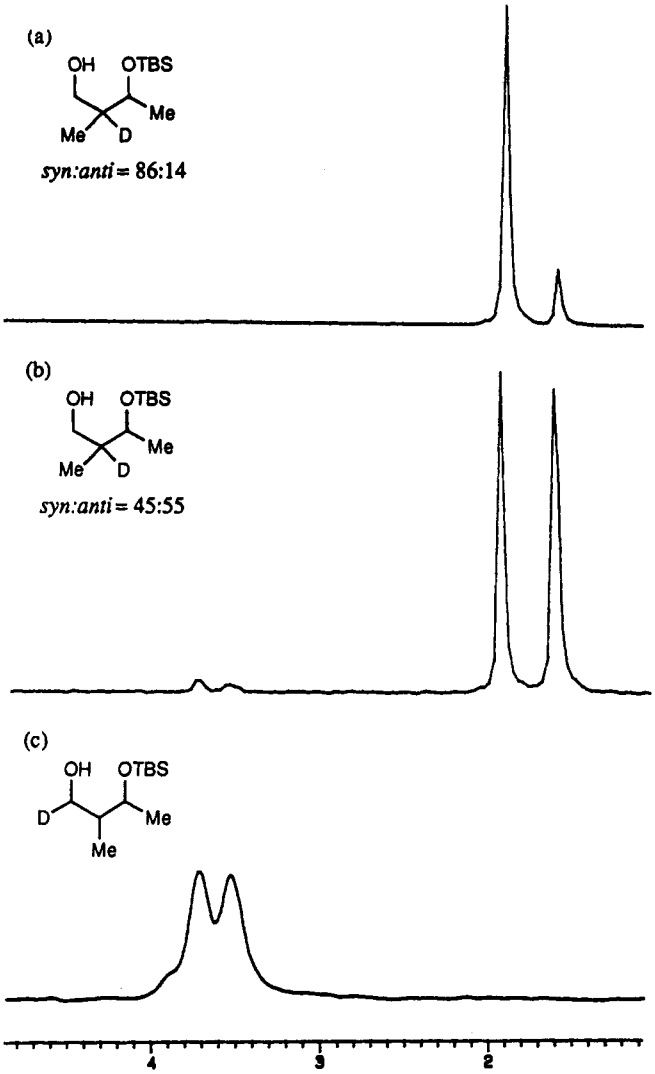
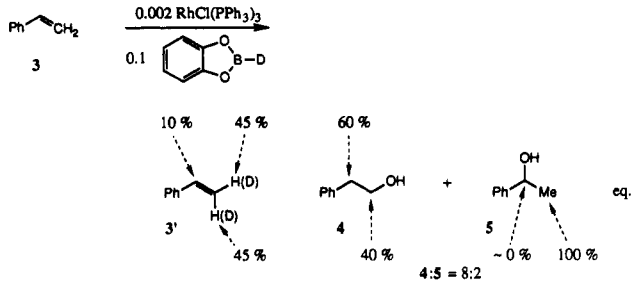


Figure 1. Key ^2H NMR spectra (δ ppm, 76.7 MHz, $CHCl_3$): (a) compound 2 from the experiment depicted in eq 2; (b) mixture of diastereomers from uncatalyzed hydroboration of 1 with BD_3 [note this spectrum shows more deuterium at 3.7–3.5 ppm than in spectrum (a)]; and, (c) a similar alcohol, labeled at C^1, prepared by reaction of BD_4^- on the corresponding aldehyde.

Phenylethene (3). Hayashi and co-workers reported[8] $[RhCl(PPh_3)_3]$-mediated hydroboration of phenylethene

(4) Kabalka, G. W.; Yang, D. T. C.; Chandler, J. H.; Baker, J. D. *Synthesis* **1977**, 124.
(5) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. In *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975.
(6) Constitutes 1% of the total label as indicated by the ^2H NMR spectrum of crude material from eq 2.
(7) Determined via ^2H NMR of isolated 1'.
(8) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426.

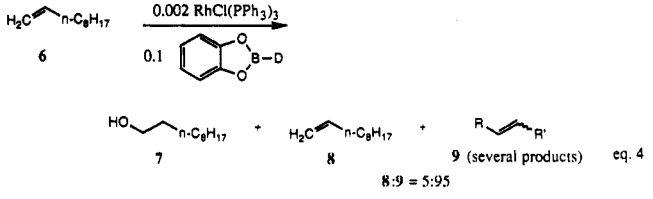
(3) gives alcohols 4 and 5 in a ratio of 9:1, whereas Evans and Fu obtained[1] exclusive formation of 5. Our results (eq 3, 4:5 from calibrated GC analysis) are consistent with the findings of Hayashi et al. insofar as we observed the primary alcohol 4 is the major product. We repeated this



% of total D, 3':4:5 = 40:46:14

experiment four times using slightly modified conditions and found the product and label distribution varies slightly with reaction conditions. Investigation of this reaction is still in progress, but at this stage it seems that the proportion of product 5 increases with the amount of phosphine in the catalyst precursor; differences between results reported by various groups therefore could be due to catalyst purity.[14] The distribution of label in product 5 agrees with that originally reported, but in our experiments most of the label is distributed between the α- and β-positions of primary alcohol 4. Moreover, high-resolution mass spectroscopy indicates *some molecules of products 3', 4, and 5 contain more than one deuterium atom, while others contain no deuterium at all*, indicating deuterium is widely scrambled between the products and recovered alkene. Furthermore, the α:β ratio (.e. $PhCH_2CH_2OH$: $PhCHDCH_2OH$) for deuterium label distribution in product 4 increases with the number of equivalents of deuteriocatecholborane added.

1-Decene (6). Hydroboration of this substrate with $C_6H_4O_2BD$ is the most complicated of the examples we have studied so far. Using 0.002 equiv of $RhCl(PPh_3)_3$ and 0.1 equiv of deuteriocatecholborane (THF, 20 °C, 30 min) we observed deuterium label distributed amongst all positions along the decyl chain of alcohol 7. Furthermore, migration of the double bond had occurred; GC/^{2}H NMR studies indicate 1-decene constitutes only 5% of the alkenes in the crude reaction mixture, the other 95% consists of randomly labeled decene isomers 9 (eq 4). This ex-



deuterium observed in all possible C D positions in 7, 8, and 9

periment was repeated four times; the product distribution was found to vary with reaction time, extended reaction times favor formation of internal alkenes (9).

Conclusions. *These labeling studies provide very little information concerning the mechanism(s) of rhodium-catalyzed hydroboration reactions.* Our results indicate hydroboration of substrate 1 proceeds predominantly via a primary rhodium alkyl, just as one might expect. Catalyzed deuterioborations of the other substrates are even less informative because the results are sensitive to variations in reaction parameters. This is because $RhCl(PPh_3)_3$ and catecholborane do not react to give a single complex; ^{31}P NMR studies indicate[9,10] several products are formed, and Marder et al. have identified[10] the presumed catalytic intermediate $RhClH(BO_2C_6H_4)(PPh_3)_2$ (10) (cf. intermediate A, Scheme I), $RhH(PPh_3)_3$ (11), and $RhH_2Cl(PPh_3)_3$[11] (12). Hydridorhodium complexes like 11 and 12 readily undergo insertion/β-elimination reactions causing migration of double bonds.[12,13] Similarly, the deuterated analogues $RhD_2Cl(PPh_3)_3$ and $RhD(PPh_3)_3$ presumably are capable of distributing label in the alkene substrate *before and after the $C_6H_4O_2BD$ available in these experiments (0.1 equiv)* is consumed. Consequently, one can explain data depicted in eqs 2–4 in terms of catalyzed hydroboration competing with insertion/β-elimination processes mediated by $RhClD(BO_2C_6H_4)(PPh_3)_2$, $RhD_2Cl(PPh_3)_3$, $RhD(PPh_3)_3$, and/or other metal deuterides. Furthermore, there is absolutely no evidence that the very small amounts of tertiary rhodium alkyl apparently formed in the hydroboration of 1 is a *boryl*rhodium complex; indeed, the absence of tertiary alcohol product formed via reductive elimination from intermediate I implies it is not.

Reversible insertion/β-elimination reactions are significant in catalyzed hydroborations of phenylethene (3) and 1-decene (6), but again there is no evidence that the rhodium deuteride catalyzing such processes is directly related to the hydroboration event. Indeed, competing reactions could account for formation of *polydeuterated* 3'–5 in the phenylethene experiment, and the multitude of labeled compounds formed from 1-decene (eq 4). It is reasonable to expect the distribution of deuterium labels in catalyzed hydroborations of 3 and 6 to vary with slight changes of reaction conditions if competing reactions occur, hence the discrepancies between this study and the previous work.[14]

Results presented here for the deuteroboration of substrate 1 differ significantly from those in the original report.[1] We have no reason to doubt results reported for the other labeling experiments because our efforts show these particular transformations are sensitive to reaction conditions and/or catalyst purity; however, our findings are different so we conclude *these experiments are relatively uninformative.* Finally, we would like to stress that *any conclusions drawn from these deuterium labeling studies must allow for the possibility that competing processes could influence deuterium distribution.*

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Supplementary Material Available: Procedures and data for the experiments depicted in eqs 2–4, tabulated results for the other experiments mentioned (9 pages). Ordering information is given on any current masthead page.

(9) Burgess, K.; Ohlmeyer, M. J.; Donk, W. A. v. d. unpublished results.

(10) Westcott, S. A.; Taylor, N. J.; Marder, T. B.; Baker, R. T.; Jones, N. J.; Calabrese, J. C. *J. Chem. Soc., Chem. Commun.*, in press. Complexes 10 and 12 predominate under the standard conditions for catalyzed hydroboration.

(11) Sacco, A.; Ugo, R.; Moles, A. *J. Chem. Soc. A* **1966**, 1670.

(12) Matsuda, I.; Kato, T.; Sato, S.; Izumi, Y. *Tetrahedron Lett.* **1986**, *27*, 5747.

(13) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.

(14) After this paper was submitted, Zhang et al. reported the regiochemistry of the catalyzed hydroboration of styrene varies with the proportion of phosphine in the catalyst. See: Zhang, J.; Lou, B.; Guo, G.; Dai, L. *J. Org. Chem.* **1991**, *56*, 1670.