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Surprisingly Facile C–H Activation in the Course of Oxime-Directed Catalytic Asymmetric Hydroboration

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Abstract

Deuterium-labeling studies carried out in conjunction with investigations into the directed catalytic asymmetric hydroboration of unsaturated oxime ethers reveal a surprisingly facile *ortho*-metallation or σ-bond metathesis pathway that that diverts the expected course of CAHB to a tandem C-H activation/hydroboration reaction pathway.

Keywords

directed metallation; C-H activation; rhodium-catalyzed borylation; rhodium-catalyzed hydroboration

Introduction

The catalytic asymmetric hydroboration (CAHB) of alkenes has enjoyed a long history largely focused on the successful reactions of vinyl arene substrates and a recent resurgence in interest for the preparation of chiral organoboronates.[1,2] We have developed efficient carbonyl-directed CAHBs of unsaturated amides and esters capable of chelating to Rh(I) through a two-point binding mechanism[3] and shown that the presence of an aryl substituent on the alkene is not required to obtain high levels of enantioselectivity.[4,5] For example, rhodium-catalyzed CAHBs of the β,γ-unsaturated amides and esters illustrated in Figure 1 lead, in the case of (*E*)- or (*Z*)-1,2-disubstituted and -trisubstituted alkenes **1**, to enantioselective borylation at the β-carbon yielding the β-hydroxycarbonyl compounds **2** after oxidation. In the case of β,γ-methylidene derivatives **3**, CAHB affords a γ-borylated intermediate which upon oxidation affords the γ–hydroxycarbonyl derivative **4**. The successful catalyst system employs a cationic Rh(I) complex with a chiral BINOL- or TADDOL-derived phosphite or phosphoramidite (e.g., **L1** and **L2**); enantioselectivities up to 99% ee have been obtained. Encouraged by the successful results in carbonyl-directed CAHB, we looked to explore the effectiveness of other potential directing groups. Inspired

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Supplementary Material

Experimental procedures and spectral characterization are available free of charge via the Internet at http://_____.

by the recent report of the oxime ether-directed asymmetric dioxygenation of alkenes[6] and the novel structural features of oximes, the benzophenone-derived oxime **5a** was prepared.

Results and Discussion

The β,γ-methylidene oxime ether **5a** was subjected to rhodium-catalyzed CAHB under reaction conditions identical to those used for the structurally similar 1,1-disubstituted-β,γ-unsaturated *N*-phenyl amide **3** (R = Me, X = N(H)Ph) (2% [(**L1**)$_2$Rh(nbd)]BF$_4$, 2 equiv. tmdBH (**B1**), THF, rt). The starting material was completely consumed within 16 h, but after oxidative workup with NaBO$_3$•monhydrate (1:3 water in THF), the expected γ-alcohol **6a** was isolated in only 6% yield. Two reduced byproducts are formed in a roughly 2:1 ratio and account for approximately 90% of the mass recovered from the reaction. The minor of the two products, compound **8a**, results from apparent hydrogenation of the alkene moiety. Its presence is not particularly surprising; a small amount of reduced alkene is a common byproduct in metal-catalyzed hydroborations. The ^{1}H NMR spectrum of the major byproduct shows only nine aromatic hydrogens accompanied by a singlet at δ 11.2 ppm (integrates to one hydrogen); the latter is readily exchangeable upon treatment with D$_2$O. High-resolution mass spectrometry and ultimately independent synthesis confirm the structure is the *ortho*-hydroxylated/alkene reduction product **7a**. While we were unable to cleanly isolate its corresponding *ortho*-borylated intermediate, we hypothesize that **7a** is formed via oxime-directed *ortho*-CH activation followed by borylation and conversion to the phenol upon oxidative workup. Alkene reduction must also occur at some point. We find no evidence for any doubly or poly-borylated products; for example, the *ortho*-and γ-borylated product compound **9** is not found.

Although we had not anticipated *ortho*-metallation under the conditions of rhodium-catalyzed CAHB, oximes are increasingly finding use as direction groups for *ortho*-metallation reactions in other contexts; reactions leading to *ortho*-acetoxylation, *ortho*-amidation and carbon-carbon bond formation have been recently reported (Figure 2). For example, Sanford and Dong reported the palladium-catalyzed oxime-directed oxidation of unactivated sp^3 and sp^2 C-H bonds.[7] The reaction uses Pd(OAc)$_2$ (5 mol%) as the catalyst precursor in an HOAc/Ac$_2$O reaction medium at elevated temperatures (80–100 °C). Several groups have recently reported the use of (Cp*)Rh(III) complexes to catalyze the directed *ortho*-metallation of oxime ethers for the formation of C−N bonds.[8] For example, Li and coworkers reported the oxime ether-directed *ortho*-amidation by N-hydroxycarbamates.[8a]

Oxime ether-directed *ortho*-metallation has also been utilized as a C-C bond forming cross-coupling strategy by a number of research groups. For example, as illustrated in Figure 2, Yu and coworkers reported the oxime-directed (Cp*)Rh(III)-catalyzed *ortho*-C−H cross-coupling with diazomalonates.[9] In other work, Li[10] and Cheng[11] reported the oxime-directed alkynylation of arenes. In Cheng's work the presence of both *ortho*-hydroxy and *ortho*-oxime groups lead to dual-directed C-H activation followed by cyclization and formation of highly substituted benzofurans. Organopalladium intermediates, generated by oxime-directed C-H activation, have also been intercepted by with aryl or acyl radicals to effect C−C bond formation.[12]

In spite of the ample precedents for the use of oxime ethers as directing groups for *ortho*-metallation, the formation of **7** under the conditions of CAHB is unusual in some respects. For example, in each of the rhodium-catalyzed *ortho*-metallations cited above, the reactions are run at elevated temperatures under mildly oxidizing conditions, and the catalyst precursor is a (Cp*)Rh(III) complex; Rh(I)-catalysts are relatively rarely used.[13] In contrast, the formation of **7a** arises from a Rh(I) precatalyst under reducing conditions.

The yield of **7a** varies widely as a function of the ligand (e.g., **L1** and **L2**) and borane (e.g., (±)-**B1** (tmdBH), pinacolborane (pinBH, **B2**), or catecholborane (catBH, **B3**)) employed (Table 1). For example, the reaction using $[(\mathbf{L1})_2\text{Rh(nbd)}]\text{BF}_4$ with tmdBH (**B1**) afforded *ortho*-hydroxylated **7a** as the major product (Table 1, entry 1). In contrast, the reaction using $[(\mathbf{L2})_2\text{Rh(nbd)}]\text{BF}_4$ under the same conditions gave γ-alcohol **6** as the major product (58%) although **7a** is also formed in significant amounts (31%) (Table 1, entry 2). Electronically and sterically similar boranes tmdBH (**B1**) and pinBH (**B2**) give substantially different product distributions. Although the ratio of **7a**:**8a** is again about 2:1, pinBH affords in addition, an isomer of **6**, the β-hydroxylated product (16%) (Table 1, entry 3). The more electron deficient and relatively more reactive borane, catBH (**B3**), again gives a very different product mixture. Little alkene reduction is observed (approximately 7% in total) and product 7a is isolated in only trace amounts (ca 1% yield). Overall, γ-alcohol **6a** (63%) is the predominant product using catBH, although the product obtained is nearly racemic (Table 1, entry 4).

In related studies of the carbonyl-directed CAHB, the nature of the alkene substituent proved important. Increasing the size of the substituent generally increased the yield of the desired γ-borylated products. In contrast, the bulkier substituents have little effect on the observed product distribution in the present case (Table 1, entries 5–8). Increasing the size of the substituent does lead to a modest increase in the enantiomeric ratio (er) for the CAHB reactions with **L2** and tmdBH (**B1**). However, this may simply be the consequence of more easily differentiating the prochiral faces of the reacting alkene due the greater difference in bulk of the substituents.

Following the distribution of products obtained over the course of the reaction using the $[(\mathbf{L2})_2\text{Rh(nbd)}]\text{BF}_4$ catalyst precursor with tmdBH (**B1**) gives useful insight into the reaction (Figure 2). Employing slightly modified reaction conditions for this experiment, the reaction mixture was stirred at 0 °C for 30 minutes after complete addition of borane, and then allowed to warm to room temperature; aliquots were removed, quenched by oxidative workup and the product distributions shown graphically in Figure 3. The majority of reduced product **8a** is formed within the first 30 minutes at 0 °C, and then only slowly increases thereafter. Meanwhile, the γ-borylated product **6a** and *ortho*-borylated product **7** are formed at a relatively constant rate and ratio over the course of the reaction. These results suggest that non-borylated product **8a** is formed by an independent pathway while the γ-borylated and *ortho*-borylated products, **6a** and **7**, diverge from a common intermediate. Furthermore, resubjecting isolated **8a** to the standard reaction conditions does not lead to the formation of **7a**; **8a** is recovered unchanged. In light of the concurrent formation of γ-borylated product **6a** and *ortho*-borylated product **7a**, we prepared

deuterium-labelled d^{10}-**10** to follow the fate of the hydrogen involved in apparent *ortho*-metallation. The reaction of d^{10}-**10** under conditions used previously (2 mol% [(**L2**)$_2$Rh(nbd)]BF$_4$ and 2 equiv tmdBH (**B1**)) yields surprising results. Ignoring for the moment the precise isotope distribution, the labeled and unlabeled substrates give virtually identical product distributions (see Figure 4 vs Table 1, entry 2). However, it was surprising to find evidence for *ortho*-metallation and H/D-exchange not only for the *ortho*-hydroxylated product but for the products of all three reaction modes, **11–13**!

Deuterated product **12**, derived from *ortho*-borylation and alkene reduction, shows clean redistribution of one *ortho*-deuterium to the terminus of what was the methylidene group (i.e., the methyl group in the product) with apparent incorporation of boron in the *ortho*-position; the latter replaced by OH upon oxidative workup. We see evidence for partial H/D exchange at the other *ortho*-position of the same phenyl substituent resulting in approximately 60% proton incorporation at that position. However, we see no evidence for H/D-exchange on the other oxime phenyl substituent. For reduced product **13**, one *ortho*-deuterium is replaced by hydrogen virtually quantitatively, and the deuterium is again cleanly incorporated into a methyl group in **13**.

One *ortho*-deuterium atom is also redistributed in the course CAHB leading to the major product **11**. Quantitative substitution of one deuterium by hydrogen at the *ortho*-position of the aromatic ring is accompanied by its complete transfer to the propenyl moiety affording a 50:50 mixture of **11a** and **11b**. One possible explanation that accounts for distribution of deuterium to both carbons is a tandem two-step dehydrogenative borylation and reduction.[14]

The nature of the borane has a significant impact on the propensity to *ortho*-C–H activation. Treating d^{10}-**10** with 2 mol% [((**L2**)$_2$Rh(nbd)]BF$_4$ and 2 equivalents catBH (**B3**) in place of tmdBH (**B1**) affords γ-alcohol d^{10}-**14**. While the yield is low (20%), no H/D exchange is observed in either d^{10}-**14** or the recovered starting material (Figure 5). Given the relatively low conversion when using catBH in lieu of tmdBH, we considered that the lack of *ortho*-H/D exchange could be simply due to the background reaction of catBH in a non-catalyzed hydroboration of the alkene rather than rhodium-catalyzed hydroboration. However, this proved not to be the case. Attempted hydroboration using catBH in the absence of a rhodium catalyst resulted in the isolation of only trace amounts of d^{10}-**14** after oxidative workup.

It is important to note that the redistribution of the *ortho*-deuterium, now inferred to occur in **5** as well, is completely transparent in the proteo substrate. A simple explanation that could potentially account for the quantitative exchange of the *ortho*-deuterium is that of an unexpectedly facile oxime-directed *ortho*-metallation and H/D-exchange. To further explore this possibility, d^{10}-**13** was independently synthesized and subjected to standard CAHB conditions. No H/D exchange is observed and d^{10}-**13** is not converted to either **11** or **12** under the reaction conditions (Figure 5). Since *ortho*-H/D exchange was essentially quantitative in all the observed CAHB products (Figure 4) and yet does not occur in reduced byproduct d^{10}-**13** (Figure 5), H/D exchange must occur only from intermediates generated in the course of the alkene reacting.

While the mechanistic details are not yet clear, based on our previous mechanistic studies,[3] we propose the model in Figure 6 to account for the ligand and borane dependent formation of the *ortho*-borylated/alkene reduction product **12**. The substrate presumable chelates rhodium forming a complex such as **15**. Oxidative addition of borane would generate a Rh(III) intermediate such as **16** suitably disposed for alkene insertion into the Rh-H bond affording a coordinately unsaturated intermediate such as **17**. Reductive elimination to form the C-B bond is the expected CAHB pathway that would lead, and in the case of catBH does lead (Figure 5), to a γ-borylated intermediate and ultimately to alcohol d^{10}-**14** after oxidation.

We speculate that if reductive elimination from **17** is slow, the interchange of H/D with boron, whether by formal Rh(III) to Rh(V) oxidative addition (i.e., *ortho*-metallation),[15] σ-bond metathesis, or a σ-cam mechanism,[16] may compete favorably to form an intermediate such as **18**. While the analogy is somewhat indirect, this type of "exchange" during Rh-CAHB has been previously reported for the Rh-catalyzed addition of CCl_4 to alkenes using Wilkinson's catalyst and pinBH (**B2**).[17] Reductive elimination from **18** would release **19** that upon oxidative workup would account for the formation of the *ortho*-borylated/alkene reduction product **12**. A similar sequence, perhaps involving diastereomers of **16** and/or competing alkene insertion into the Rh-B bond, can be envisioned to account for *ortho*-H/D exchange *en route* to the formation of **11**. While the formation of a mixture of deuterated isomers **11a** and **11b** is an additional puzzling aspect, a well-documented dehydrogenative borylation mechanism may be involved to account for the deuterium scrambling.[14]

Conclusions

In summary, oxime ether **5** undergoes rhodium-catalyzed CAHB with tmdBH, pinBH and catBH to afford the expected products of hydroboration and, in the case of tmdBH and pinBH, an unexpected *ortho*-borylated product (Table 1, entries 1–4). Deuterium-labeling studies suggest that H/D-exchange at the *ortho*-position must be associated with hydroboration of the β,γ-alkene, and that *ortho*-metallation or σ-bond metathesis is exceptionally facile leading to a tandem C-H activation/hydroboration reaction. Studies exploring the use of other directing groups for directed CAHB are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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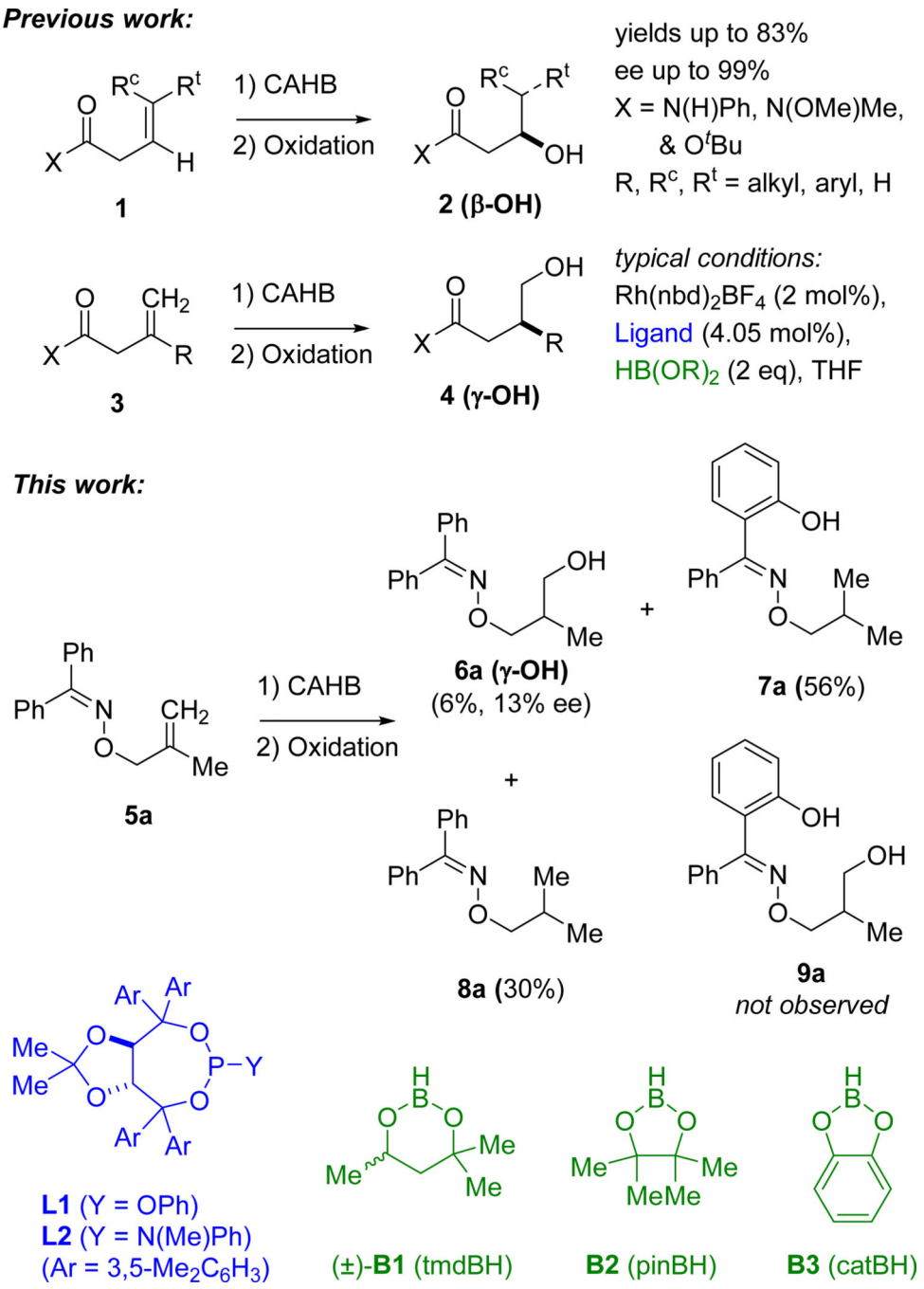


Figure 1.

Recent examples of carbonyl-directed CAHB serve as precedent for the anticipated oxime-directed CAHB.

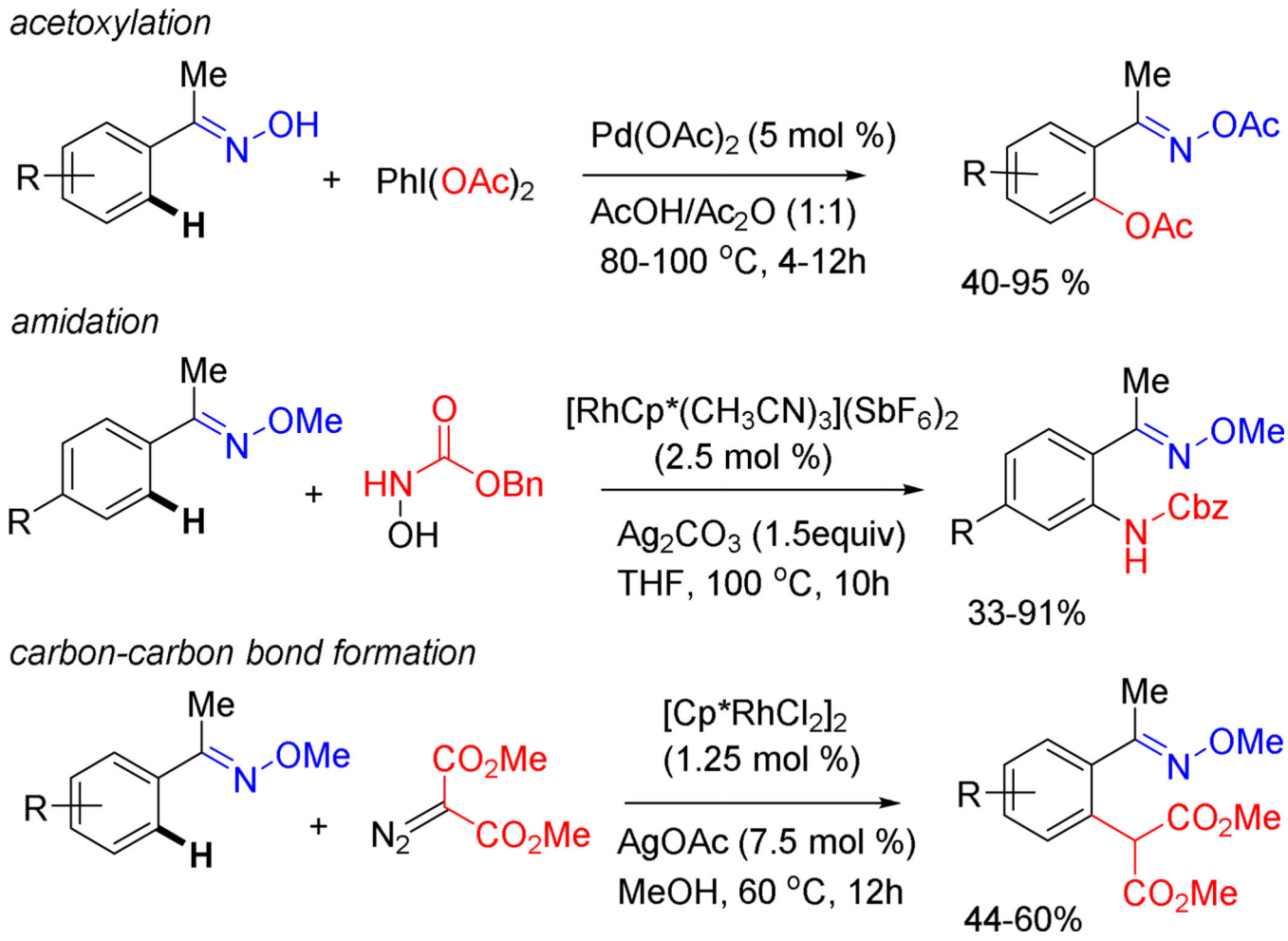


Figure 2.

Recent examples of the use of oximes and oxime ethers as directing groups for *ortho*-metallation; note Cp* = Me_5Cp.

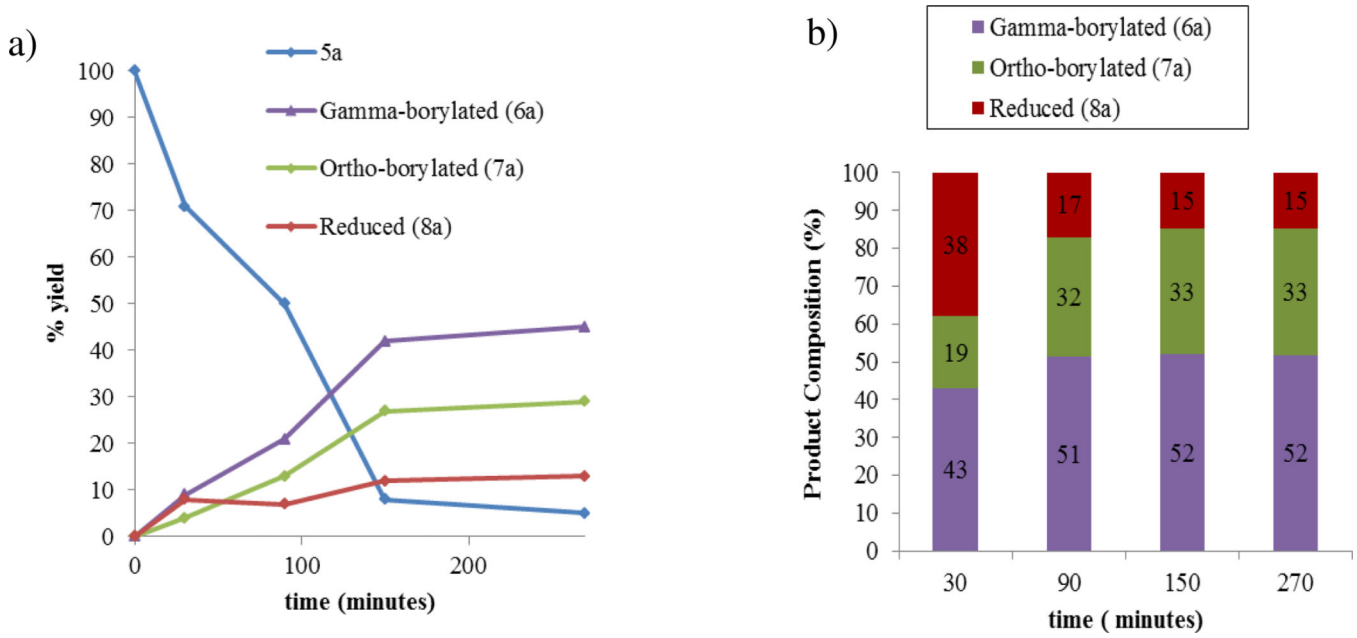


Figure 3.

a) Following the product distribution over time indicates that the non-borylated product **8a** is formed in the early stages of reaction while **6a** and **7a** are formed more or less in parallel. b) Viewing the data another way, the percent composition of the isolated reaction products over the allotted time normalized to 100 percent highlights the rapid formation of **8** at the initial stages of the reaction.

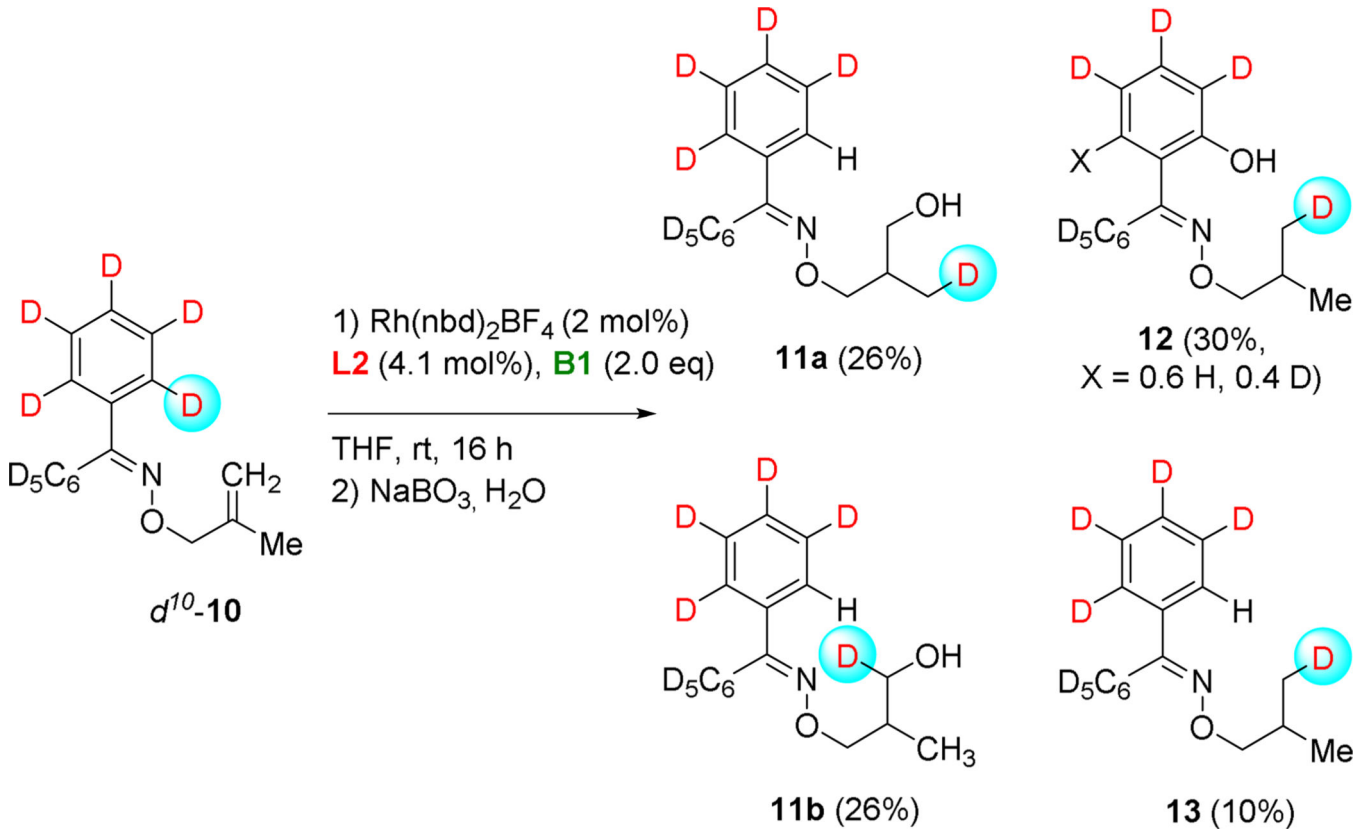


Figure 4.

The redistribution of deuterium shows that *ortho*-C-H activation is occurring in all reaction modes during the course rhodium-catalyzed CAHB.

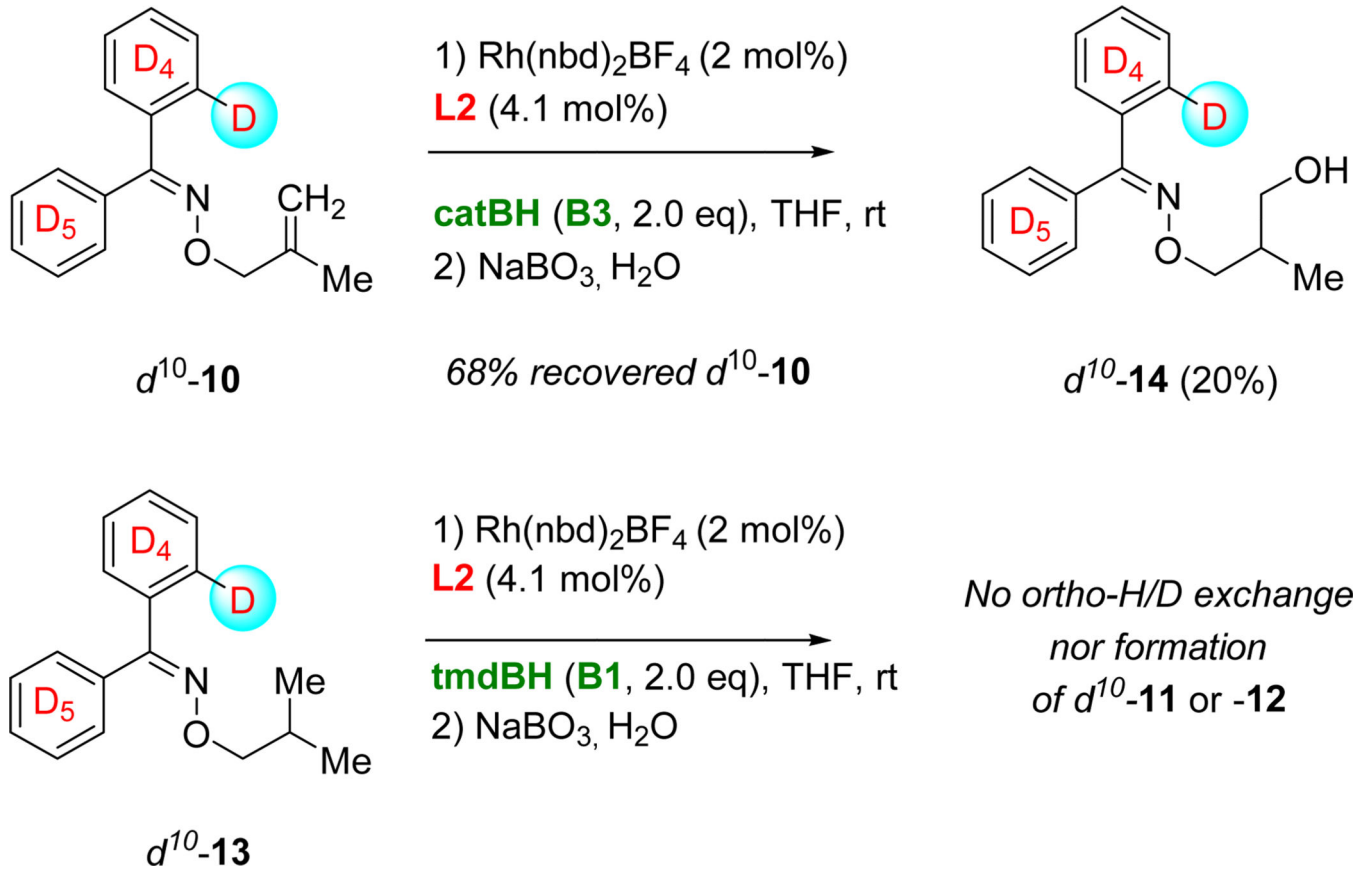


Figure 5.

catBH (**B3**) does not promote H/D exchange under the conditions of CAHB, and the labeled reduced product d^{10}-**13** does not undergo *ortho*-metallation-H/D exchange or conversion to **11** or **12**.

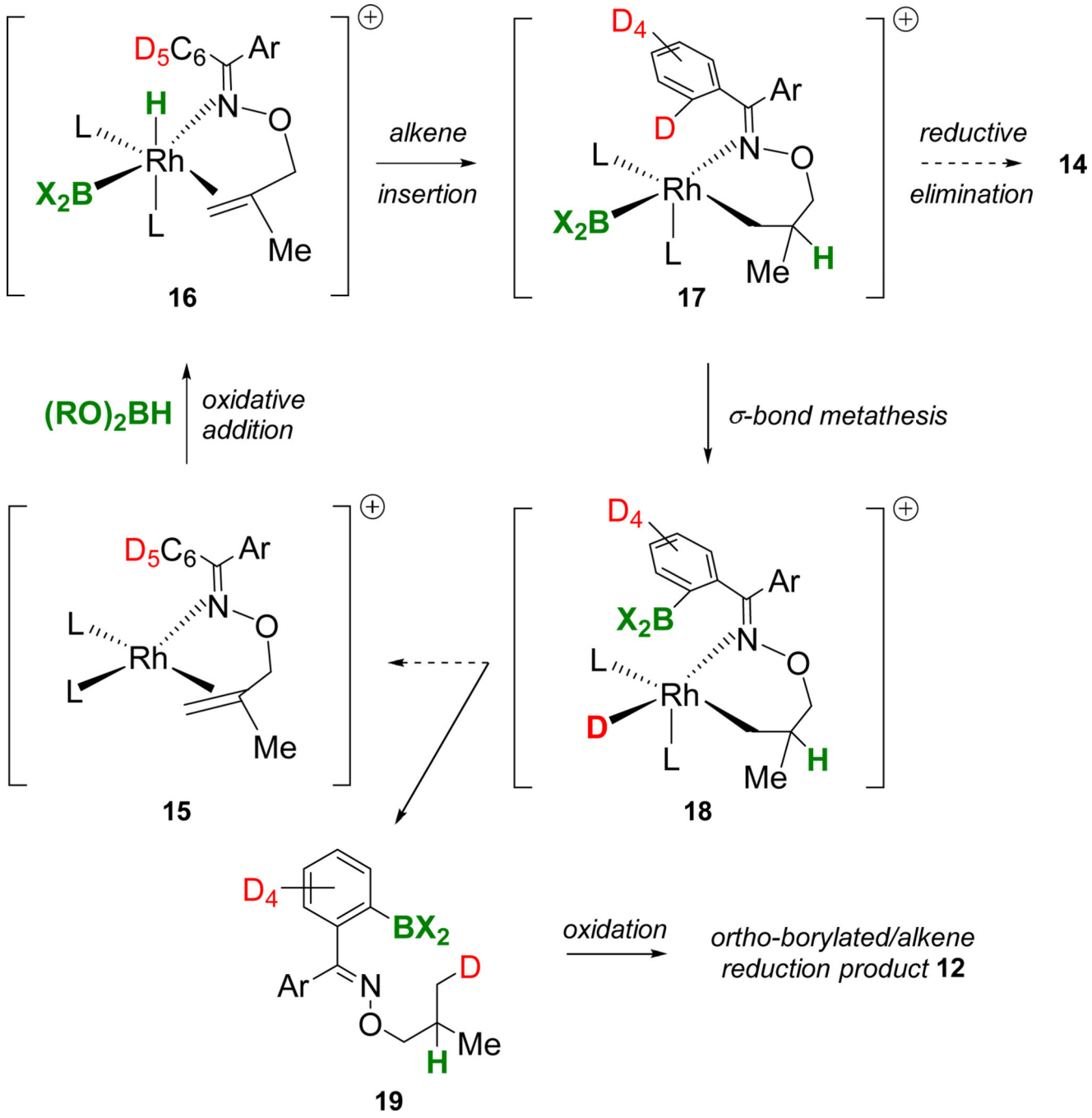
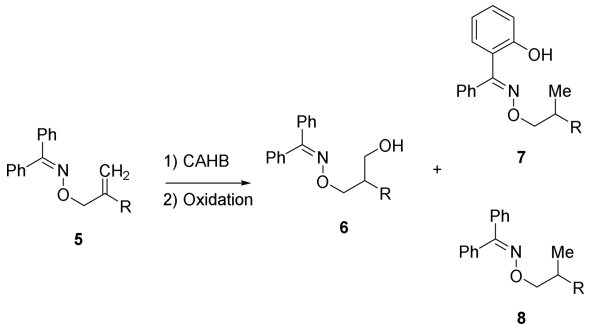


Figure 6.

A model involving σ-bond metathesis to account for facile *ortho*-borylation and deuterium scrambling in the course of CAHB of d^{10}-**10**.

Table 1

The nature of the ligand and borane affect the distribution of borylated products and their derived alcohols.[a]



entry	5 R =	L	borane	6 (er)	7	8
1	**a** Me	L1	tmdBH	6 (56:44)	56	30
2	**a** Me	L2	tmdBH	58 (67:34)	31	10
3[b]	**a** Me	L2	pinBH	30 (56:44)	16	24
4	**a** Me	L2	catBH	63 (53:47)	1	6
5	**b** ^{i}Bu	L2	tmdBH	52 (80:20)	29	16
6	**b** ^{i}Bu	L2	catBH	16 (50:50)	0	0
7	**c** $^{c}C_6H_{11}$	L2	tmdBH	60 (70:30)	11	28
8	**c** $^{c}C_6H_{11}$	L2	catBH	52 (85:15)	2	5

[a] Reaction conditions: 2% $[(\mathbf{L})_2Rh(nbd)]BF_4$, 2 equiv. borane, THF, rt.

[b] 16% of the isomeric β-hydroxy isomer also formed.