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Functionalization of Unactivated Alkenes through Iridium-Catalyzed Borylation of Carbon−Hydrogen Bonds. Mechanism and Synthetic Applications

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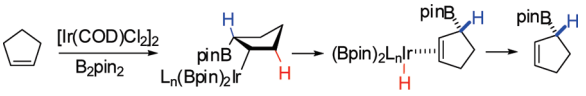

This paper describes an efficient carbon−carbon bond formation reaction, which is based on carbon−hydrogen bond functionalization of unactivated alkenes. This process is based on in situ generation of allylic and vinylic boronates by iridium-catalyzed borylation of alkenes followed by carbon−carbon bond formation reactions. The selectivity of the carbon−hydrogen bond functionalization can be efficiently controlled for cyclic alkenes. By using additives, such as methylimidazole and DBU, the iridium-catalyzed borylation led to formation of allyl boronates, which reacted with aldehydes in a one-pot sequence affording stereodefined homoallylic alcohols. Cycloalkenes without additives as well as acyclic substrates gave vinylic boronates, which were coupled with organohalides in a Suzuki−Miyaura sequence. By this process allylic and vinylic silabutadiene derivatives can be prepared from allylsilanes with excellent regio- and stereoselectivity. The mechanism of the carbon−hydrogen bond functionalization based on the borylation reaction was explored by isotope labeling experiments, measuring the kinetic isotope effect and study of the effects of the additives on the selectivity of the process. It was concluded that the reactions proceed via a dehydrogenative borylation mechanism, which shows analogous features with the palladium-catalyzed Heck coupling reaction.

Introduction

Organoboronates have emerged as a very important class of organic reagents due to their high stability toward atmospheric oxidation combined with a widespread use as synthons in selective organic transformations for carbon−carbon or carbon−heteroatom bond formation.[1−4] Therefore, selective formation of carbon−boron bonds catalyzed by transition metals is a highly important field in modern organic chemistry. Indeed, there has been a great current interest in finding new, mild methods for selective synthesis of organoboronates. Many important synthetic methods are based on transition metal catalyzed application of diboron reagents as boronate sources.[5−10] One of the most efficient methods involves carbon−hydrogen bond

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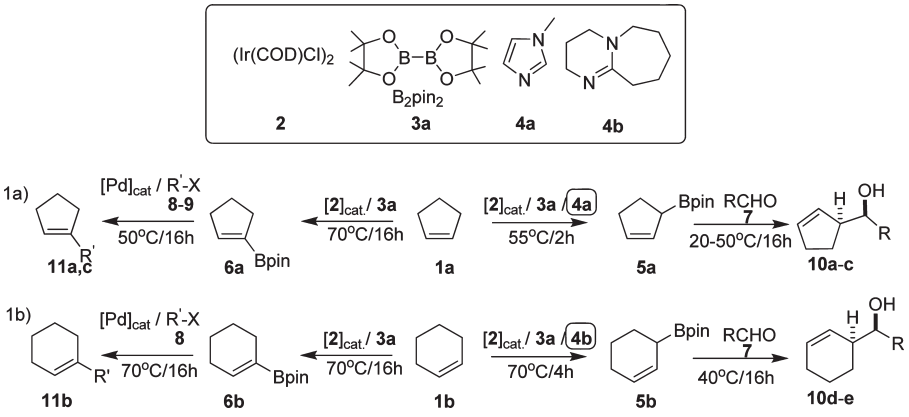

FIGURE 1. One-pot synthesis of homoallyl alcohols and styrene derivatives from cycloalkenes (**1a**,**b**) through carbon−hydrogen bond borylation reactions.

functionalization based borylation processes. Previous work[11−36] by Hartwig, Ishiyama, Marder, Miyaura, Smith, and our laboratory, as well as others, has shown that the direct borylation of alkane,[11−13] aromatic,[14−20] and alkene[21−36] substrates via catalytic carbon−hydrogen bond functionalization−borylation reaction provides an elegant synthetic route to various organoboronates. Although carbon−hydrogen bond activation based borylation reactions represent a very efficient, inexpensive synthetic method for the preparation of organoboronates, development of new catalytic procedures to functionalized boronates is a highly challenging task. As organic molecules contain many different types of carbon−hydrogen bonds, control of the regioselectivity is often very difficult. For example, in alkenes both vinylic and allylic carbon−hydrogen bonds can be activated, and after formation of the organoboronate product allylic rearrangement is also possible.

Recently, we communicated[32,33] our results on iridium-catalyzed carbon−hydrogen bond formation based borylation of unactivated alkenes. Our studies have shown[32] that in cyclohexene either the allylic or the vinylic carbon−hydrogen bond can be activated by varying the reaction conditions. On the other hand, acyclic functionalized alkenes, such as allylsilane, could be boronated at the vinylic position without formation of allyl boronates. The allyl and vinyl boronates obtained in the iridium-catalyzed carbon−hydrogen bond functionalization reactions were reacted with various reagents in a one-pot sequence. The transient allyl boronates were readily reacted with aldehydes to give stereodefined homoallylic alcohols, while the vinyl boronates were reacted in situ with aryl iodides in Suzuki−Miyaura reactions affording functionalized styrenes and butadienes. By using this approach the carbon−hydrogen bond of unactivated alkenes could be selectively replaced by a new carbon−carbon bond. In this paper, we give a full account of our results including an extension of the synthetic scope of the reaction and presenting new mechanistic studies. The most important new results involve development of inexpensive procedures for the synthesis of allylic and vinylic cyclopentene derivatives, and application of our approach for the synthesis of allylic silanes. The new mechanistic studies involve (i) isotope labeling experiments to clarify the mechanism of the C−H bond functionalization step, (ii) study of the rearrangement possibilities of the borylated products, and (iii) rationalization of the allyl versus vinyl selectivity observed for cyclic alkenes.

Results and Discussion

Synthetic Applications. Our previously communicated studies[32,33] revealed that cyclic and acyclic alkenes have a somewhat different behavior in iridium-catalyzed carbon−hydrogen bond borylation reactions. As we reported,[32] cyclohexene **1b** can be borylated (Figure 1b) at the allylic C−H bond by using iridium catalyst **2** (2 mol %) and bis(pinacolato)diboronate **3a** in the presence of DBU (**4b**) in neat **1b**. This reaction results in **5b**, which could be reacted in situ with various aldehydes (such as **7d**−**e**) to obtain stereodefined homoallyl alchols **10d**−**e** in good overall yield (Table 1, entries 4 and 5). Now, we have found that allylic borylation of cyclopentene **1a** requires somewhat different conditions. The reaction with DBU (**4b**) gave the allylic product **5a** with a relatively low regioselectivity. However, a related diamine, *N*-methylimidazole **4a**, provided the desired allylic product with high selectivity at milder reaction conditions (55 °C, 2 h) than the analogous transformation of cyclohexene **1b** (70 °C, 4 h). The boronated product **5a** was smoothly reacted with aromatic, aliphatic, or vinylic

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TABLE 1. One-Pot Catalytic CH-Borylation/CC-Coupling of Various Alkenes[a]

entry	substrates	cond.1	M	cond.2	products	yield[b]
1	**1a** + **7a**	55/2	A	20/16	**10a**	61
2	**1a** + **7b**	55/2	A	50/16	**10b**	60
3	**1a** + **7c**	55/2	A	40/3	**10c**	63
4	**1b** + **7d**	70/4	A	40/16	**10d**	60
5	**1b** + **7e**	70/4	A	40/3	**10e**	60
6	**1a** + **8a**	60/16	B	50/16	**11a**	99
7	**1b** + **8b**	70/16	B	70/16	**11b**	70
8	**1a** + **9a**	70/16	B	50/16	**11c**	80
9	**1c** + **9a**	90/4	B	60/16	**11d**	97
10	**1d** + **9b**	100/4	B	60/18	**11e**	52
11	**12a** + **8b**	70/16	B	70/16	**14a**	57
12	**12a** + **9c**	70/16	B	70/16	**14b**	59
13	**12b** + **9d**	80/16	B	50/16	**14c**	69
14	**12a** + **9e**	80/16	B	50/16[c]	**14d**	55
15	**15** + **9a**	80/16	B	50/16	**16**	80

[a]Unless otherwise stated the borylation reactions were carried out in neat alkene (4−8 equiv) with **3a** in the presence of 2 mol % of **2**. The reaction temperatures [°C]/times [h] are given in column cond. 1. The reactions were carried out with additives **4a** or **4b** [M (method) = A] or without additives [M = B]. The in situ generated boronates were reacted with aldehydes or with aryl/vinyl halides with Suzuki−Miyaura coupling conditions. [b]Yield [%]. [c]Catalyst **28** was used[41] in the second coupling step.

aldehydes **7a**−**c** to give the corresponding homoallyl alcohol products **10a**−**c** (entries 1−3). When the reaction was carried out without **4a**, vinyl boronate **6a** was formed selectively, which could be reacted in situ with aryl iodide **8a** (entry 6) or vinyl-silyl bromide **9a** (entry 8) in the presence of palladium catalyst and base under Suzuki−Miyaura conditions.[2,3] This reaction sequence is suitable for synthesis of cyclic styrene derivatives (such as **11a**) and functionalized butadienes (such as **11c**). This approach was also successfully applied for functionalization of cyclohexene **1b** (entry 7), cycloheptene **1c**

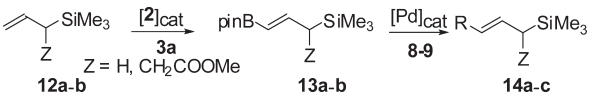

FIGURE 2. Synthesis of styrene and butadiene derivatives from acyclic substrates (**12a**,**b**) via catalytic borylation.

(entry 9), and cyclooctene **1d** (entry 10). As one goes from the five-membered-ring (**1a**) to the eight-membered-ring (**1d**) substrate (entries 6−10) the reaction temperature of the borylation has to be increased from 55 to 90 °C in the borylation step. This indicates that the activation barrier of the C−H bond functionalization increases with increasing ring size.

The overall reaction, coupling of a cycloalkene with an aryl halide, could be *in principle* performed by a standard Heck coupling reaction.[37] However, the disadvantage of the corresponding Heck coupling is that it gives unseparable mixtures of isomeric cycloalkene derivatives,[38] while our procedure affords the styrene and butadiene derivatives, such as **11a**−**e**, as sole products with excellent regio- and stereochemistry. The higher selectivity in the above (Figure 1) borylation−Suzuki coupling sequence compared to the Heck coupling can be ascribed to the mild reaction conditions. In the iridium-catalyzed process (Figure 1) the C−H bond functionalization step is performed at typically 70 °C without addition of base, while in the Heck coupling reactions 120−140 °C is employed in the presence of base.[37,38] These harsh conditions in the Heck coupling lead to isomerization of the products and cleavage of sensitive functionalities, such as silanes. The Suzuki−Miyaura coupling, which is the second step of our sequence, is performed in the presence of base, however, still under moderate conditions (50−70 °C). Accordingly, the presented one-pot reaction (performed without additives **4a**,**b**) can be a mild and highly selective alternative to the Heck coupling reactions. In particular, when the synthetic targets are stereodefined butadiene derivatives or compounds with sensitive silyl functionality, our procedure is considerably more efficient than the corresponding Heck coupling reaction.

Allyl- and vinylsilanes have been widely applied as useful building blocks in complex organic transformations and natural product synthesis.[39,40] The integrated borylation/Suzuki−Miyaura sequence offers an attractive synthetic route for synthesis of allylsilanes and silabutadienes with acyclic substrates, such as allylsilanes **12a**,**b** (Figure 2).

As we communicated[33] previously, allylsilane **12a** readily undergoes selective borylation under similar reaction conditions as the cyclic analogues **1a**,**b** (Figure 1) to provide allylsilyl boronate **13a**. The subsequent Suzki−Miyaura coupling with aryl (**8b**) and vinyl (**9c**) halides affords allylsilane (**14a**) and silabutadiene (**14b**) products (entries 11 and 12) with a very high regio- and stereoselectivity. When the coupling reaction is performed with vinyl epoxide **9e**, allylsilyl alcohol **14d** (entry 14) is formed. Our new studies show

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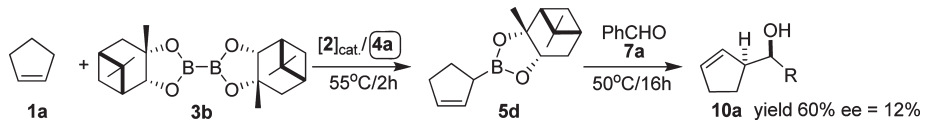

FIGURE 3. Application of chiral diboronate **3b** as boronate source in the one sequence.

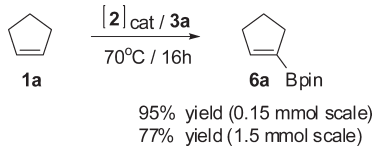

FIGURE 4. Synthesis of vinyl boronate **6a** by C−H bond borylation reaction. Isolated yield.

that the selective borylation and subsequent Suzuki−Miyaura coupling sequence is not restricted to the parent allylsilane; however, it can also be performed with carboxy-functionalized allylsilane **12b** (entry 13). This reaction provides a bifunctional butadiene derivative **14c** as the single product of the reaction sequence. Several other alkenes can be employed in place of allylsilanes.[33] For example, the borylation of **15** followed by coupling with **9a** also affords silabutadiene product (**16**) in high overall yield (entry 15). In case of acyclic substrates (**12a**,**b**, **15**) formation of allyl boronates was not observed at all. Unlike for cyclic substrates (Figure 1) employment of additives **4a**,**b** also led to exclusive formation of vinylic boronates **13**.

Synthesis of functionalized allylsilanes with the Heck coupling reaction is particularly challenging[42,43] because of formation of isomeric products usually accompanied by desilylation reactions. There are also very few reports[44] in the literature for synthesis of allyl or vinyl silyl butadiene derivatives (entries 8 and 12−15) by Heck coupling, although these processes suffered from unsatisfactory yields and selectivity. However, selective synthesis of these types of compounds can be easily performed by the presented borylation/Suzuki−Miyaura coupling sequence.

We have briefly studied the possibilities of replacing **3a** with other boronate sources (Figure 3), such as chiral boronate bis[(−)pinanediolato]diboron **3b** (Figure 3). In the presence of **4a** as additive the borylation of cyclopentene proceeds as smoothly with **3b** as with **3a**. Since the allylic functionalization reaction creates a new stereocenter, this process can be potentially useful for the synthesis of chiral allyl boronates. Unfortunately, the level of diastereoselectivity of the process is relatively low under the applied reaction conditions. As a consequence, one-pot coupling with benzaldehyde gave allyl alcohol product **10a** with a poor enantioselectivity (12% ee).

The successful application of the one-pot borylation-coupling sequence is based on the high selectivity of the reaction of allyl boronates with aldehydes (entries 1−5) and vinyl boronates in Suzuki−Miyaura coupling. However, the iridium-catalyzed reaction of cyclopentene **1a** with **3a** proceeds so cleanly that vinyl boronate **6a** can be isolated from the reaction mixture in pure form (Figure 4). Considering the use of inexpensive starting materials **1a** and **3a** in this reaction, the presented C−H borylation reaction (Figure 4) is probably the simplest and the most efficient method available for the preparation of **6a**.

The above-described procedures are based on optimized reaction conditions. The optimization studies have shown that in situ formation of cyclic allyl boronates (such as **5a**,**b**) requires application of amine additives **4a** and **5a**. Other amines and phosphines cannot efficiently replace these additives. For example, application of Et_3N did not enhance the allylic selectivity of the borylation reactions. Also, adding coordinating ligands such as TMEDA, PPh_3, $P(OPh)_3$, DPPF, or DPPB did not increase the selectivity toward the allyl boronate products. Addition of catalytic amounts of 4,4′-di-*tert*-butyl-2,2′-bipyridine, which has been widely applied as ligand in aromatic C−H borylation processes,[16,17] resulted in exclusive formation of the vinyl boronate product. We also attempted to replace **2** with other catalyst precursors, such as [(η^5-indenyl)Ir(cod)], [Ir(PCy_3)(cod)(py)]PF_6 (Cy = cyclohexyl, py = pyridine), and [{Rh(cod)Cl}$_2$]; however, these catalysts gave only traces or no product at all under the applied reaction conditions. The highly selective formation of acyclic boronates (such as **13a**,**b**) also requires directing functionalities (such as CH_2SiMe_3, OBu etc) in the alkene substrate. In the absence of a directing group, a mixture of unsaturated boronates is formed. For example, 1-decene gives an isomeric mixture of decenyl boronates.

Mechanistic Studies

As we pointed out in the introduction, C−H borylation reactions of aromatics are well documented in the literature.[14−20] However, fewer studies are available for analogous reactions for alkenes. Brown and Lloyd-Jones[24] studied the mechanism of rhodium-catalyzed vinylic functionalization of alkenes and Marder and co-workers[29,36] have presented useful synthetic applications of this process, while Sabo-Etinenne and co-workers[31] studied the ruthenium-catalyzed hydroboration/dehydrogenative borylation of cycloalkenes. These authors have concluded that the reactions proceed by a so-called "dehydrogenative borylation mechanism". The dehydrogenative borylation mechanism involves initial formation of a metal−boryl complex followed by insertion of the substrate to the metal−boron bond and finally β-hydride elimination. In our communications[32,33] we have also assumed a similar mechanism for the above-described (Figure 1) C−H bond borylation reaction. Very recently, Miyaura and co-workers[34,35] studied the iridium-catalyzed borylation of cyclic vinyl ethers. These authors concluded that the borylation of cyclic vinyl ethers proceeds by a direct C−H bond activation mechanism via Ir(V) intermediates, which is similar to the activation of aromatic C−H bonds.

Deuterium Labeling Experiments. To clarify the mechanism of the presented C−H bond functionalization based

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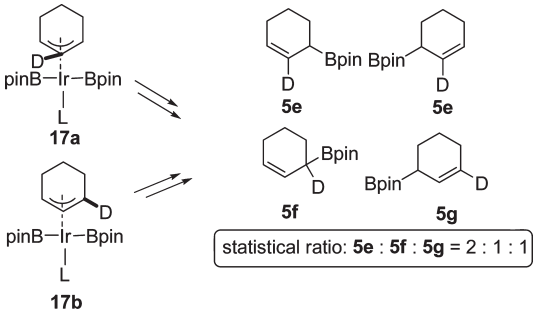

FIGURE 5. Formation of allyl boronates via (η^3-allyl)iridium complexes **17a**,**b**.

borylation process (Figures 1 and 2) we have carried out a series of isotope labeling experiments and competitive borylation reactions. The main interest was focused on two important aspects of the reaction: (i) the mechanism of the C−H bond functionalization process, which may occur by β-hydride elimination (dehydrogenative borylation mechanism) or by oxidative addition of the metal complex to the C−H bond (iridium(V) mechanism), and (ii) the allyl versus vinyl selectivity in the borylation of cycloalkenes **1a**,**b**.

As allyl boronates (such as **5b**) may also be formed in the case of C−H bond functionalization of cyclic alkenes, two basic models were considered for the borylation mechanism. The borylation may proceed via (η^3-allyl)iridium complexes **17** (Figure 5) or via insertion complexes **18** (Figure 6). The two mechanisms can be differentiated (Figure 7) by reacting monodeuterated cyclohexene **1b**-d_1 with **3a**, using catalyst **2** at 70 °C followed by quenching of the deuterated products (**5e**−**g**) by benzaldehyde (**7a**). The experimental ratio of the deuterated products **19a**−**c** was established by ^{2}H NMR spectroscopy. It was found that the ratio of **19a**:**19b**:**19c** is 3:3:1, which shows that corresponding allyl boronates were formed in a **5e**:**5f**:**5g** ratio of 3:3:1. If the borylation reactions occurred via the (η^3-allyl)iridium mechanism, the expected ratio of **5e**:**5f**:**5g** would be 2:1:1 (Figure 5). On the other hand, the statistical distribution of the deuterated allyl boronates via insertion complex **18** should be a **5e**:**5f**:**5g** ratio of 1:1:0 (Figure 6). The observed (Figure 7) ratio (1:1:$^1/_3$) is closer to this latter value, and therefore, we assume that the borylation reaction proceeds via insertion complex **18**. A possible explanation for the minor formation of **5g** is iridium-catalyzed partial allyl rearrangement of **1b**-d_1 prior to the borylation process.

When the reaction time of the borylation step was extended to 16 h, which is the optimized condition for generation of transient vinyl boronates followed by Suzuki−Miyaura coupling with aryl iodide, the process resulted in **20a**−**e**, in which the deuterium label is fully scrambled indicating that a complete scrambling of the deuterium labels occurred under formation of the vinyl boronate products (Figure 8). This scrambling can be explained by initial formation of allyl boronates **5e**,**f** followed by a series of iridium-catalyzed rearrangements of the double bond.

Kinetic Isotope Effect. Further mechanistic insights can be obtained by comparison of the rate of iridium-catalyzed borylation for cyclohexene **1b** and its perdeuterated analogue **1b**-d_{10} (see SI) in neat **1b** and **1b**-d_{10}, respectively. Monitoring the reaction by gas chromatography has shown that the rate of consumption of **3a** with **1b** and **1b**-d_{10} is

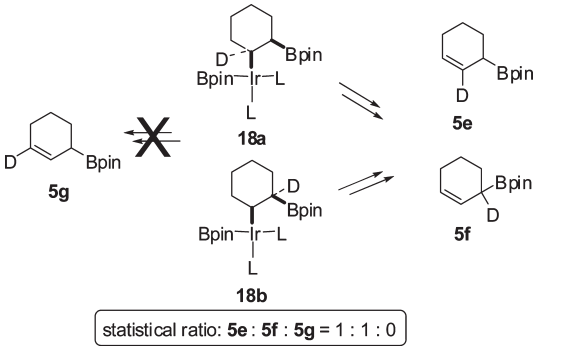

FIGURE 6. Formation of allyl boronates via insertion complexes **18a**,**b**.

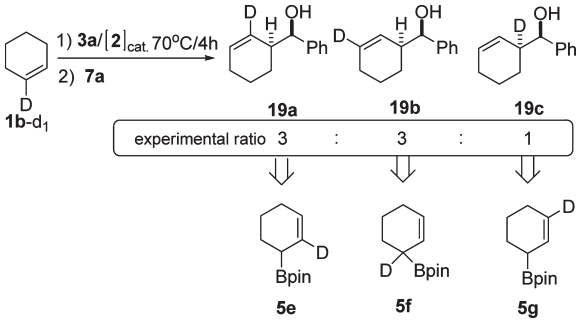

FIGURE 7. Distribution of the deuterated homoallyl alcohols obtained via allyl boronate products.

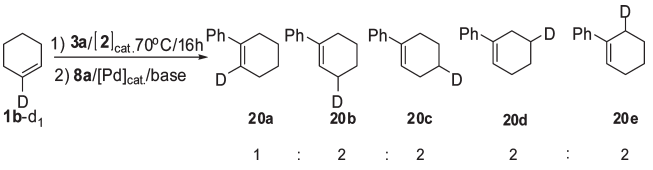

FIGURE 8. Distribution of the deuterated styrene derivatives obtained via vinyl boronate products.

identical. Both reactions displayed first-order kinetics for **3a** and the comparison of the rate constants gave a k_H/k_D value of 1.0. Accordingly, a kinetic isotope effect cannot be observed for the borylation process indicating that the C−H bond cleavage is not the rate-determining step of the process. This finding is interesting to compare to the results of Miyaura and co-workers.[35] These authors found that their iridium-catalyzed C−H borylation of cyclic vinyl ethers displays a sizable deuterium isotope effect (k_H/k_D = 3.2). On the basis of these results Miyaura and co-workers[35] concluded that their process occurs via oxidative addition of iridium to the C−H bond of the substrate. Considering the k_H/k_D value for **1b**/**1b**-d_{10} is 1.0, we conclude that the reaction is unlikely to proceed via C−H oxidative addition,[35] but probably by a dehydrogenative borylation mechanism. In dehydrogenative borylation, the C−H bond cleavage takes place by β-hydride elimination, which usually proceeds with a relatively low activation barrier, and therefore this process is seldom rate determining in the catalytic cycle. An alternative mechanistic interpretation would be that coordination of the alkene to iridium is the rate-determining step, which is followed by a fast C−H oxidative addition. If alkene

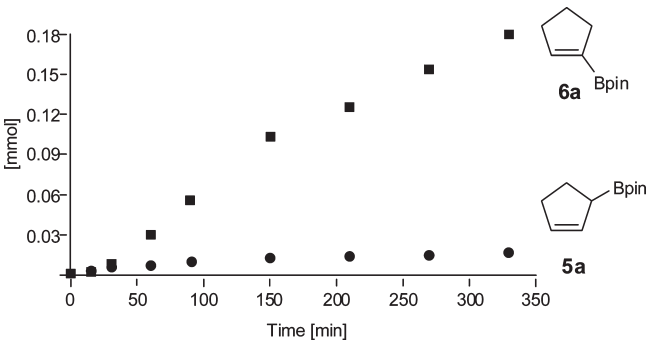

FIGURE 9. Monitoring of the relative concentrations of allyl boronate (●) and vinyl boronate (■) product by GC in the reaction of cyclopentene **1a** with diboronate **3a** in the presence of catalyst **2**.

coordination is rate limiting, then the deuterium isotope effect would be not observed. However, this interpretation does not account for the observed regioselectivity of the process. If the reaction proceeded via C−H oxidative addition, allyl functionalized products (e.g., **5a**,**b**) would not be expected to form.

Study of the Regioselectivity of the C−H Bond Functionalization. Probably one of the most useful synthetic aspects of the presented reactions is that the regioselectivity of the borylation process of cyloalkenes **1a**,**b** can be controlled by choice of the reaction conditions. When borylation of cyclopentene **1a** was carried out with iridium catalyst **2** and **3a** as boronate source at 55 °C without any additive, formation of both allyl boronate **5a** and vinyl boronate **6a** can be observed (Figure 9). However, after about 25 min the amount of vinyl boronate **6a** sharply increases, while the amount of allyl boronate **5a** remains constant at a relatively low level.

However, when the reaction is performed under the same conditions, except that imidazole derivative **4a** was also added to the reaction mixture, the selectivity is reversed and now the concentration of allyl boronate **5a** increases considerably, while the amount of vinyl boronate **6a** is the minor product of the process (Figure 10). Obviously imidazole derivative **4a** has an important role in changing the regioselectivity of the process, and thus providing access to the allylic product in boronation of cyclopentene **1a**. A similar effect arises by application of DBU **4b**, for selective synthesis of allyl boronate **5b**.

We attempted to explore the fate of additives **4a**,**b** in the presented allylic C−H borylation process. Analysis of the reaction mixture by MS (in positive ion mode) indicated that *N*-borylated species **21a** and **21b** (Figure 11) are formed in the allylic activation of cycloalkenes **1a** and **1b** from **4a** and **4b**, respectively. Formation of a nitrogen−boron bond could be determined by NMR spectroscopy. The counterion of cations **21a**,**b** could not be established; however, it is probably a hydride ion under the catalytic process.

Catalytic Cycle. On the basis of the above synthetic and mechanistic results, as well as the literature data available for related processes,[24,29,31,36] a catalytic cycle can be constructed for the presented C−H bond functionalization based borylation reaction. Extensive studies by Hartwig,

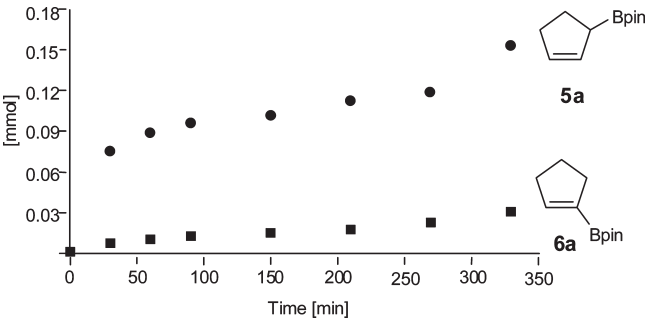

FIGURE 10. Monitoring of the relative concentrations of allyl boronate (●) and vinyl boronate (■) product by GC in the reaction of cyclopentene **1a** with diboronate **3a** in the presence of catalyst **2** and imidazole **4a** as additive.

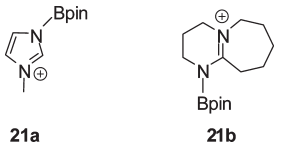

FIGURE 11. Species formed from the additives **4a**,**b** after the borylation process.

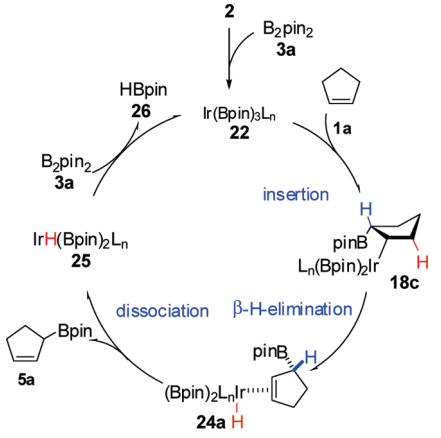

FIGURE 12. Catalytic cycle for the borylation of cyclic alkenes leading to allylic C−H functionalization.

Miyaura, Marder, Smith, and co-workers[12,16,45−48] have shown that Ir(I) complexes readily react with **3a** and other diboronates affording tris(boryl)Ir(III) complexes. We expect that this is the introducing step in the present reaction as well. Thus catalyst **2** reacts with diboronate **3a** providing complex **22** (Figure 12), which is followed by coordination of the corresponding cycloalkene (such as **1a**). The next step is insertion of the iridium−boron bond to the double bond to give insertion complex **18c** (or **18a**,**b** with cyclohexene, Figure 6). Formation of this complex is the first step of the dehydrogenative borylation mechanism.[24,29,31,36] Our deuterium-labeling experiments (cf. Figures 5 and 6) confirmed that the reaction proceeds via these types of (η^1-alkyl)iridium complexes (**18**) instead of an (η^3-allyl)iridium complex (**17**).

(45) Nguyen, P.; Blom, H. P.; Westcott, S. A.; Taylor, N. J.; Marder, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 9329–9330.
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(47) Irvine, G. J.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R.; Robins, E. G.; Roper, W. R.; Whittell, G. R.; Wright, L. J. *Chem. Rev.* **1998**, *98*, 2685–2722.
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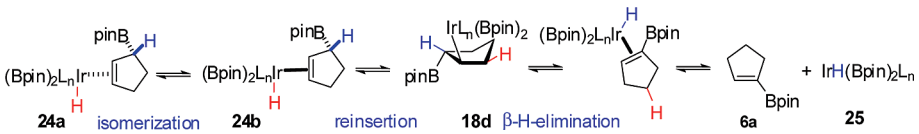

FIGURE 13. Proposed mechanism of the allylic rearrangement of the cyclic allyl boronates.

Results from the measurement of the deuterium isotope effect ($k_H/k_D = 1.0$) also confirm a dehydrogenative borylation mechanism, as C−H oxidative addition or σ-bond metathesis would require high activation energy, and thus generate a significant deuterium isotope effect.[16,35]

Formation of **18c** proceeds via stereoselective *syn* addition mechanism, and therefore the iridium−carbon and boron−carbon bonds are on the same side of the cycloalkyl ring. This is an important factor as the ring topology does not allow free rotation of the carbon−carbon single bonds, and therefore the *syn* relationship of the Ir−C and B−C bonds cannot be altered before the next catalytic step. The next step is β-hydride elimination of **18c** to **24a**. The β-hydride elimination requires a special, nearly zero degree dihedral angle for the C−H and the Ir−C bonds. Such an eclipsed conformation for the Ir−C bond can only be realized with a (neighboring) C−H bond, which is in the same side of the ring (red H in Figure 12). Accordingly, the syn elimination of iridium-hydride provides the allyl boronate product. Elimination of the trans-hydride of the boronated carbon (blue H) is not allowed for steric reasons, and therefore vinyl boronate product cannot be obtained as the *primary* product of the β-hydride elimination. The next step can be decomplexation of the allylic product **5a** and formation of iridium-hydride **25**. Subsequently, complex **25** reacts with **3a** by regenerating the active catalyst **22** and producing pinacolborane **26**. Pinacolborane **26** is known to undergo iridium-catalyzed hydroboration[49,50] with alkenes to form alkyl boronates. Fortunately, alkyl boronates are inert to aldehyde substrates and also under the applied Suzuki−Miyaura reaction, and therefore they do not interfere in the one-pot sequence. Since one the boronate groups of **3a** is sacrificed to form **26**, the presented reaction is only able to employ one of the boronate groups of **3a**. Sacrificial hydroboration and hydrogenation is a usual problem in C−H borylation of alkenes, and so far there are relatively few catalytic systems, such as Marder's[29,36] rhodium-catalyst system, that offer the possibility of avoiding this process.

As can be seen in Figure 9, when the reaction is conducted without **4a** as an additive, allyl boronate **5a** and vinyl boronate **6a** can be observed in similar concentrations at the beginning of the reaction; however, after a couple of hours the major component is vinyl boronate **6a**, while **5a** is present only in small amounts. The most probable explanation is an allylic rearrangement of the initially formed cyclic allyl boronate to the corresponding vinyl boronate (Figure 13). The driving force of this rearrangement could be the higher thermodynamic stability of the vinyl boronate species compared to that of the isomeric allyl boronates.[33] As far as we know, iridium-catalyzed rearrangement of allyl boronates to vinyl boronates has not previously been reported in the literature. A possible mechanism for such an allylic isomerization process (for the initially formed complex **24a**) is given in Figure 13. In cyclic substrates (such as in **24a**) the prerequisite for the syn β-hydride elimination from the boronated carbon (blue H in Figure 13) is a stereoface exchange of the iridium atom to form complex **24b**. This isomerization of **24a** may occur by dissociation of the iridium atom from the double bond followed by reassociation from the opposite face to give complex **24b**. Thus, the C−H bond of the boronated carbon (blue H) and the Ir−C bond may enter into an eclipsed conformation (**18d**), and therefore the stereoelectronic requirements of the *syn* β-hydride elimination are satisfied. This equilibrium process ultimately leads to formation of vinyl boronate **6a**.

We assume that additives **4a**,**b** inhibit the allylic isomerization process shown in Figure 13, and thus the initially formed allyl boronate (such as **5a**) is the major product of the C−H borylation process. Detection of *N*-borylated species **21a**,**b** in the reaction mixture (Figure 11) indicates that **4a**,**b** probably removes pinacolborane (**26**) from **24a**, and thus hinders the isomarization and reinsertion (**24a** → **18d**) of the iridium-hydride to the double bond. This process probably involves coordination of the additive (**4a**,**b**) to iridium followed by formation of the hydride salt **21a** or **21b**. As mentioned above *N*-methylimidazole **4a** specifically hinders the rearrangement of cyclopentenyl derivative **5a**, while DBU **4b** specifically hinders the rearrangement of **5b**. This suggests a substrate/product specific action of the additives, which may be most efficient when they are coordinated to the iridium center in complex **24a**. Exploration of the exact mechanism of the allylic rearrangement and its possible inhibition by additives **4a**,**b** is the subject of ongoing in-depth mechanistic and DFT modeling studies.

The selectivity and mechanistic features of this dehydrogenative borylation reaction show many similarities to those of the palladium-catalyzed Heck coupling reaction,[37] which has a very similar stereochemistry in palladium-catalyzed coupling of alkenes with aryl halides. As we indicated above, an important difference is that the dehydrogenative borylation does not require base for the C−H bond activation step, and the reactions can be performed under lower temperature than the Heck coupling process.

By using the above mechanistic model, formation of the sole vinylic product from acyclic alkenes can easily be explained (Figure 14). Insertion of **22** to allylsilane **12a** leads to formation of insertion complex **18e**. This reaction also proceeds by a *syn* mechanism; however, **18e** may easily undergo C−C σ-bond rotation, and thus the hydrogen atom of the boronated carbon can be eliminated to give **27**, which after dissociation provides vinyl boronate **13a** as the primary product of the reaction.

Conclusions

In this paper we have shown that selective carbon−carbon bond formation can be carried out by carbon−hydrogen

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(50) Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2004**, *60*, 10695–10700.

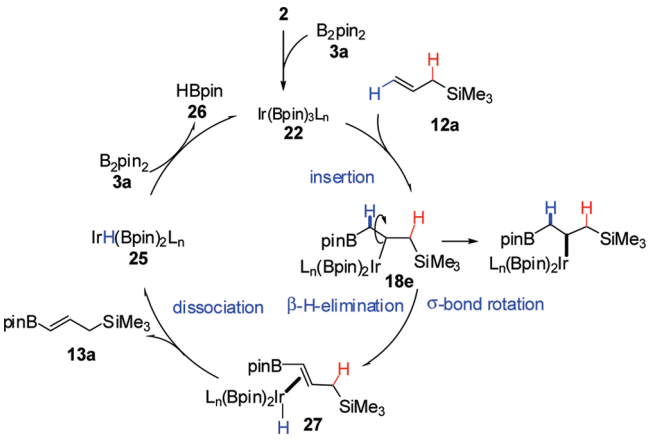

FIGURE 14. Catalytic cycle of the borylation of acyclic substrates with vinylic C−H bond functionalization.

bond functionalization of unactivated alkenes. The key step of this procedure is iridium-catalyzed borylation of the C−H bond followed by coupling reactions. For cyclic alkenes, such as cyclopentene and cyclohexene, the regioselectivity of the C−H bond functionalization can be controlled by proper choice of the reaction conditions. In the presence of **4a**,**b** the reaction will be selective for the formation of the allyl boronate product. This allyl boronate product readily reacts with aldehydes affording stereodefined allylic alcohols. As far as we know, this is the first synthetic application for allylic functionalization of cyclic alkenes based on catalytic borylation reactions. In the absence of additives, as well as for acyclic substrates, vinylic C−H bond functionalization can be carried out. The in situ formed vinyl boronates readily react with aryl halides in the Suzuki−Miyaura reaction. These processes can be exploited for the synthesis of stereodefined allyl- and vinyl-silylbutadienes. The reactions take place under milder conditions than the corresponding Heck coupling offering an attractive, highly selective synthetic route for the preparation of regio- and stereodefined functionalized butadienes. Our mechanistic studies strongly indicate that the reaction proceeds via a dehydrogenative borylation mechanism, which in many mechanistic features is similar to the Heck coupling reaction. The presented synthetic and mechanistic results open new routes to densely functionalized butadiene derivatives and stereodefined homoallyl alcohols, which are useful building blocks in natural product synthesis and also may serve as drug intermediates.[39,40] By application of appropriate ligands or additives the process has a high potential in asymmetric synthesis. In this respect two strategies can be employed: diastereoselective boronation of cycloalkenes by application of chiral boronates (such as **3b**) or synthesis of chiral allyl boronates by asymmetric catalysis.

Experimental Section

Method A: General Procedure for Allylation Reactions. Iridium catalyst **2** (0.003 mmol, 2 mol %, 2 mg), **3a** (0.15 mmol, 38 mg), and **4a** (0.075 mmol, 11.4 mg) were dissolved in neat alkene (0.2 mL). Then this reaction mixture was stirred at the temperatures and times given in Table 1 (cond. 1). After cooling to room temperature the corresponding aldehyde **7a**−**e** (0.18 mmol) was added to the mixture and the stirring was continued for the allotted times and temperatures given in Table 1 (cond. 2). The crude reaction mixture was evaporated and the residue was purified by silica gel column chromatography.

Method B: General Procedure for Vinylic Functionalization. Iridium catalyst **2** (0.003 mmol, 2 mol %, 2 mg) and **3a** (0.15 mmol, 38 mg) were dissolved in neat alkene (0.1 mL). The reaction mixture was stirred for the given times and temperatures in Table 1 (cond. 1). After cooling to room temperature the reaction mixture was diluted with a THF/water (4:1) mixture (0.25 mL), whereafter **8a**−**b**, **9a**−**d** (0.15 mmol), $Pd(OAc)_2$ (0.0075 mmol, 5 mol %, 1.8 mg), PPh_3 (0.015 mmol, 20 mol %, 8 mg), and Cs_2CO_3 (0.30 mmol, 97 mg) were added. Then stirring was continued for the allotted times and temperatures given in Table 1. (cond. 2). The crude reaction mixture was evaporated and the residue was purified by silica gel column chromatography.

Synthesis of 2-Cyclopentenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6a). Iridium-catalyst **2** (0.003 mmol, 2 mol %, 2 mg) and **3** (0.15 mmol, 38 mg) were dissolved in neat **1a** (0.1 mL). The reaction mixture was stirred at 60 °C for 24 h whereafter the crude reaction mixture was evaporated and the residue was purified by silica gel column chromatography. The NMR data obtained for **6a** are identical with the literature values.[51] ^{1}H NMR ($CDCl_3$) δ 6.53 (t, J = 1.9 Hz, 1H), 2.40 (m, 4H), 1.81 (p, J = 7.5 Hz, 2H), 1.26 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 147.7, 83.2, 34.9, 34.6, 24.9, 24.0; HRMS (ESI) calcd for $[C_{11}H_{19}BO_2Na]^+$ m/z 217.1370, found 217.1379.

2-Cyclopentenyl(phenyl)methanol (10a). This compound was prepared according to method A from **1a**. The NMR data obtained for **10a** are identical with the literature values.[52] ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 4H), 7.28 (m, 1H), 5.86 (dd, J = 2.2, 5.7 Hz, 1H), 5.41 (dt, J = 2.2, 5.7 Hz, 1H), 4.58 (d, J = 6.5 Hz, 1H), 3.11 (m, 1H), 2.34 (m, 2H), 1.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 143.6, 133.8, 131.4, 128.4, 127.5, 126.4, 77.1, 54.1, 32.4, 25.2; HRMS (ESI) calcd for $[C_{12}H_{14}ONa]^+$ m/z 197.0937, found 197.0939.

1-(Cyclopent-2-enyl)heptan-1-ol (10b). This compound was prepared according to method A from **1a**. The diastereoselectivity of **10b** is assigned on the basis of ^{1}H NMR data given in the literature for analogous stereodefined homoallyl alcohols.[52] ^{1}H NMR ($CDCl_3$) δ 5.88 (dd, J = 2.2, 5.8 Hz, 1H), 5.60 (dt, J = 2.2, 5.8 Hz, 1H), 3.59 (m, 1H), 2.81 (m, 1H), 2.34 (m, 2H), 1.90 (m, 1H), 1.77 (m, 1H), 1.46 (m, 3H), 1.30 (m, 8H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 133.7, 131.8, 73.9, 52.2, 35.1, 32.5, 32.0, 29.6, 26.1, 23.7, 22.8, 14.2; HRMS (ESI) calcd for $[C_{12}H_{22}ONa]^+$ m/z 205.1563, found 205.1564.

(*E*)-1-(2-Cyclopentenyl)-3-phenyl-2-propen-1ol (10c). This compound was prepared according to method A from **1a**. The NMR data obtained for **10c** are identical with the literature values.[52] ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 15.5 Hz, 1H), 6.24 (dd, J = 6.5, 15.5 Hz, 1H), 5.92 (m, 1H), 5.67 (m, 1H), 4.24 (t, J = 6.5 Hz, 1H), 2.98 (m, 1H), 2.37 (m, 2H), 2.00 (m, 1H), 1.81 (m, 1H), 1.69 (br, 1H, *OH*); ^{13}C NMR ($CDCl_3$) δ 137.0, 134.0, 131.1, 131.0, 130.9, 128.7, 127.7, 126.6, 75.6, 52.5, 32.4, 24.7; HRMS (ESI) calcd for $[C_{14}H_{16}ONa]^+$ m/z 223.1093, found 223.1094.

Cyclopentenylbenzene (11a). This compound was prepared according to method B from **1a** and **8a** except that barium hydroxide (0.3 mmol, 95 mg) was used as base for the second step coupling reaction. The NMR data obtained for **11a** are identical with the literature values.[53,54] ^{1}H NMR ($CDCl_3$) δ 7.45

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(52) Nishio, K.; Kobayashi, S. *J. Org. Chem.* **1994**, *59*, 6620.
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(d, J = 7.7 Hz, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.22 (t, J = 7.7 Hz, 1H), 6.20 (s, 1H), 2.72 (m, 2H), 2.54 (m, 2H), 2.03 (p, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 128.4, 127.0, 126.2, 125.7, 33.5, 33.3, 23.5; HRMS (APCI) calcd for $[C_{11}H_{12}]^+$ m/z 144.0939, found 144.0933.

1-Chloro-2-(1-cyclohexenyl)benzene (11b). This compound was prepared according to method B from **1b** and **8b** except that a dioxane/water (4:1) mixture (0.25 mL) was used as solvent and barium hydroxide (0.3 mmol, 95 mg) was used as base for the second step coupling reaction. ^{1}H NMR ($CDCl_3$) δ 7.33 (d, J = 6.5 Hz, 1H), 7.16 (m, 3H), 5.66 (ddd, J = 1.8, 3.9, 5.8 Hz, 1H), 2.29 (m, 2H), 2.18 (m, 2H), 1.76 (m, 2H), 1.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 143.8, 138.0, 132.8, 130.5, 129.8, 128.1, 127.6, 126.9, 29.5, 25.7, 23.2, 22.4; HRMS (APCI) calcd for $[C_{12}H_{13}Cl]^+$ m/z, 192.0700, found 192.0706.

(*E*)-(2-Cyclopentenylvinyl)trimethylsilane (11c). This compound was prepared according to method B from **1a** and **9a** except that barium hydroxide (0.3 mmol, 95 mg) was used as base for the second step coupling reaction. The NMR data obtained for **11c** are in close agreement with literature values.[44] ^{1}H NMR ($CDCl_3$) δ 6.77 (d, J = 19.2 Hz, 1H), 5.72 (m, 2H), 2.43 (t, J = 7.6 Hz, 4H), 1.91 (p, J = 7.6 Hz, 2H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 140.8, 131.7, 129.6, 33.1, 30.9, 23.2, −1.0; HRMS (APCI) calcd for $[C_{10}H_{17}Si]^+$ m/z 165.1094, found 165.1088.

[(*E*)-3-(2-Chlorophenyl)-2-propenyl](trimethyl)silane (14a). This compound was prepared according to the above general procedure from **12a** and **8b**. ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.59 (d, J = 15.6 Hz, 1H), 6.22 (dt, J = 15.6, 8.3 Hz, 1H), 1.73 (d, J = 8.3 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 131.2, 129.7, 127.4, 126.8, 126.5, 124.7, 24.5, −1.7; MS (EI) m/z (rel intensity) 224 (M^+, 1), 113 (34), 111 (89), 75 (100), 73 (18).

Trimethyl[(2*E*)-4-phenyl-2,4-pentadienyl]silane (14b). This compound was prepared according to the above general procedure from **12a** and **9c**. ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5H), 6.17 (d, J = 15.5 Hz, 1H), 5.65 (dt, J = 15.5, 8.5 Hz, 1H), 5.10 (s, 1H), 4.97 (s, 1H), 1.57 (d, J = 8.5 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 148.7, 141.2, 131.7, 130.1, 128.4, 128.1, 127.3, 113.0, 23.9, −1.7; MS (EI) m/z (rel intensity) 216 (M^+, 13), 201 (14), 142 (100), 129 (17), 73 (95).

(*E*)-Methyl 7-Methyl-3-(trimethylsilyl)octa-4,6-dienoate (14c). This compound was prepared according to the above general procedure from **12b** and **9d** except that a dioxane/water (4:1) mixture (0.25 mL) was used as solvent for the second step coupling reaction. ^{1}H NMR ($CDCl_3$) δ 6.08 (dd, J = 15.2, 10.7 Hz, 1H), 5.76 (d, J = 10.7 Hz, 1H), 5.43 (dd, J = 15.2, 9.3 Hz, 1H), 3.64 (s, 3H), 2.41 (m, 2H), 2.09 (dt, J = 9.3, 5.0 Hz, 1H), 1.73 (s, 3H), 1.71 (s, 3H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 131.9, 131.2, 125.5, 125.4, 51.7, 34.4, 30.1, 26.0, 18.3, −3.1; HRMS (ESI) calcd for $[C_{13}H_{24}SiO_2Na]^+$ m/z 263.1438, found 263.1437.

Allylation Reaction with Labeled Cyclohexene 1b-d_1. Iridium-catalyst **2** (0.003 mmol, 2 mol %, 2 mg) and **3a** (0.15 mmol, 38 mg) were dissolved in neat **1b**-d_1 (200 mg). The reaction mixture was stirred at 70 °C for 16 h. After cooling to room temperature aldehyde **7a** (0.18 mmol) was added to the mixture and the stirring was continued at 40 °C for 5 h, whereafter the crude reaction mixture was evaporated and the residue was purified by silica gel column chromatography. Except for the integral values the ^{1}H NMR ($CDCl_3$) spectrum of **19** agrees with the previously reported data for the nondeuturated analogue.[32] ^{2}H NMR ($CDCl_3$) δ 5.87, 5.43, 2.51 (3:3:1 ratio).

Vinylic Arylation with Labeled Cyclohexene 1b-d_1. Iridium-catalyst **2** (0.003 mmol, 2 mol %, 2 mg) and **3** (0.15 mmol, 38 mg) were dissolved in neat **1a**-d_1 (100 mg). The reaction mixture was stirred at 80 °C for 36 h. After cooling to room temperature the reaction mixture was diluted with a dioxane/water (4:1) mixture (0.25 mL), whereafter **6a** (0.15 mmol), $Pd(OAc)_2$ (0.0075 mmol, 5 mol %, 1.8 mg), DPPF (0.015 mmol, 10 mol %, 4 mg), and Cs_2CO_3 (0.30 mmol, 97 mg) were added. Then stirring was continued at 60 °C for 16 h. The crude reaction mixture was evaporated and the residue was purified by silica gel column chromatography. The ^{1}H NMR ($CDCl_3$) chemical shifts obtained for **20** are similar to previously reported values for the nondeuturated analogue.[32] ^{2}H NMR ($CDCl_3$) δ 6.16, 2.41, 2.19, 1.76, 1.64.

Determination of the Kinetic Isotope Effect with 1b-d_{10}. Iridium-catalyst **2** (0.009 mmol, 6 mol %, 6 mg) and **3** (0.15 mmol, 38 mg) were dissolved in neat **1b** or **1b**-d_{10} (1.22 mmol). Nonane (0.15 mmol, 19.2 mg) was added to the reaction mixture as internal standard with stirring at 75 °C. The progress of the reactions was monitored by gas chromatography.

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Supporting Information Available: Experimental procedures and compound characterizations (which are not given above) as well as NMR spectra for **5a**, **10a**−**e**, **11a**−**e**, **14a**−**d**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.