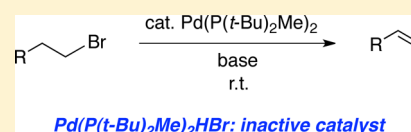


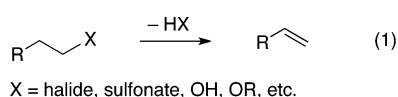
# A Mild, Palladium-Catalyzed Method for the Dehydrohalogenation of Alkyl Bromides: Synthetic and Mechanistic Studies

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**ABSTRACT:** We have exploited a typically undesired elementary step in cross-coupling reactions,  $\beta$ -hydride elimination, to accomplish palladium-catalyzed dehydrohalogenations of alkyl bromides to form terminal olefins. We have applied this method, which proceeds in excellent yield at room temperature in the presence of a variety of functional groups, to a formal total synthesis of (R)-mevalonolactone. Our mechanistic studies have established that the rate-determining step can vary with the structure of the alkyl bromide and, most significantly, that  $L_2PdHBr$  ( $L$  = phosphine), an intermediate that is often invoked in palladium-catalyzed processes such as the Heck reaction, is *not* an intermediate in the active catalytic cycle.

**■ INTRODUCTION**

The elimination of HX to form an olefin is one of the most elementary transformations in organic chemistry (eq 1).<sup>1,2</sup>



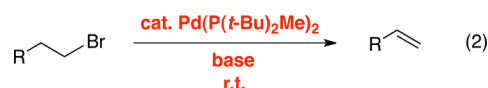
However, harsh conditions, such as the use of a strong Brønsted acid, a strong Brønsted base, or a high temperature (which can lead to poor functional-group compatibility and olefin isomerization) are often necessary for this seemingly straightforward process. For example, many classical methods for the dehydration of alcohols, such as the Chugaev elimination via a xanthate ester,<sup>3</sup> require elevated temperatures (e.g., 100–250 °C). More recently, through the development of sophisticated derivatizing agents such as the Burgess<sup>4</sup> and Martin<sup>5</sup> reagents, some of the deficiencies of the older approaches have been remedied; however, while these particular methods are effective for net dehydrations of secondary and tertiary alcohols, they are not generally useful for primary alcohols.

For the dehydration of primary alcohols, the Sharpless–Grieco reaction, wherein the alcohol is converted into a selenide and then a selenoxide prior to elimination, is a particularly effective approach.<sup>6</sup> Because of the mildness of the conditions (e.g., elimination at room temperature or below), this method has been widely used in organic synthesis.<sup>7</sup> However, drawbacks of this reaction include the generation of a stoichiometric amount of a toxic arylselenol byproduct and difficulties in separating the desired olefin from selenium-based impurities.

With respect to metal-catalyzed methods for HX elimination, Oshima reported in 2008 that  $CoCl_2/IMes\cdot HCl$  effects the formation of olefins from alkyl halides (but not sulfonates) in the presence of 2 equiv of a Grignard reagent

( $Me_2PhSiCH_2MgCl$ ).<sup>8</sup> Although this investigation focused on the regioselective synthesis of terminal olefins from secondary alkyl bromides, Oshima also applied his method to two primary alkyl halides, which provided good yields of the terminal olefin (79–96%) along with small amounts of the internal olefin (2–8%). Furthermore, while our study was underway, Frantz reported that  $Pd(P(t-Bu)_3)_2$  catalyzes the elimination/isomerization of certain enol triflates to 1,3-dienes.<sup>9</sup>

The development of new mild methods for the elimination of HX to generate an olefin, a fundamental transformation in organic synthesis, persists as a worthwhile endeavor. In this report, we describe the use of a palladium catalyst to achieve elimination reactions of primary alkyl electrophiles and furnish terminal olefins in excellent yield at room temperature (eq 2).

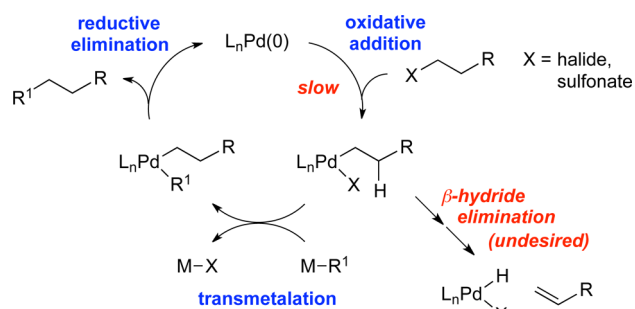
**■ RESULTS AND DISCUSSION**

In recent years, we and others have pursued the development of metal-catalyzed cross-coupling reactions of alkyl electrophiles that contain  $\beta$ -hydrogens.<sup>10</sup> Historically, it was believed that two substantial impediments to accomplishing this objective were *slow oxidative addition* and, if oxidative addition could be achieved, *rapid  $\beta$ -hydride elimination* in preference to transmetalation (Figure 1).

Having made progress in the development of palladium-based catalysts for cross-coupling of alkyl electrophiles,<sup>10d,f</sup> we sought to exploit these advances to devise a mild method for HX elimination of alkyl electrophiles to form olefins, since the oxidative addition challenge had presumably been solved and

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**Figure 1.** Outline of a possible pathway for (and impediments to) palladium-catalyzed cross-coupling of an alkyl electrophile.

the “deleterious”  $\beta$ -hydride elimination process (Figure 1) would now be the desired pathway. Indeed, in our earlier efforts to achieve cross-coupling reactions of alkyl electrophiles, we had noted that significant, although not synthetically useful, quantities of the olefin were sometimes observed as undesired side products (e.g., up to 31% in the case of a Suzuki coupling<sup>11</sup>).

After examining an array of reaction parameters, we have been able to develop a palladium-catalyzed method for olefin synthesis that accomplishes the dehydrohalogenation of a primary alkyl bromide at room temperature with excellent efficiency (Table 1, entry 1). The ligand of choice is  $P(t\text{-Bu})_2\text{Me}_2$ .

**Table 1. Palladium-Catalyzed Elimination of an Alkyl Bromide To Generate an Olefin: Influence of Reaction Parameters**

| $\text{R-CH}_2\text{-CH}_2\text{-Br} \xrightarrow[\text{10\% KOt-Bu, 1.2 equiv Cy}_2\text{NH, dioxane, r.t., 24 h}]{\text{6\% Pd(P}(t\text{-Bu})_2\text{Me}_2)_2} \text{R-CH=CH}_2$ <p>R = <i>n</i>-decyl<br/>"standard" conditions</p> |                                                                                                                                 |                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|------------------------|
| entry                                                                                                                                                                                                                                   | variation from the "standard" conditions                                                                                        | yield (%) <sup>a</sup> |
| 1                                                                                                                                                                                                                                       | none                                                                                                                            | 98 (91)                |
| 2                                                                                                                                                                                                                                       | no $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$                                                                                   | 3                      |
| 3                                                                                                                                                                                                                                       | no KOt-Bu                                                                                                                       | 95 (81)                |
| 4                                                                                                                                                                                                                                       | no $\text{Cy}_2\text{NH}$                                                                                                       | 13                     |
| 5                                                                                                                                                                                                                                       | $\text{Pd(P}(t\text{-Bu})_3)_2$ , instead of $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$                                         | 3                      |
| 6                                                                                                                                                                                                                                       | $\text{Pd(PCy}_3)_2$ , instead of $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$                                                    | 12                     |
| 7                                                                                                                                                                                                                                       | $\text{Pd(PPh}_3)_4$ , instead of $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$                                                    | 3                      |
| 8                                                                                                                                                                                                                                       | $\text{Cy}_2\text{NMe}$ , instead of $\text{Cy}_2\text{NH}$                                                                     | 42                     |
| 9                                                                                                                                                                                                                                       | $\text{Cs}_2\text{CO}_3$ , instead of $\text{Cy}_2\text{NH}$                                                                    | 28                     |
| 10                                                                                                                                                                                                                                      | 3% $\text{Pd}_2(\text{dba})_3$ + 12% $\text{P}(t\text{-Bu})_2\text{Me}$ , instead of $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$ | 96 (76)                |
| 11                                                                                                                                                                                                                                      | 3%, instead of 6%, $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$                                                                   | 90 (75)                |

<sup>a</sup>Determined via gas chromatography with the aid of a calibrated internal standard (averages of two experiments); yields after 4 h are given in parentheses.

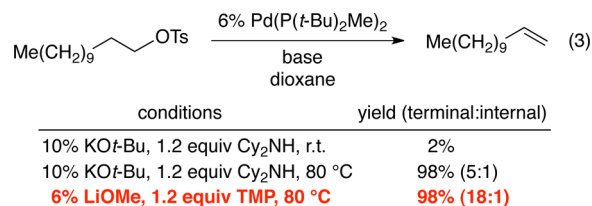
$\text{Bu})_2\text{Me}$ , which we have previously established to be useful for palladium-catalyzed Suzuki reactions of alkyl electrophiles.<sup>12</sup> Essentially no 2-dodecene is detected (<1%).<sup>13</sup>

In the absence of  $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$ , virtually no olefin is formed (Table 1, entry 2). Although KOt-Bu is not necessary (entry 3), a poor yield is obtained in the absence of  $\text{Cy}_2\text{NH}$  (entry 4). Palladium complexes bearing other hindered trialkylphosphines (entries 5 and 6) or  $\text{PPh}_3$  (entry 7) are comparatively ineffective, as are other Brønsted bases (entries 8 and 9). An active catalyst can be generated in situ from

$\text{Pd}_2(\text{dba})_3$  and  $\text{P}(t\text{-Bu})_2\text{Me}$  (entry 10), and a lower loading of  $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$  can be employed with only a small loss in yield (entry 11).

We have determined that this  $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$ -catalyzed method can be applied to the room-temperature dehydrohalogenation of a range of primary alkyl bromides, furnishing the desired terminal olefins in generally high yields [Table 2; for each reaction, essentially no product (<2%) is formed in the absence of  $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$ ].<sup>14</sup> Through the use of a higher catalyst loading (compare entries 1–3), more hindered ( $\gamma$ - and  $\beta$ -branched) electrophiles can be converted to olefins nearly quantitatively. Allylbenzene can also be generated in excellent yield and with no isomerization to  $\beta$ -methylstyrene (entry 4). A wide array of functional groups are compatible with this mild method for elimination of HBr, including a silyl ether (entry 5), a carbamate (entry 6), esters (entries 7–12), an aryl chloride (entry 8), heteroaromatic substituents (oxygen, sulfur, and nitrogen; entries 9–13), and a ketone (entry 14). On the other hand, preliminary studies indicate that the presence of a primary alcohol, an aldehyde, or a nitroarene can be problematic.<sup>15</sup> A primary alkyl bromide reacts exclusively in the presence of a secondary bromide (entry 15),<sup>16</sup> a primary tosylate (entry 16), or a primary chloride (entry 17). For most of these elimination processes, virtually no isomerization to the internal olefin (<2%) is observed.

When 1-iodododecane is subjected to the method developed for the dehydrohalogenation of alkyl bromides (Table 1), only a small amount of 1-dodecene (20% yield) is generated; *N*-alkylation of dicyclohexylamine is the major product. Furthermore, under the same conditions, essentially no elimination is observed with a primary alkyl chloride or tosylate, presumably because of the relatively high barrier for oxidative addition to  $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$ .<sup>17</sup> On the other hand, at elevated temperature, elimination of a primary tosylate to give the desired terminal olefin proceeds in excellent yield (eq 3). It



is worth noting that alkyl tosylates are not suitable substrates for Oshima's cobalt-catalyzed elimination, likely because of the difficulty in achieving homolytic cleavage of the C–O bond,<sup>8</sup> in contrast, under our conditions, C–O scission is probably accomplished through an  $\text{S}_{\text{N}}2$  pathway.<sup>12a,c</sup>

Palladium-catalyzed eliminations of more hindered ( $\gamma$ - and  $\beta$ -branched) primary alkyl tosylates also proceed in excellent yield (Table 3, entries 2 and 3). Interestingly, a secondary alkyl tosylate undergoes elimination, predominantly generating the internal 2-alkene (2:1 internal:terminal; entry 4). Furthermore, not only an alkyl tosylate, but also a mesylate, can be eliminated to form an olefin with good efficiency (entry 5). Perhaps in part because of the elevated reaction temperature, small amounts of olefin isomerization are sometimes observed in eliminations of alkyl sulfonates (entries 1 and 5), and preliminary experiments indicate that the functional-group tolerance of the method is limited. For each elimination illustrated in Table 3, essentially no olefin is produced in the absence of  $\text{Pd(P}(t\text{-Bu})_2\text{Me}_2)_2$  (<2%).

Table 2. Palladium-Catalyzed Elimination Reactions of Alkyl Bromides

| $\text{R-CH}_2\text{CH}_2\text{Br} \xrightarrow[\text{1.2 equiv Cy}_2\text{NH, dioxane, r.t.}]{\text{cat. Pd(P}(t\text{-Bu)}_2\text{Me)}_2, 10\% \text{ KO}t\text{-Bu}}$ |                                                                                                                    |                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| entry                                                                                                                                                                    | substrate                                                                                                          | yield (cat. loading) <sup>a</sup> |
| 1                                                                                                                                                                        | Me(CH <sub>2</sub> ) <sub>8</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                               | 94 (6)                            |
| 2                                                                                                                                                                        | Me(CH <sub>2</sub> ) <sub>10</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                              | 98 (14)                           |
| 3                                                                                                                                                                        | Me(CH <sub>2</sub> ) <sub>11</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                              | 99 (30)                           |
| 4                                                                                                                                                                        | PhCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                                               | 100 <sup>b</sup> (8)              |
| 5                                                                                                                                                                        | TBSO(CH <sub>2</sub> ) <sub>7</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                             | 88 (8)                            |
| 6                                                                                                                                                                        | PhCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                               | 98 (8)                            |
| 7                                                                                                                                                                        | F <sub>3</sub> C-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br | 86 (8)                            |
| 8                                                                                                                                                                        | Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br               | 91 (5)                            |
| 9                                                                                                                                                                        | 2-furyl-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                         | 86 (8)                            |
| 10                                                                                                                                                                       | 2-thienyl-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                       | 96 (8)                            |
| 11 <sup>c</sup>                                                                                                                                                          | 2-pyrrolyl-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                      | 92 (8) [17:1]                     |
| 12                                                                                                                                                                       | 2-quinolyl-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                      | 96 (12)                           |
| 13                                                                                                                                                                       | Me-2-indolyl-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                    | 84 (7)                            |
| 14                                                                                                                                                                       | C <sub>6</sub> H <sub>13</sub> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br                 | 92 (15)                           |
| 15 <sup>d</sup>                                                                                                                                                          | PhCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                               | 78 (12)                           |
| 16                                                                                                                                                                       | TsO(CH <sub>2</sub> ) <sub>10</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                             | 86 (11) [6:1]                     |
| 17                                                                                                                                                                       | Cl(CH <sub>2</sub> ) <sub>8</sub> CH <sub>2</sub> CH <sub>2</sub> Br                                               | 89 (6)                            |

<sup>a</sup>Both values are percentages. Isolated yields (averages of two experiments) are provided. In all cases, >98% of the unpurified elimination product is the terminal olefin, with the exception of entries 11 and 16, for which the terminal:internal olefin ratios (determined via <sup>1</sup>H NMR spectroscopy) are given in brackets. <sup>b</sup>Because of the volatility of allylbenzene, the yield was determined via gas chromatography vs a calibrated internal standard (average of two experiments). <sup>c</sup>KOt-Bu loading: 2.5%. <sup>d</sup>KOt-Bu loading: 20%.

We applied our palladium-catalyzed elimination process to a formal total synthesis of (R)-mevalonolactone. Spencer

Table 3. Palladium-Catalyzed Elimination Reactions of Alkyl Sulfonates

| $\text{R-CH}_2\text{CH}_2\text{OSO}_2\text{R}^1 \xrightarrow[\text{1.2 equiv TMP, dioxane}]{\text{x\% Pd(P}(t\text{-Bu)}_2\text{Me)}_2, \text{x\% LiOMe}}$ |                                                                        |                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------|
| entry                                                                                                                                                      | substrate                                                              | temperature (°C), x yield <sup>a</sup> |
| 1                                                                                                                                                          | Me(CH <sub>2</sub> ) <sub>8</sub> CH <sub>2</sub> CH <sub>2</sub> OTs  | 80, 6 98 [18:1]                        |
| 2                                                                                                                                                          | Me(CH <sub>2</sub> ) <sub>10</sub> CH <sub>2</sub> CH <sub>2</sub> OTs | 90, 6 97                               |
| 3                                                                                                                                                          | Me(CH <sub>2</sub> ) <sub>11</sub> CH <sub>2</sub> CH <sub>2</sub> OTs | 100, 17 96                             |
| 4                                                                                                                                                          | Me(CH <sub>2</sub> ) <sub>7</sub> CH <sub>2</sub> CH <sub>2</sub> OTs  | 100, 25 94 [1:2]                       |
| 5                                                                                                                                                          | Me(CH <sub>2</sub> ) <sub>8</sub> CH <sub>2</sub> CH <sub>2</sub> OMs  | 80, 12 90 [14:1]                       |

<sup>a</sup>Percent yields of isolated products (averages of two experiments) are provided. For each elimination in which a >2% yield of the internal olefin was generated, the terminal:internal olefin ratio (determined via <sup>1</sup>H NMR spectroscopy) is given in brackets.

described the preparation of this bioactive compound from nerol via alcohol A, which was transformed into olefin C via a Sharpless–Grieco sequence (top pathway in Figure 2).<sup>18</sup> Spencer noted that the conversion of the alcohol to the selenide “proved to be the only difficult step in the synthesis”.<sup>19</sup>

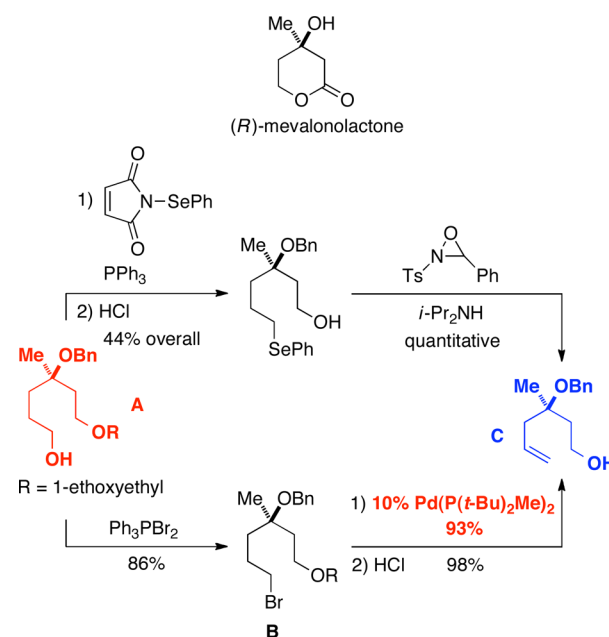
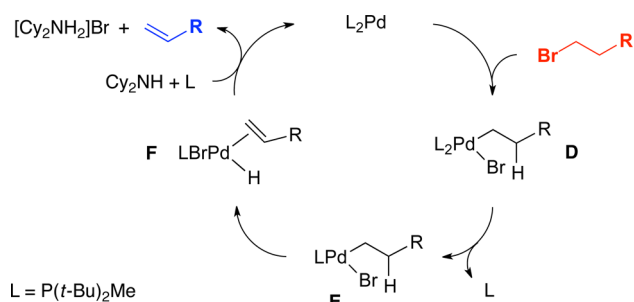


Figure 2. Conversions of an alcohol to an olefin en route to (R)-mevalonolactone: (top) Spencer;<sup>18</sup> (bottom) this study.

We effected the transformation of alcohol A into olefin C in 78% overall yield through our palladium-catalyzed elimination process (bottom pathway in Figure 2). Thus, treatment of A with Ph<sub>3</sub>PBr<sub>2</sub> furnishes primary alkyl bromide B, and subsequent palladium-catalyzed dehydrohalogenation under our standard conditions at room temperature affords the desired olefin in excellent yield (93%). Finally, removal of the

1-ethoxyethyl protecting group generates Spencer's intermediate **C**.

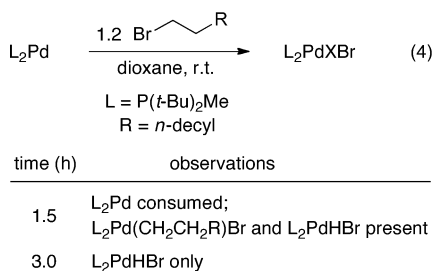
**Mechanism.** Our current hypothesis is that these palladium-catalyzed elimination reactions follow the pathway outlined in Figure 3 [throughout this section,  $L = P(t\text{-Bu})_2\text{Me}$ ].



**Figure 3.** Outline of a possible mechanism for  $\text{Pd}(\text{P}(t\text{-Bu})_2\text{Me})_2$ -catalyzed dehydrobromination reactions.

Thus, oxidative addition of the alkyl bromide to  $\text{L}_2\text{Pd}$  proceeds via an  $\text{S}_{\text{N}}2$  process to generate  $\text{L}_2\text{Pd}(\text{CH}_2\text{CH}_2\text{R})\text{Br}$  (**D**).<sup>12a,c</sup> Dissociation of one phosphine furnishes 14-electron palladium adduct **E**, which undergoes  $\beta$ -hydride elimination to provide palladium olefin-hydride intermediate **F**. In the presence of base ( $\text{Cy}_2\text{NH}$ ) and  $\text{L}$ , palladium complex **F** affords  $[\text{Cy}_2\text{NH}_2]^+\text{Br}^-$ , the olefin, and  $\text{L}_2\text{Pd}$ .

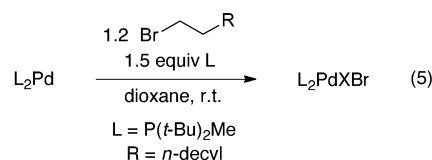
To make our mechanistic study more tractable, we chose to focus our investigation on palladium-catalyzed dehydrobrominations in the absence of  $\text{KO}t\text{-Bu}$ , a process that also occurs in excellent yield (Table 1, entry 3).<sup>20</sup> With regard to the oxidative addition step of the proposed catalytic cycle, we previously established that  $\text{L}_2\text{Pd}$  reacts with 1-bromo-3-phenylpropane in  $\text{Et}_2\text{O}$  at  $0^\circ\text{C}$  and crystallographically characterized the  $\text{Pd}(\text{II})$  adduct.<sup>12b</sup> Here we examined the reaction of 1-bromododecane with  $\text{L}_2\text{Pd}$  in dioxane at room temperature and determined that oxidative addition is complete within 1.5 h, affording a mixture of  $\text{L}_2\text{Pd}(\text{CH}_2\text{CH}_2\text{R})\text{Br}$  and  $\text{L}_2\text{PdHBr}$ <sup>21</sup> (eq 4). After an



additional 1.5 h, this mixture proceeds to form  $\text{L}_2\text{PdHBr}$  quantitatively. Taken together, these data indicate that oxidative addition and then  $\beta$ -hydride elimination are chemically and kinetically competent initial steps of the catalytic cycle.

We also investigated the impact of added  $\text{P}(t\text{-Bu})_2\text{Me}$  on the reaction of 1-bromododecane with  $\text{L}_2\text{Pd}$  (eq 5). The rate of consumption of  $\text{L}_2\text{Pd}$  is unaffected by the additional ligand, whereas the formation of  $\text{L}_2\text{PdHBr}$  is inhibited, consistent with the suggestion that  $\text{L}_2\text{Pd}$  (rather than  $\text{L}_1\text{Pd}$  or  $\text{L}_3\text{Pd}$ ) is the species undergoing oxidative addition and that ligand dissociation precedes  $\beta$ -hydride elimination.<sup>22</sup>

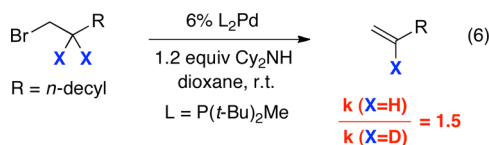
The rate law for the palladium-catalyzed dehydrobromination of 1-bromododecane is first order with respect to  $\text{L}_2\text{Pd}$ , fractional order (first order at lower concentration, zeroth order



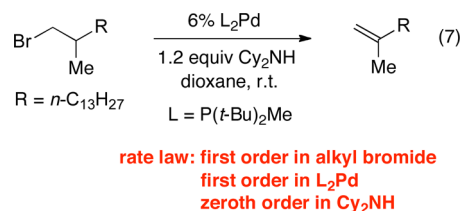
| time (h) | observations                                                                                                                           |
|----------|----------------------------------------------------------------------------------------------------------------------------------------|
| 1.5      | $\text{L}_2\text{Pd}$ consumed;<br>$\text{L}_2\text{Pd}(\text{CH}_2\text{CH}_2\text{R})\text{Br}$ and $\text{L}_2\text{PdHBr}$ present |
| 3.0      | $\text{L}_2\text{Pd}(\text{CH}_2\text{CH}_2\text{R})\text{Br}$ and $\text{L}_2\text{PdHBr}$ present                                    |
| 12       | $\text{L}_2\text{PdHBr}$ only                                                                                                          |

at higher concentration) with respect to the alkyl bromide, and zeroth order with respect to  $\text{Cy}_2\text{NH}$ . According to  $^{31}\text{P}$  NMR spectroscopy,  $\text{L}_2\text{Pd}(\text{CH}_2\text{CH}_2\text{R})\text{Br}$  is the predominant resting state of palladium during the early stages of the reaction (small amounts of  $\text{L}_2\text{Pd}$  and  $\text{L}_2\text{PdHBr}$  are also present; as the reaction progresses, the proportion of  $\text{L}_2\text{PdHBr}$  increases). These data are consistent with oxidative addition and a subsequent step each being partially rate-determining.

For the stoichiometric chemistry of  $\text{L}_2\text{Pd}$ , we have established that  $\beta$ -hydride elimination is impeded by the addition of excess  $\text{P}(t\text{-Bu})_2\text{Me}$  (eq 5); we have similarly determined that the palladium-catalyzed dehydrohalogenation of 1-bromododecane is inhibited by added  $\text{P}(t\text{-Bu})_2\text{Me}$ . Furthermore, we observe a modest kinetic isotope effect when comparing the rate of elimination of 1-bromododecane with that of 1-bromo-2,2-dideuteriododecane ( $k_{\text{H}}/k_{\text{D}} = 1.5$ ; eq 6). Collectively, these data are consistent with  $\beta$ -hydride elimination being the other partially rate-determining step.



In a previous study, we demonstrated that oxidative addition of a primary alkyl electrophile to  $\text{Pd}/\text{P}(t\text{-Bu})_2\text{Me}$  preferentially proceeds through an  $\text{S}_{\text{N}}2$  pathway.<sup>12a,c</sup> If oxidative addition is indeed partially rate-determining for the dehydrohalogenation of 1-bromododecane, then one might anticipate that, in the case of a more hindered alkyl bromide, oxidative addition would be entirely rate-determining. We determined the rate law for the dehydrobromination of a  $\beta$ -branched primary alkyl bromide and established that it is first order in the alkyl bromide, first order in  $\text{L}_2\text{Pd}$ , and zeroth order in  $\text{Cy}_2\text{NH}$  (eq 7). Furthermore,  $^{31}\text{P}$  NMR spectroscopy revealed that  $\text{L}_2\text{Pd}$  is

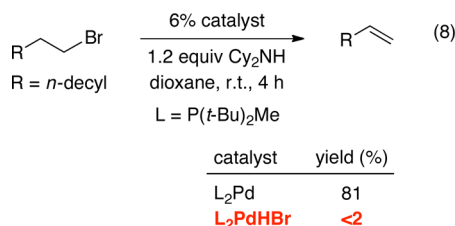


the predominant resting state of the catalyst. Taken together, these observations are consistent with oxidative addition being the rate-determining step for the palladium-catalyzed elimination of this more hindered alkyl bromide.

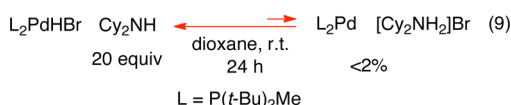
Interestingly,  $\text{L}_2\text{PdHBr}$  is *not* an intermediate in the primary catalytic cycle. Thus, treatment of 1-bromododecane with 6%



$L_2PdHBr$ , rather than  $L_2Pd$ , produces essentially no 1-dodecene (eq 8).



We have established that  $Cy_2NH$  is not a sufficiently strong Brønsted base to drive the acid–base equilibrium illustrated in eq 9 to the right, thereby producing  $L_2Pd$  from  $L_2PdHBr$ .<sup>23,24</sup>



Thus, it appears that, during our palladium-catalyzed dehydrobromination process, a palladium hydride other than  $L_2PdHBr$  undergoes reductive elimination to regenerate  $Pd(0)$ .

Because each turnover of the catalyst generates  $[Cy_2NH_2]Br$ , a question arises as to why this ammonium salt does not protonate  $L_2Pd$  to form  $L_2PdHBr$ , thereby deactivating the palladium catalyst. In fact, during the course of the dehydrobromination process, we do observe a slow accumulation of  $L_2PdHBr$ . Fortunately, however, the poor solubility of  $[Cy_2NH_2]Br$  in dioxane impedes this deleterious protonation (i.e.,  $[Cy_2NH_2]Br$  precipitates faster than it protonates  $L_2Pd$ ).<sup>25</sup>

Although we previously postulated that the formation of a relatively stable  $L_2PdHCl$  ( $L = PCy_3$ ) complex could be the origin of the low catalyst activity in a Heck reaction of an aryl chloride,<sup>23</sup> we had not fully appreciated the importance of avoiding the formation of  $L_2PdHBr$  in developing a mild  $Pd/P(t\text{-Bu})_2Me$ -catalyzed method for the dehydrohalogenation of alkyl bromides. The fortuitous solubility properties of  $[Cy_2NH_2]Br$ , combined with the unanticipated regeneration of  $Pd(0)$  prior to the formation of  $L_2PdHBr$  ( $L = phosphine$ ), are likely critical to the success of this process. The latter observation regarding the timing of reductive elimination is worth considering when contemplating the mechanism of Heck reactions.<sup>26</sup>

## CONCLUSIONS

Although the elimination of  $HX$  to form an olefin is a classic transformation in organic chemistry, there remains a need for new mild methods to accomplish this fundamental process. Herein we have exploited a generally undesired elementary step in cross-coupling reactions,  $\beta$ -hydride elimination, to achieve palladium-catalyzed dehydrohalogenations of alkyl bromides. This method, which we have applied to a formal total synthesis of (*R*)-mevalonolactone, enables the efficient synthesis of terminal olefins at room temperature in the presence of a variety of functional groups, including heterocycles. Our mechanistic studies have established that the rate-determining step can vary with the structure of the alkyl bromide. Most significantly, we have determined that  $L_2PdHBr$  ( $L = phosphine$ ), an intermediate that is often invoked in palladium-catalyzed processes such as the Heck reaction, is not an intermediate in the active catalytic cycle.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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couplings. For recent examples of isomerizations of olefins catalyzed by palladium hydrides, including  $\text{Pd}(\text{P}(t\text{-Bu})_3)_2\text{HCl}$ , see: Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. *J. Am. Chem. Soc.* **2010**, *132*, 7998–8009.

(14) The proportion of internal olefin does not increase as the reaction progresses, and treatment of 1-dodecene with  $\text{L}_2\text{PdHBr}$  in dioxane at room temperature does not lead to the generation of internal olefins (although isomerization is observed at elevated temperatures).

(15) Under our standard conditions (Table 1), in the presence of 1 equiv of a primary-amine additive, the dehydrobromination of 1-bromododecane proceeded in ~95% yield. The dehydrobromination was slightly inhibited (55–70% yield, with the balance being unreacted 1-bromododecane) by the addition of 1 equiv of an unprotected indole or a nitrile.

(16) The relative rate of dehydrobromination of 1-bromododecane vs 1-bromo-2-methylpentadecane (a  $\beta$ -branched alkyl bromide) is ~13.

(17) For a study of the relative rates of oxidative addition of  $n$ -nonyl-X ( $X = \text{I}, \text{Br}, \text{Cl}, \text{F}, \text{OTs}$ ) to  $\text{Pd}(\text{P}(t\text{-Bu})_2\text{Me})_2$  in THF, see ref 12c.

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(19) Spencer also noted that the selenide was “tenaciously contaminated” by a selenium-containing impurity.

(20) Because of the slow accumulation of  $\text{L}_2\text{PdHBr}$  during the course of the palladium-catalyzed dehydrobromination (as discussed later), we focused our mechanistic studies on the early stages of the reaction.

(21) Throughout this discussion,  $\text{L}_2\text{PdHBr}$  refers to *trans*- $\text{L}_2\text{PdHBr}$ .

(22) This contrasts with Yamamoto’s studies of thermal decomposition of *trans*- $\text{L}_2\text{PdEt}_2$ , wherein  $\beta$ -hydride elimination proceeds predominantly *without* ligand dissociation. See: Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457–6463.

(23) Treatment of  $\text{L}_2\text{Pd}$  with  $[\text{Cy}_2\text{NH}_2]\text{Br}$  in dioxane at room temperature leads to very slow formation of  $\text{L}_2\text{PdHBr}$ . For related observations with a different ligand ( $\text{PCy}_3$ ), halide ( $\text{Cl}$ ), and base ( $\text{Cy}_2\text{NMe}$ ), see: Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178–13179.

(24) On the other hand,  $\text{KO}t\text{-Bu}$  does react with  $\text{L}_2\text{PdHBr}$  to generate  $\text{L}_2\text{Pd}$  in quantitative yield. However, when  $\text{KO}t\text{-Bu}$  rather than  $\text{Cy}_2\text{NH}$  is employed as the stoichiometric base, the elimination does not proceed cleanly, and there is a considerable background reaction (E2).

(25) The decreased efficiency of  $\text{Cy}_2\text{NMe}$  relative to  $\text{Cy}_2\text{NH}$  (Table 1, entry 8 vs entry 1) may be due to the greater solubility in dioxane of  $[\text{Cy}_2\text{NHMe}]\text{Br}$  compared with  $[\text{Cy}_2\text{NH}_2]\text{Br}$ , which leads to more protonation of  $\text{L}_2\text{Pd}$  to form inactive  $\text{L}_2\text{PdHBr}$ .

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