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

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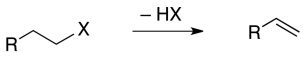
Abstract

We have exploited a typically undesired elementary step in cross-coupling reactions, β-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 establish that the rate-determining step can vary with the structure of the alkyl bromide, and, most significantly, that L_2PdHBr (L=phosphine), an often-invoked intermediate 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).[1,2] However, harsh conditions, such as the use of a strong Brønsted acid/base or a high temperature (which can lead to poor functional-group compatibility and to 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,[3] require elevated temperature (e.g., 100–250 °C). More recently, through the development of sophisticated derivatizing agents such as the Burgess[4] and Martin[5] 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.



X = halide, sulfonate, OH, OR, etc.

(1)

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Supporting Information

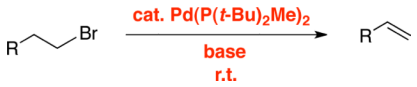
Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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.[6] Due to the mildness of the conditions (e.g., elimination at room temperature or below), this method has been widely used in organic synthesis.[7] 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•HCl effects the formation of olefins from alkyl halides (but not sulfonates) in the presence of two equivalents of a Grignard reagent ($Me_2PhSiCH_2MgCl$).[8] 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 $Pd(P(t\text{-}Bu)_3)_2$ catalyzes the elimination/isomerization of certain enol triflates to 1,3-dienes.[9]

The development of mild new 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).



(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 β-hydrogens.[10] Historically, it was believed that two substantial impediments to accomplishing this objective were *slow oxidative addition* and, if oxidative addition could be achieved, *rapid* β*-hydride elimination* in preference to transmetalation (Figure 1).

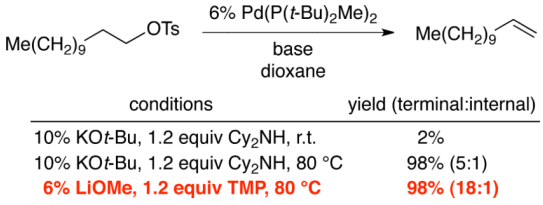
Having made progress in the development of palladium-based catalysts for cross-coupling alkyl electrophiles,[10d,f] we sought to exploit these advances to devise a mild method for H–X elimination of alkyl electrophiles to form olefins, since the oxidative-addition challenge had presumably been solved, and the "deleterious" β-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[11]).

Upon 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 $P(t\text{-}Bu)_2Me$, which we have previously established is useful for palladium-catalyzed Suzuki reactions of alkyl electrophiles.[12] Essentially no 2-dodecene is detected (<1%).[13]

In the absence of Pd(P(*t*-Bu)$_2$Me)$_2$, virtually no olefin is formed (Table 1, entry 2). Although KO*t*-Bu is not necessary (entry 3), a poor yield is obtained in the absence of Cy_2NH (entry 4). Palladium complexes that bear other hindered trialkylphosphines (entries 5 and 6) or 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 $Pd_2(dba)_3$ and P(*t*-Bu)$_2$Me (entry 10), and a lower loading of Pd(P(*t*-Bu)$_2$Me)$_2$ can be employed with only a small loss in yield (entry 11). termined via ^{1}H NMR spectroscopy) is given in brackets. [b]Due to the volatility of allylbenzene, the yield was determined via gas chromatography versus a calibrated internal standard (average of two experiments). [c]KO*t*-Bu loading: 2.5%. [d]KO*t*-Bu loading: 20%.

We have determined that this Pd(P(*t*-Bu)$_2$Me)$_2$-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 (<2%) product is formed in the absence of Pd(P(*t*-Bu)$_2$Me)$_2$).[14] Through the use of a higher catalyst loading (compare entries 1–3), more hindered (γ- and β-branched) electrophiles can be converted to olefins nearly quantitatively. Allylbenzene, too, can be generated in excellent yield and with no isomerization to β-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 chlo-ride (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.[15] A primary alkyl bromide reacts exclusively in the presence of a secondary bromide (entry 15),[16] a primary tosylate (entry 16), and a primary chloride (entry 17). For most of these elimination processes, virtually no (<2%) isomerization to the internal olefin 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 due to the relatively high barrier to oxidative addition to Pd(P(*t*-Bu)$_2$Me)$_2$.[17] On the other hand, at elevated temperature, elimination of a primary tosylate to the desired terminal olefin can proceed 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 difficulty in achieving homolytic cleavage of the C–O bond;[8] in contrast, under our conditions, C–O scission is probably accomplished through an S_N2 pathway.[12a,c]



conditions	yield (terminal:internal)
10% KO*t*-Bu, 1.2 equiv Cy_2NH, r.t.	2%
10% KO*t*-Bu, 1.2 equiv Cy_2NH, 80 °C	98% (5:1)
6% LiOMe, 1.2 equiv TMP, 80 °C	**98% (18:1)**

(3)

Palladium-catalyzed eliminations of more hindered (γ- and β-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 (entry 4; 2:1 internal:terminal). Furthermore, not only an alkyl tosylate, but also a mesylate, can be eliminated to form an olefin with good efficiency (entry 5). Perhaps due in part to 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 $Pd(P(t\text{-}Bu)_2Me)_2$ (<2%).

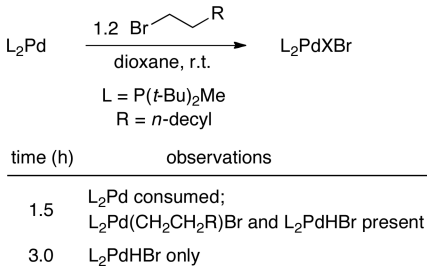
We have applied our palladium-catalyzed elimination process to a formal total synthesis of (*R*)-mevalonolactone. Spencer described the preparation of this bioactive compound from nerol via alcohol **A**, which was transformed into olefin **C** via a Sharpless–Grieco sequence (top of Figure 2).[18] Spencer noted that the conversion of the alcohol to the selenide "proved to be the only difficult step in the synthesis".[19]

We have effected the transformation of alcohol **A** into olefin **C** in 78% overall yield through our palladium-catalyzed elimination process (bottom of Figure 2). Thus, treatment of **A** with Ph_3PBr_2 furnishes primary alkyl bromide **B**. Next, 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= $P(t\text{-}Bu)_2Me$). Thus, oxidative addition of the alkyl bromide to L_2Pd proceeds via an S_N2 process to generate $L_2Pd(CH_2CH_2R)Br$ (**D**).[12a,c] Dissociation of one phosphine furnishes a 14-electron palladium adduct (**E**), which undergoes β-hydride elimination to provide a palladium olefin–hydride intermediate (**F**). In the presence of base (Cy_2NH) and L, palladium complex **F** affords $[Cy_2NH_2]Br$, the olefin, and L_2Pd.

In order for our mechanistic study to be more tractable, we chose to focus our investigation on palladium-catalyzed dehydrobrominations in the absence of KO*t*-Bu, a process that also occurs in excellent yield (entry 3 of Table 1).[20] With regard to the oxidative-addition step of the proposed catalytic cycle, we have previously established that L_2Pd reacts with 1-bromo-3-phenylpropane in Et_2O at 0 °C, and we have crystallographically characterized the Pd(II) adduct.[12b] We have now examined the reaction of 1-bromododecane with L_2Pd in dioxane at room temperature, and we have determined that oxidative addition is complete within 1.5 hours, affording a mixture of $L_2Pd(CH_2CH_2R)Br$ and L_2PdHBr[21] (eq 4). After an additional 1.5 hours, this mixture has proceeded to form L_2PdHBr quantitatively. Taken together, these data indicate that oxidative addition and then β-hydride elimination are chemically and kinetically competent initial steps of the catalytic cycle.

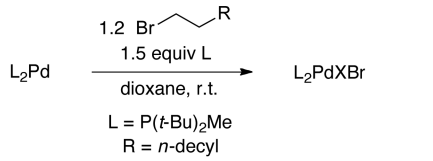


(4)

We have investigated the impact of added $P(t\text{-}Bu)_2Me$ on the reaction of 1-bromododecane with L_2Pd (eq 5). The rate of consumption of L_2Pd is unaffected by the additional ligand, whereas the rate of formation of L_2PdHBr is inhibited, consistent with the suggestion that

L_2Pd (rather than L_1Pd or L_3Pd) is the species undergoing oxidative addition and that ligand dissociation precedes β-hydride elimination.[22]

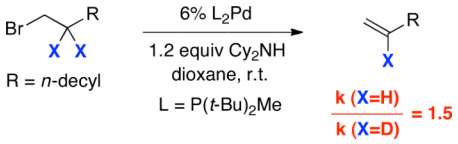
The rate law for the palladium-catalyzed dehydrobromination of 1-bromododecane is first order in L_2Pd, fractional (first order at lower concentration, zeroth order at higher concentration) order in the alkyl bromide, and zeroth order in Cy_2NH. According to ^{31}P NMR spectroscopy, $L_2Pd(CH_2CH_2R)Br$ is the predominant resting state of palladium during the early stages of the reaction (small amounts of L_2Pd and L_2PdHBr are also present; as the reaction progresses, the proportion of L_2PdHBr increases). These data are consistent with oxidative addition and a subsequent step each being partially rate-determining.



time (h)	observations
1.5	L_2Pd consumed; $L_2Pd(CH_2CH_2R)Br$ and L_2PdHBr present
3.0	$L_2Pd(CH_2CH_2R)Br$ and L_2PdHBr present
12	L_2PdHBr only

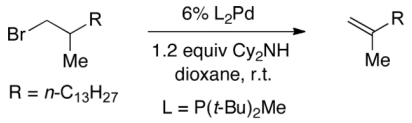
(5)

For the stoichiometric chemistry of L_2Pd, we have established that β-hydride elimination is impeded by the addition of excess $P(t\text{-}Bu)_2Me$ (eq 5); we have similarly determined that the palladium-catalyzed dehydrohalogenation of 1-bromododecane is inhibited by added $P(t\text{-}Bu)_2Me$. 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_H/k_D = 1.5; eq 6). Collectively, these data are consistent with β-hydride elimination being the other partially rate-determining step.



(6)

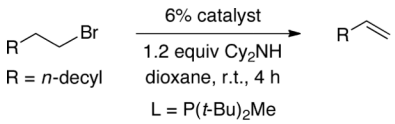
In a previous study, we have demonstrated that oxidative addition of a primary alkyl electrophile to $Pd/P(t\text{-}Bu)_2Me$ preferentially proceeds through an S_N2 pathway.[12a,c] If oxidative addition is indeed partially rate-determining for the dehydrohalogenation of 1-bromododecane, then one might anticipate that, in the case of a more hindered alkyl bromide, oxidative addition would be entirely rate-determining. The rate law the dehydrobromination of a β-branched primary alkyl bromide and established that the rate law is first order in the alkyl bromide, first order in L_2Pd, and zeroth order in Cy_2NH (eq 7). Furthermore, ^{31}P NMR spectroscopy reveals that L_2Pd 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.



rate law: first order in alkyl bromide
first order in L_2Pd
zeroth order in Cy_2NH

(7)

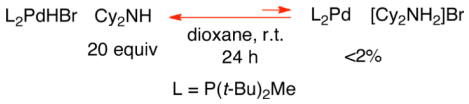
Interestingly, L_2PdHBr is *not* an intermediate in the primary catalytic cycle. Thus, treatment of 1-bromododecane with 6% L_2PdHBr, rather than L_2Pd, results in essentially no 1-dodecene (eq 8).



catalyst	yield (%)
L_2Pd	81
L_2PdHBr	**<2**

(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.[23,24] Thus, it appears that, during our palladium-catalyzed dehydrobromination process, a palladium–hydride other than L_2PdHBr is undergoing reductive elimination to regenerate Pd(0).



(9)

Because each turnover of 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.[25]

Although we had previously postulated that the formation of a relatively stable L_2PdHCl ($L=PCy_3$) complex could be the origin of low catalyst activity in a Heck reaction of an aryl chloride,[23] we had not fully appreciated the importance of avoiding the formation of L_2PdHBr in developing a mild Pd/P(*t*-Bu)$_2$Me-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.[26]

CONCLUSIONS

Although the elimination of HX to form an olefin is a classic transformation in organic chemistry, there remains a need for mild new methods for accomplishing this fundamental process. Herein, we have exploited a generally undesired elementary step in cross-coupling reactions, β-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 establish 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 often-invoked intermediate in palladium-catalyzed processes such as the Heck reaction, is *not* an intermediate in the active catalytic cycle.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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13. Isomerization of the initially generated olefin by a palladium–hydride intermediate is a well-established side reaction in Heck couplings. For recent examples of isomerizations of olefins catalyzed by palladium hydrides, including $Pd(P(t\text{-}Bu)_3)_2HCl$, see: Gauthier D, Lindhardt AT, Olsen EPK, Overgaard J, Skrydstrup T. J. Am. Chem. Soc. 2010; 132:7998–8009. [PubMed: 20481527]
14. The proportion of internal olefin does not increase as the reaction progresses, and treatment of 1-dodecene with L_2PdHBr in dioxane at room temperature does not lead to the generation of internal olefins (however, isomerization *is* observed at elevated temperature).
15. Under our standard conditions (Table 1), in the presence of one equivalent 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 one equivalent of an unprotected indole or a nitrile.
16. The relative rate of dehydrobromination of 1-bromododecane vs. 1-bromo-2-methylpentadecane (a β-branched alkyl bromide) is ~13.
17. For a study of the relative rates of oxidative addition of *n*-nonyl–X (X=I, Br, Cl, F, OTs) to $Pd(P(t\text{-}Bu)_2Me)_2$ in THF, see Ref. 12c.
18. Ray NC, Raveendranath PC, Spencer TA. Tetrahedron. 1992; 48:9427–9432.
19. Spencer also notes that the selenide was “tenaciously contaminated” by a selenium-containing impurity.
20. Due to the slow accumulation of L_2PdHBr during the course of the palladium-catalyzed dehydrobromination (vide infra), our mechanistic studies have focused on the early stages of the reaction.
21. Throughout this discussion, L_2PdHBr refers to *trans*-L_2PdHBr.
22. This contrasts with Yamamoto's studies of thermal decomposition of *trans*-L_2PdEt_2, wherein β-hydride elimination proceeds predominantly without ligand dissociation: Ozawa F, Ito T, Yamamoto A. J. Am. Chem. Soc. 1980; 102:6457–6463.
23. Treatment of L_2Pd with $[Cy_2NH_2]Br$ in dioxane at room temperature leads to very slow formation of L_2PdHBr. For related observations with a different ligand (PCy_3), halide (Cl), and base (Cy_2NMe), see: Hills ID, Fu GC. J. Am. Chem. Soc. 2004; 126:13178–13179. [PubMed: 15479044]
24. On the other hand, KO*t*-Bu does react with L_2PdHBr to generate L_2Pd in quantitative yield. However, if KO*t*-Bu, rather than Cy_2NH, is employed as the stoichiometric base, then the elimination does not proceed cleanly, and there is a considerable background reaction (E2).
25. The decreased efficiency of Cy_2NMe relative to Cy_2NH (Table 1, entry 8 versus entry 1) may be due to the greater solubility in dioxane of $[Cy_2NHMe]Br$ compared with $[Cy_2NH_2]Br$, which leads to more protonation of L_2Pd to form inactive L_2PdHBr.
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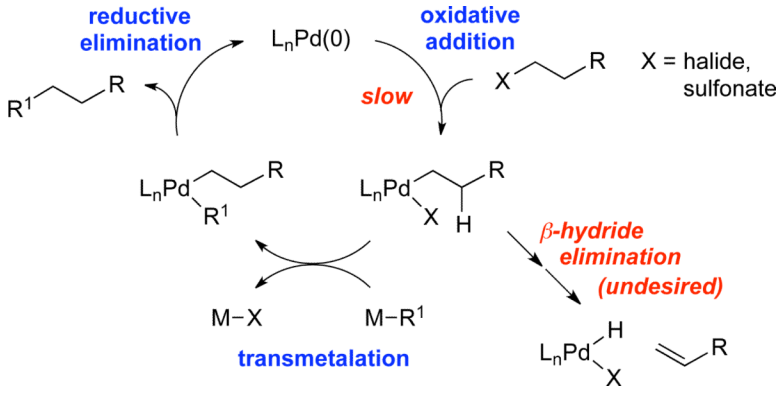


Figure 1.
Outline of a possible pathway for (and impediments to) palladium-catalyzed cross-coupling of an alkyl electrophile.

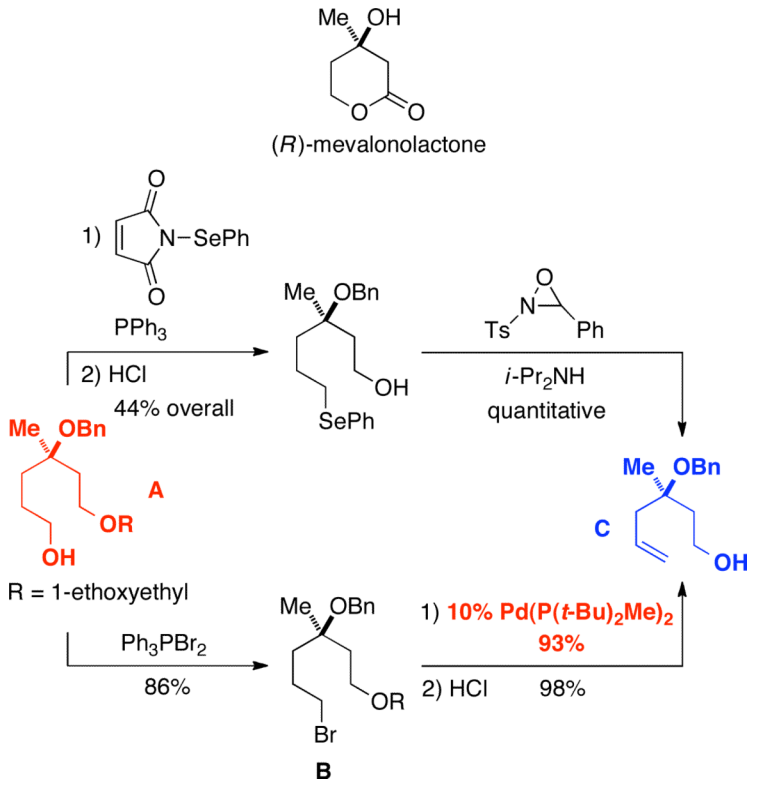


Figure 2.
Conversion of an alcohol to an olefin, en route to (*R*)-mevalonolactone: Spencer (top); this study (bottom).

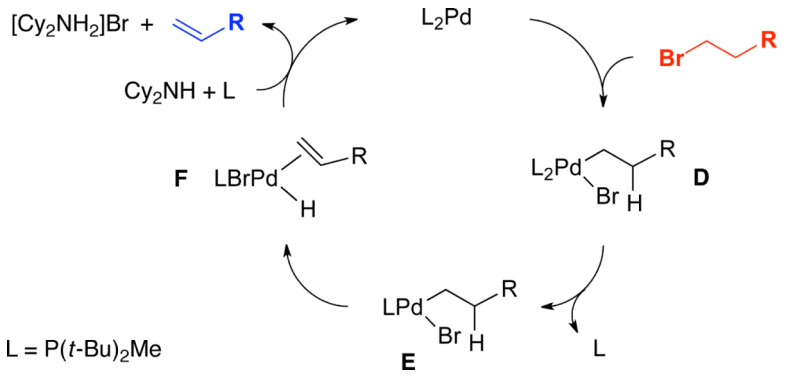
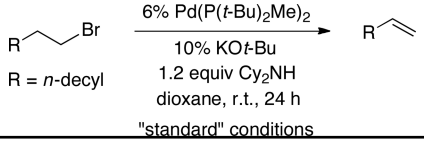


Figure 3.
Outline of a possible mechanism for Pd(P(*t*-Bu)$_2$Me)$_2$-catalyzed dehydrobromination reactions.

Table 1

Palladium-Catalyzed Elimination of an Alkyl Bromide to Generate an Olefin: Influence of Reaction Parameters

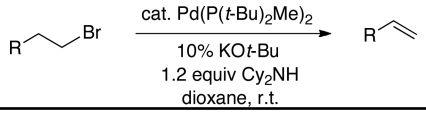


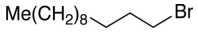
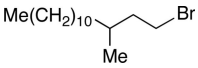
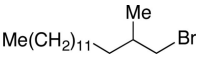
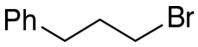
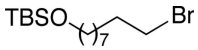
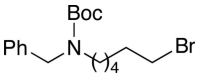
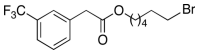
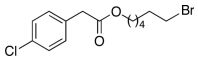
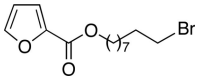
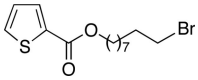
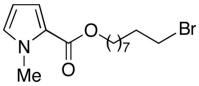
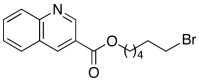
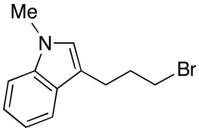
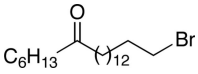
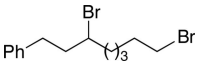
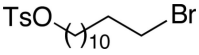
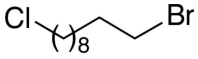
entry	variation from the “standard” conditions	yield (%)[a]
1	none	98 (91)
2	no $Pd(P(t\text{-}Bu)_2Me)_2$	3
3	no KO*t*-Bu	95 (81)
4	no Cy_2NH	13
5	$Pd(P(t\text{-}Bu)_3)_2$, instead of $Pd(P(t\text{-}Bu)_2Me)_2$	3
6	$Pd(PCy_3)_2$, instead of $Pd(P(t\text{-}Bu)_2Me)_2$	12
7	$Pd(PPh_3)_4$, instead of $Pd(P(t\text{-}Bu)_2Me)_2$	3
8	Cy_2NMe, instead of Cy_2NH	42
9	Cs_2CO_3, instead of Cy_2NH	28
10	3% $Pd_2(dba)_3$ + 12% $P(t\text{-}Bu)_2Me$, instead of $Pd(P(t\text{-}Bu)_2Me)_2$	96 (76)
11	3%, instead of 6%, $Pd(P(t\text{-}Bu)_2Me)_2$	90 (75)

[a]Determined via gas chromatography with the aid of a calibrated internal standard (average of two experiments); the yield after 4 h is given in parentheses.

Table 2

Palladium-Catalyzed Elimination Reactions of Alkyl Bromides



entry	substrate	yield (cat. loading) [a]
1		94 (6)
2		98 (14)
3		99 (30)
4		100 [b] (8)
5		88 (8)
6		98 (8)
7		86 (8)
8		91 (5)
9		86 (8)
10		96 (8)
11 [c]		92 (8) [17:1]
12		96 (12)
13		84 (7)
14		92 (15)
15 [d]		78 (12)
16		86 (11) [6:1]
17		89 (6)

[a] Both values are percentages. The isolated yield is provided (average of two experiments). In all cases, >98% of the unpurified elimination product is the terminal olefin, with the exception of entries 11 and 16, where the ratio of terminal:internal olefins (determined via ^{1}H NMR spectroscopy) is given in brackets.

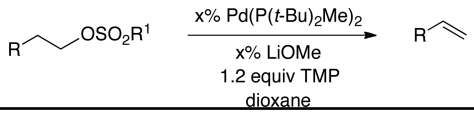
[b] Due to the volatility of allylbenzene, the yield was determined via gas chromatography versus a calibrated internal standard (average of two experiments).

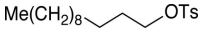
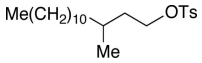
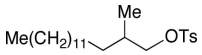
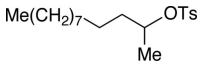
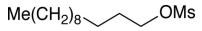
[c] KO*t*-Bu loading: 2.5%.

[d] KO*t*-Bu loading: 20%.

Table 3

Palladium-Catalyzed Elimination Reactions of Alkyl Sulfonates



entry	substrate	temperature (°C), x	yield [a]
1		80, 6	98 [18:1]
2		90, 6	97
3		100, 17	96
4		100, 25	94 [1:2]
5		80, 12	90 [14:1]

[a]The isolated yield (%) is provided (average of two experiments). For eliminations in which >2% of the internal olefin is generated, the ratio of terminal:internal olefins (determined via ^{1}H NMR spectroscopy) is given in brackets.