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Palladium-Catalyzed Hydrohalogenation of 1,6-Enynes: Hydrogen Halide Salts and Alkyl Halides as Convenient HX Surrogates

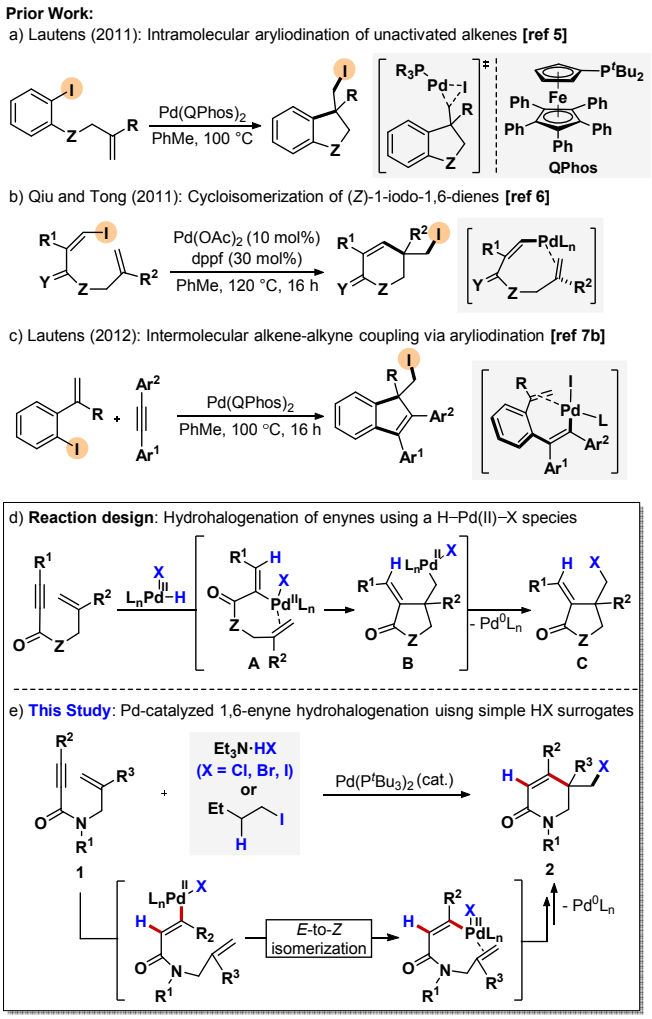
David A. Petrone[†1], Ivan Franzoni[†1], Juntao Ye[1], José F. Rodríguez[1], Amalia I. Poblador-Bahamonde*[2], and Mark Lautens*[1]

Abstract: Difficulties associated with the handling H_2 and CO in metal-catalyzed processes has led to the development of chemical surrogates to these species. Despite many successful examples using this strategy, the application of convenient hydrogen halide (HX) surrogates in catalysis has lagged behind considerably. We now report the use of ammonium halides as HX surrogates to accomplish a novel Pd-catalyzed hydrohalogenation of enynes. These safe and practical salts avoid many drawbacks associated with traditional HX sources including toxicity and corrosiveness. Experimental and computational studies support a reaction mechanism involving a crucial *E*-to-*Z* vinyl–Pd isomerization and a carbon–halogen bond-forming reductive elimination. Furthermore, rare examples of C(sp^3)–Br and –Cl reductive elimination from Pd(II) as well as transfer hydroiodination using 1-iodobutane as an alternate HI surrogate are also presented.

INTRODUCTION

The carbon–halogen bond is an essential functional group in organic chemistry, and its high utility is made apparent by the multitude of available methods used for their installation into organic molecules.[1] In 2010, our group reported a Pd-catalyzed synthesis of 2-bromoindoles[2] rooted in Hartwig's seminal work on reversible reductive elimination of aryl halides from Pd(II) complexes.[3,4] These studies prompted our discovery of a catalytic alkene aryliodination involving a novel C(sp^3)–I bond-forming reductive elimination from an alkyl–Pd(II)–I species (Figure 1a).[5] In a related study, Qiu and Tong showed that Pd(0) could catalyze the cycloisomerization of vinyl iodides leading to various heterocyclic scaffolds with high efficiencies (Figure 1b).[6] Several other contributions invoking this mode of reactivity have since been made, yet all have employed substrates containing *pre-installed* carbon–halogen bonds (i.e. aryl and vinyl halides).[7] This functional group facilitates substrate activation to occur via oxidative addition of Pd(0), and it is ultimately recycled into the product.[8] Despite the complete atom economy achieved by these methodologies,[9] the prerequisite for halogenated substrates often limits their synthetic utility. Therefore, the use of *external* halogen sources as a way to develop new cyclohalogenation reactions of substrates devoid of a pre-installed carbon–halogen bond would be a significant advance.[10]

A 2012 report from our group regarding the synthesis of indenes via a conjunctive alkene-alkyne coupling (Figure 1c) led us to consider catalytic cyclohalogenation reactions of non-halogenated enynes.[11] Due to their facile and modular preparation, enynes represent an ideal framework on which to explore new catalytic reactivity.[12] More specifically, the 1,6-enynes motif has served well as a template for developing numerous cyclizative hydrofunctionalization methods including hydroboration,[13] hydrosilylation,[14] hydrostannylation[15] and hydrofluorination[16] among others.[17] Therefore, we hypothesized that a novel hydrohalogenation of 1,6-enynes could be accomplished by using a discrete H–Pd(II)–X species (where X is a halogen) as a catalytic intermediate (Figure 1d).[18] A regioselective hydropalladation would act to engage the this class of substrate resulting in the formation of a key vinyl–Pd(II)–X intermediate (i.e. **A**).[19] A subsequent intramolecular alkene insertion and a terminating C(sp^3)–halogen bond-forming reductive elimination (via **B**) could be realized if the palladium species were to be modified by an appropriate phosphine ligand (i.e. P^{t}Bu$_3$ or QPhos).[2-7]



Scheme 1. Previous work on Pd-catalyzed aryl and vinyl iodination of alkenes and alkynes and the design of the enyne hydrohalogenation reaction involving simple HX surrogates.

While alkene and alkyne hydrohalogenation is a classic transformation that has been used for over a century, reports of metal-catalyzed hydrohalogenations have been scarce.[1p,20] This

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paucity of methods can be partly attributed to the limited number of practical hydrogen halide (HX) sources available. Diatomic feedstocks like HX are routinely used industrially to upgrade the value and function of commodity chemicals.[21] Although large quantities of these building blocks are consumed each year, the laboratory use of these volatile and often toxic compounds can be thwarted by the challenges associated with their safe handling. As a result, methods exist which obviate this drawback by allowing for *in situ* HX generation via the combination of reagents,[22] and have been used together with transition metals to affect catalytic hydrohalogenation in rare instances.[23] Unfortunately, these methods commonly employ reagents which narrow functional group tolerance and involve strongly acidic reaction media. Conversely, catalytic methods that employ a single and well-defined reagent which acts as a surrogate to a hazardous chemical have become increasingly popular.[24] Therein, a metal catalyst reacts with the chosen surrogate in order to simultaneously release and activate the problematic small molecule of interest. Transfer hydrogenations using alcohols as practical precursors to H_2 (e.g. ^{i}PrOH) illustrate this concept.[25] Numerous metal-catalyzed transformations have also been reported which conveniently generate CO either *in situ*[26,27] Other recent examples relying on this concept[24] include a Rh-catalyzed transfer hydroformylation by Dong and co-workers,[28] and a reversible Ni-catalyzed transfer hydrocyanation by Morandi and co-workers.[29] These technologies use aliphatic aldehydes and nitriles as surrogates to syngas and HCN, respectively. Despite these enabling achievements, the use of convenient HX surrogates in transition-metal catalysis remains unexplored. Accordingly, it would be of interest to develop a robust hydrohalogenation protocol whereby a H–Pd(II)–X species is generated catalytically *in situ* by employing a mild, simple and convenient HX surrogate.[30]

In the turnover-enabling step of the Heck reaction, an exogenous base (e.g. Et_3N) is used to convert H–Pd(II)–X back into the active Pd(0) catalyst while concomitantly forming an equivalent of base·HX waste.[31] Considering this sequence in reverse, we envisioned that base·HX species could be used as practical HX surrogates to controllably generate the desired H–Pd(II)–X species *in situ*.[32] This would then promote the desired enyne hydrohalogenation via the transfer of both the hydride and halide ligands to the substrate.

Herein, we examine the ability of Et_3N·HI to act as a safe and practical replacement for HI in the development of a conceptually and mechanistically novel hydroiodination of 1,6-enynes. Through a combination of experiment and theory, we have demonstrated the feasibility of a formal *anti* alkyne hydropalladation which occurs via a counter-intuitive two-step *cis* alkyne hydropalladation/vinyl–Pd(II) *E*-to-*Z* isomerization. Our theoretical investigation has also led to the development of the analogous hydrobromination and hydrochlorination reactions that represent rare examples of C(sp^3)–Br and C(sp^3)–Cl reductive elimination from Pd(II).[33] As such, the iodinated, brominated and chlorinated products can be obtained by simply changing the HX surrogate. Furthermore, this report also outlines our preliminary findings regarding the use of 1-iodobutane as a non-ionic HX surrogate in a novel transfer hydroiodination involving a dehydrohalogenation/hydrohalogenation sequence.

RESULTS AND DISCUSSION

The precedence for carbon–iodine bond-forming reductive elimination from Pd(II) promoted us to initially target the hydroiodination reaction of enynes **1** using Et_3N·HI as an HI surrogate (Figure 1).[2-6,7a-g] During our preliminary experiments, the expected 5-membered products of hydroiodination **C** were not observed, and instead 6-membered heterocycles **2** were found to be the sole hydroiodination products which were accompanied by 1,6-enyne cycloisomerization products **3**[11] and the corresponding isomers **4**. Compounds **2** and **3** are thought to arise from hydropalladations that proceed with opposite regioselectivities (*vide infra*). Pyridinone **2** originates from the hydropalladation resulting in the transfer of the hydride moiety to the α-carbon, whereas **3** (and ultimately **4**) arises from a hydropalladation resulting in the transfer of the hydride moiety to the β-carbon. After screening a wide array of parameters, Pd(P^tBu_3)$_2$ (10 mol%) and Et_3N·HI (1.2 equiv) in PhMe (0.05 M) at 120 °C for 2 hours was found to be the optimal combination. Under these conditions, **1a** could be converted to **2a** in 47% yield (Figure 1). Changing reaction conditions was found to markedly affected the overall reaction efficiency, yet had little or no impact on the key ratio of **2**:(**3**+**4**). The *N*-protecting group was the variable that allowed for the greatest perturbation of this key ratio that directly relates to the yield of desired product. We postulate that the *N*-protecting group plays a key role in dictating the regioselectivity of hydropalladation, which manifests itself in the observed changes to the **2:**(**3**+**4**) ratio.

Unprotected **1b** led to product **2b** being afforded in 16% yield, while protecting the nitrogen with *N*-*para*-trifluoromethylphenyl (**1c**) led to only slightly improved results (35% yield). Substrates possessing *N*-alkyl groups such as –^{t}Bu and –Me (**1d** and **1e**) performed marginally better, and in both cases products were obtained in 54% yield (**2d** and **2e**). Substrates possessing *N*-Ph **1f** and *N*-3,5-dimethoxyphenyl groups **1g** afforded similar results with respect to the *N*-alkyl analogs, whereas *N*-*para*-methoxyphenyl **1h** led to a moderate improvement (61% yield). In general, substrates possessing electron-rich *N*-substituents undergo the hydroiodination process in higher yield, which is likely a manifestation of their ability to promote a more regioselective hydropalladation. It was hypothesized that employing substrates containing *N*–O(alkyl) bonds could further increase the electron richness of the amide functionality, and thus improve the resulting selectivity of the reaction. In this regard, *N*–OBn **1i** and *N*–OMe **1j** were prepared and tested under the reaction conditions. These analogs provided incremental improvements with respect to **1h**, and pyridinones **2i** and **2j** could be obtained in 63% and 68% yield, respectively. In an effort to further increase the electron richness of the substrate, the *N*–SMe analog **1k** was prepared. However, the products of hydroiodination (**2k**) or cycloisomerization (**3k**/**4k**) were not observed, and instead, the *N*–SMe bond was cleaved under these conditions leading to enyne **1b** in 64% yield. Furthermore, it was found that the *N*–SMe bond was cleaved even in the absence of the Pd(0) catalyst leading to quantitative formation of **1b**. When analog **1la** containing an *N*–O^{t}Bu moiety was utilized,[34] product **2la** could be obtained in 75% yield along with 18% of cycloisomerized products.

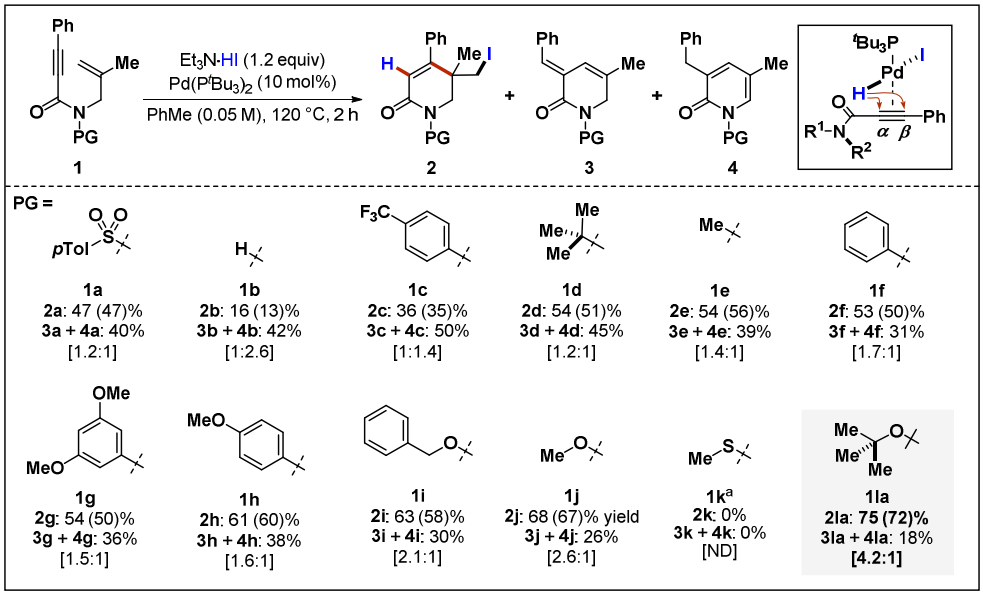
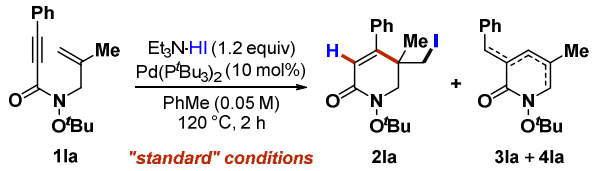


Figure 1. Pd-catalyzed hydroiodination of 1,6-enynes using $Et_3N{\cdot}HI$ as an HI surrogate: Effect of the *N*-protecting group. Notes: Reactions were run on a 0.2 mmol scale, yields determined by ^1H NMR analysis of the crude reaction mixture, values in parentheses represent the isolated yield of **2**, the ratios in square brackets represent yields in the form of [**2**:(**3**+**4**)]. [a] Subjection of **1k** to the reaction conditions led to formation of **1b** in 64% yield. ND = not determined.

With both the optimal reaction conditions and *N*-protecting group in hand, we next examined the effect that altering various reaction parameters had on the efficiency of the hydroiodination reaction (Table 1). In the absence of the Pd(0) catalyst, the products of hydroiodination **2la** or cycloisomerization (**3la** and **4la**) were not observed, and the starting material was recovered intact (entry 2). Moreover, the absence of products resulting from direct alkyne hydroiodination speaks to the mild nature of the HI surrogate used herein.[22] The use of dioxane as solvent led to comparable results to those obtained using PhMe (entry 3), while decreasing the reaction temperature to 110 °C or 100 °C led to lower product yields and incomplete conversion of **1la** (entries 4 and 5). QPhos has been shown by our group to be an effective ligand for aryliodination reactions involving C(sp^3)–I bond-forming reductive elimination from alky–Pd(II)I species.[5,7a,b,d,e,g] However, the use of 10 mol% of $Pd(QPhos)_2$ led to greatly attenuated reactivity, and **2la** was obtained in 30% yield (entry 7). Carrow and co-workers have recently shown tri(1-adamantyl)phosphine to be an isosteric, but more electron donating analog to tri(*tert*-butyl)phosphine.[35] Remarkably, **2la** could be obtained in 56% yield when this reaction was run using $Pd_2(dba)_3$ (5 mol%) and P(1-Ad)$_3$ (20 mol%) (entry 8). Furthermore, the reaction efficiency decreased significantly when di(*tert*-butyl)neopentylphosphine (DTBNpP)[36] was used in place of P(^{t}Bu)$_3$, and **2la** was only obtained in 24% yield (entry 9). It is plausible that either the ability of DTBNpP to promote the required C(sp^3)–I bond-forming reductive elimination and/or the stability of the resulting catalyst under the reaction conditions is greatly diminished. Decreasing the loading of $Pd(P^tBu_3)_2$ to 5 mol% renders the hydroiodination less efficient, and incomplete conversion of the starting material is observed in this case (entry 10). Furthermore, changing the loading of $Et_3N{\cdot}HI$ to 1.0 or 2.0 equivalents led to similarly inferior results (entries 11 and 12).

Table 1. Pd-catalyzed hydroiodination of 1,6-enynes: Effect of reaction parameters[a]



entry	variation from the *"standard" conditions*	yield **2la** (%)[b,c]	yield **3la+4la** (%)[b]
1	**none**	**75(72)**	**18**
2	no $Pd(P^tBu_3)_2$	0	0
3	1,4-dioxane instead of PhMe	75	21
4	110 °C instead of 120 °C	61	15
5	100 °C instead of 120 °C	56	13
6	0.1 M instead of 0.05 M	72	18
7	$Pd(QPhos)_2$ instead of $Pd(P^tBu_3)_2$	30	15
8[d]	P(1-Ad)$_3$/$Pd_2(dba)_3$ instead of $Pd(P^tBu_3)_2$	56	17
9[d]	DTBNpP/$Pd_2(dba)_3$ instead of $Pd(P^tBu_3)_2$	24	9
10	5 mol% $Pd(P^tBu_3)_2$	65	19
11	1.0 equiv $Et_3N{\cdot}HI$	68	17
12	2.0 equiv $Et_3N{\cdot}HI$	69	17
13	$Me_3N{\cdot}HI$ instead of $Et_3N{\cdot}HI$	37	8
14	$Me_3N{\cdot}HI$/1,4-dioxane instead of $Et_3N{\cdot}HI$/PhMe	66	15
15	^{n}Bu$_3$N·HI instead of $Et_3N{\cdot}HI$	71	24

[a] Reactions were run on a 0.2 mmol scale. [b] Determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] Value in brackets parentheses represents the isolated yield. [d] [Pd] = 10 mol%, phosphine = 20 mol%. 1-Ad = 1-adamantyl. DTBNpP = di(*tert*-butyl)neopentylphosphine.

We wished to determine whether changing the amine component of the hydroiodide salt had any significant effect. When $Et_3N{\cdot}HI$ was substituted for $Me_3N{\cdot}HI$, **2la** was obtained in only 37% yield (entry 13). During this experiment, $Me_3N{\cdot}HI$ appeared to be much less soluble than $Et_3N{\cdot}HI$. This observation, in combination with the fact that $NEt_3{\cdot}HI$ was found to be more soluble in 1,4-dioxane than in PhMe, led us to examine the reaction utilizing $Me_3N{\cdot}HI$ in 1,4-dioxane. Although much of the reactivity was restored under these conditions, $Et_3N{\cdot}HI$ still proved to be a superior HI surrogate (entry 14). Interestingly, more soluble $^nBu_3N{\cdot}HI$ performed nearly as well as $Et_3N{\cdot}HI$, and **2la** could be obtained in 71% yield. The scope of the Pd-catalyzed enyne hydroiodination was next examined (Figure 2).

Our optimization studies revealed that toluene and 1,4-dioxane provided nearly identical results, and all substrates were therefore tested in both solvents to obtain the highest product yield. Electron-rich aryl substituents on the alkyne were well tolerated under the reaction conditions, and products containing *para*–Me (**2lb**), –Ph (**2lc**), –OMe (**2ld**) and –OTBS (**2le**) groups could be obtained in 56%-81% yield. Substrates with electron-withdrawing *para*–Cl (**1lf**), $–CF_3$ (**1lg**) and –CN (**1lh**) groups were also suitable substrates, affording the corresponding products in 69%-80% yield. The reaction conditions were tolerant of both ketone and ester functionalities, and products **2li** and **2lj** were obtained in 61% and 69% yield, respectively. Similar efficiencies were observed when substrates containing various *meta* substituents were tested (**1lk**-**1lr**). Electron-donating *meta*–Me (**1lk**) and –OMe (**1ll**) groups were tolerated, leading to the products **2lk** and **2ll** in 69% and 72% yield, respectively. Products containing phenol, aldehyde and nitrile groups at the *meta*-position (**2ln**-**2lp**) could be obtained in 52%, 62% and 76% yield, respectively. Substrates possessing a 3,5-difluorophenyl (**1lq**) or a 3,5-di(trifluoromethyl)phenyl (**1lr**) group could undergo the desired hydroiodination reaction, leading to the corresponding fluorinated pyridinones **2lq** and **2lr** in 67% and 70% yield, respectively. Substrates containing various *ortho* substituents (**1ls**-**1lu**) could also undergo hydroiodination to generate products **3ls**-**2lt** in 40-66% yield. Notably, the conditions were also compatible with a series of heteroaromatic groups. Substrates containing a 3-pyridyl (**1lv**) or a 2-thienyl (**1lw**) group underwent the desired transformation in 78% and 76% yield, respectively. Enyne **1lx** containing a 5-*N*–Boc indolyl group could be transformed to the corresponding product **2lx** in 48% yield. To highlight the scalability of this transformation, a gram scale reaction was conducted using **1la** where pyridinone **2la** could be obtained in 66% isolated yield. Substitution on the alkene which deviates from –Me resulting in a less efficient reaction, and the corresponding –Ph and –Et analogs were isolated in only 6% and 36% yield, respectively. The major byproducts observed in these cases were that of alkene isomerization (*vide infra*).

In 2012, Fu reported a room-temperature dehydrohalogenation of alkyl bromides catalyzed by $Pd[P(^tBu)_2Me]_2$ (Scheme 2a).[37] The mechanism of this transformation involves S_N2-type oxidative addition of $L_2Pd(0)$ to an alkyl bromide leading to alkyl–Pd(II)–Br species **D** which contains two phosphine ligands. Loss of a single phosphine affords 14-electron species **E**, which undergoes β-hydride elimination to generate H–Pd(II)–Br species **F**. Alkene dissociation presumably affords H–Pd(II)–Br species **G** which is converted to $L_2Pd(0)$ in the presence of Cy_2NH and phosphine. *We envisioned that this mechanistic scenario could be applied as the basis for a transfer hydrohalogenation reaction where alkyl halides act as HX surrogates to generate H–Pd(II)–X* (**H**) *in situ via an analogous release mechanism* (Scheme 2b).[38] The preliminary results obtained for this process are displayed in Scheme 2c. After screening various reaction parameters, the optimal conditions were identified to be enyne (1 equiv), $Pd(P^tBu_3)_2$ (10 mol%) and 1-iodobutane (2.0 equiv) in PhMe (0.05 M) at 120 °C for 16 hours. Enynes possessing various *N*-protecting groups were tested under these conditions. *N*-Ts (**1a**) and *N*-Me (**1e**) enynes could be converted to pyridinones 2**a** and **2e** in 41% and 48% yield, respectively. *N*-aryl substrates **1f** and **1h** were converted to the corresponding products **2f** and **2h** in 54% and 60% yield, respectively. Substrate **1la** possessing an *N*-O^{t}Bu moiety was also converted into pyridinone **2la** in 53% yield. In all cases, the cycloisomerization products **3** and **4** were observed.

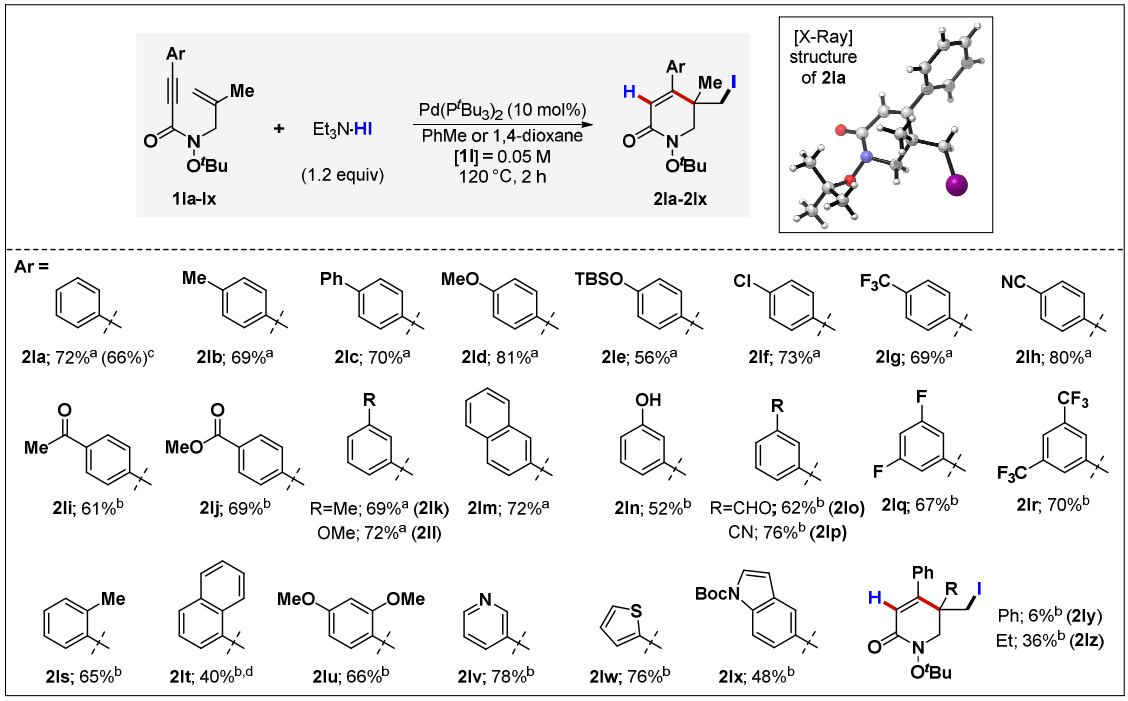
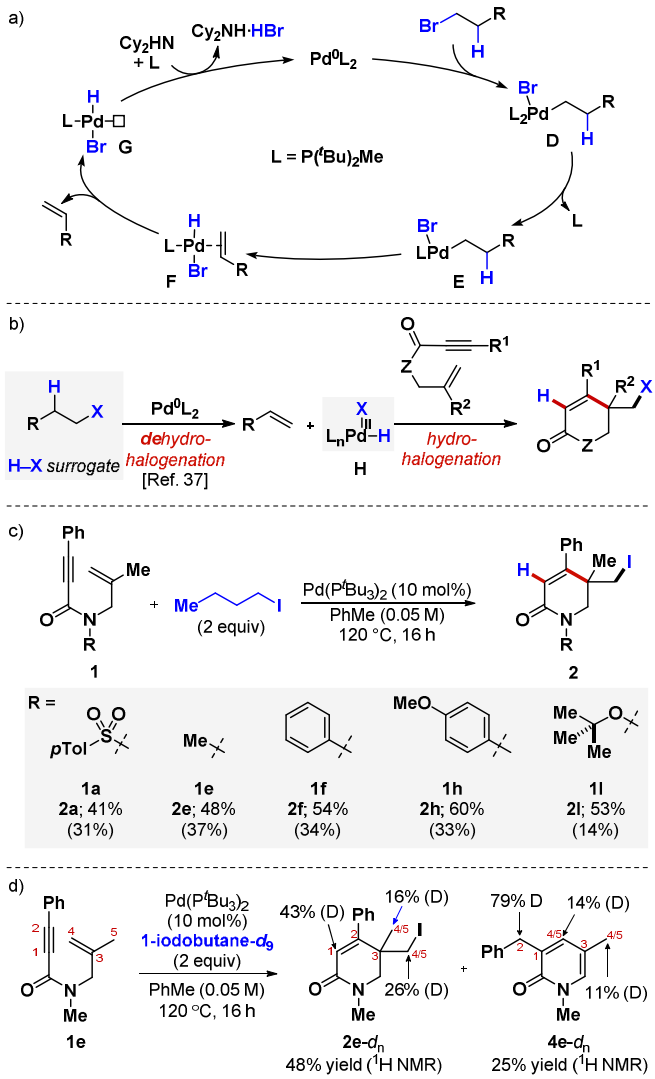


Figure 2. Reaction scope for the Pd-catalyzed hydroiodination of 1,6-enynes using $Et_3N{\cdot}HI$. Reactions were run on a 0.2 mmol scale. Values represent isolated yields after column chromatography. [a] Reaction run in PhMe. [b] Reaction run in 1,4-dioxane. [c] Isolated yield from the reaction run on a 1.0 g scale in 1,4-dioxane. [d] Product **2lt** was obtained a 1.1:1 mixture of atropdiastereomers. TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.

Although this variation of the protocol is still less efficient than when $Et_3N{\cdot}HI$ is used, it represents the first example of a transfer hydroiodination to the best of our knowledge.



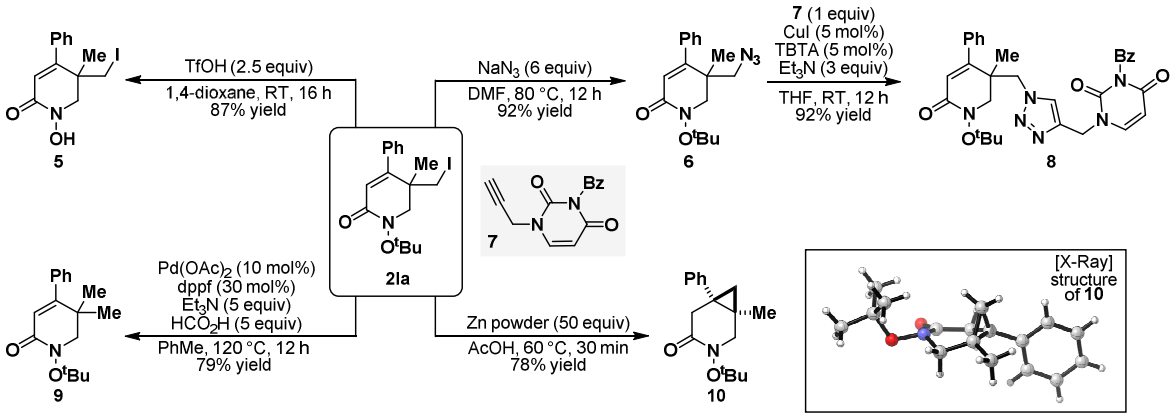
Scheme 2. a) Catalytic cycle for the Pd(0)-catalyzed dehydrohalogenation by Fu and co-workers (Ref. 37). b) Strategy for transfer hydroiodination of 1,6-enynes, c) Reaction scope for the Pd-catalyzed transfer hydroiodination of 1,6-enynes using 1-iodobutane as a HI surrogate. Reactions were run on a 0.2 mmol scale. Yields obtained by ^1H NMR. *p*Tol = *para*-tolyl. Values in parenthesis represent yield of **4**. d) Transfer hydroiodination reaction of **1e** using 1-iodobutane-d_9 as a DI surrogate.

Enyne **1e** was subjected to the transfer hydroiodination reaction conditions using 1-iodobutane-d_9 in place of 1-iodobutane (Scheme 2d). Full consumption of **1e** was observed via proton NMR analysis of the crude reaction mixture after 16 hours at 120 °C, and **2e**-d_n and **4e**-d_n were measured in 48% and 25% yield, respectively. The direct cycloisomerization product (i.e. **3e**) was not observed under the reaction conditions. NMR analysis of purified **2e**-d_n indicated that deuterium had been incorporated at three positions in the product to various extents. Deuteration was observed on the CH_3 group (16% D) as well as the methylene carbon which is bonded to iodine (26% D). Based on the general mechanism proposed in Scheme 1e, observation of this specific deuteration pattern should not be expected. However, it is reasoned that species **H**-*d* can catalyze isopropene isomerization by way of an iterative alkene insertion/elimination mechanism that results in substrate H/D scrambling. When this is followed by the desired deutero/hydroiodination reaction, the partially deuterated isopropene moiety is incorporated into the heterocyclic scaffold resulting in deuteration at positions other than α-C(sp^2). Furthermore, only partial deuteration (43% D) was observed at α-C(sp^2) in the product which must arise from both palladium hydrides (generated via the aforementioned H/D scrambling or via formation of byproduct **4**) and palladium deuterides (generated from iodobutane-d_9) undergoing the desired hydro/deuterohalogenation reaction. It should also be noted that no substantial difference in the amount of incorporated deuterium was observed when PhMe-d_8 was used as solvent in place of PhMe, which suggests that solvent is not a factor in obtaining partial deuteration. Byproduct **4e**-d_n was observed to have deuterium incorporated at the same positions, albeit to a different extent (*vide infra*).

To exhibit the versatility of the pyridinone products, various synthetic manipulations were carried out using product **2la** (Scheme 3). The *tert*-butyl group could be readily cleaved using TfOH in dioxane to unmask hydroxamic acid **5** in 87% yield. Azide **6** could be obtained in 92% yield via a nucleophilic substitution of the neopentyl C(sp^3)–I bond using NaN_3 in DMF. A Cu-catalyzed Huisgen [3+2] cycloaddition between azide **6** and propargylated uracil derivative **7** provided triazole **8** in 92% yield. A Pd-catalyzed reduction of the C(sp^3)–I bond in **2la** could be employed to generate **9** containing a γ-geminal dimethyl motif in 79% yield.[6] Cyclopropane **10** bearing a [4.1.0] bicyclic scaffold could be generated in 78% yield via an intramolecular conjugate cyclization using Zn powder in AcOH.

MECHANISTIC AND COMPUTATIONAL STUDIES

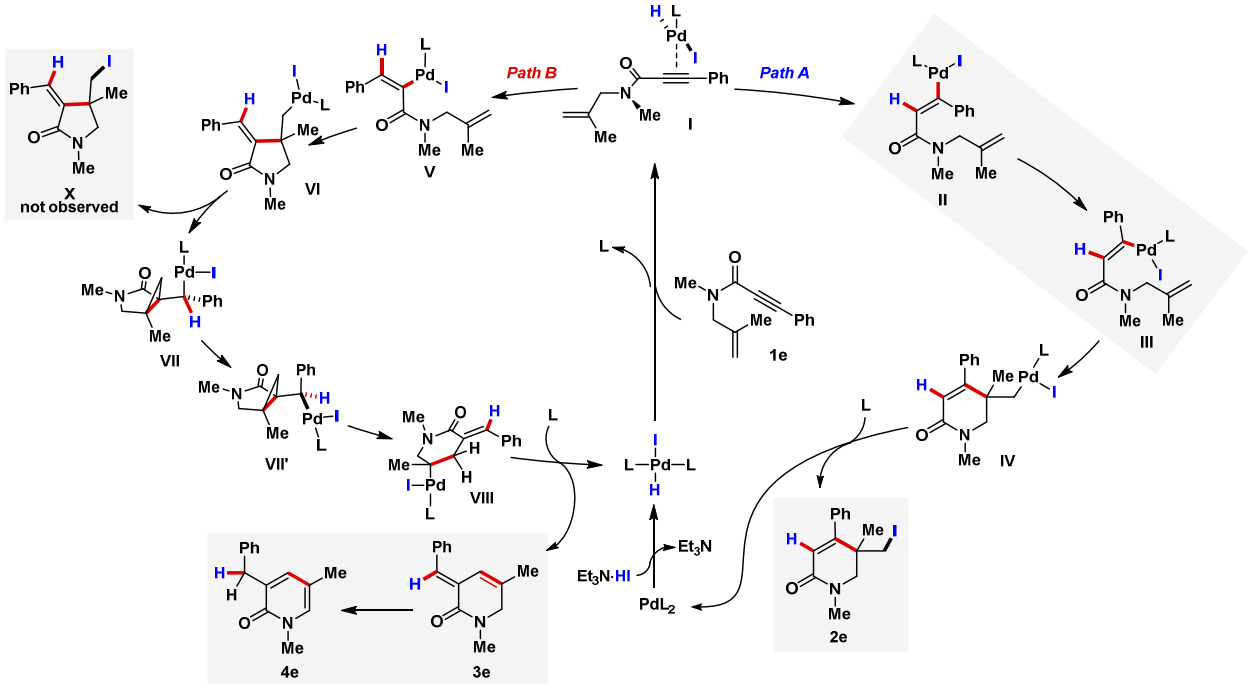
A plausible mechanism for the reaction is presented in Scheme 4. The reaction between PdL_2 (L = P^tBu_3) and $Et_3N{\cdot}HI$ generates the active PdL_2HI species that upon coordination to the substrate **1e** produces intermediate **I**. Insertion of the alkyne moiety into the Pd–H bond can follow two different pathways. In **Path A**, hydropalladation placing the Pd atom on the β–carbon leads to intermediate **II**. A key *E*-to-*Z* isomerization of this vinyl–Pd(II) intermediate affords **III** which after alkene coordination and 6-*exo*-trig carbopalladation gives intermediate **IV**. Final C(sp^3)–I bond-forming reductive elimination furnishes the desired product **2e** and regenerates PdL_2. In competing **Path B**, a reversal in the regioselectivity of the hydropalladation step places the Pd atom on the α–carbon. The resulting intermediate **V** undergoes a 5-*exo*-trig carbopalladation which leads to **VI**. In analogy to **IV**, neopentyl-Pd intermediate **VI** could undergo C–I bond-forming reductive elimination to provide alkyl iodide product **X**. However, the formation of this product was not observed during our investigations. Instead, ring closure occurs to generate cyclopropylcarbinyl species **VII**, which undergoes C–C σ–bond rotation and ring expansion via β–carbon elimination to produce **VIII**.[39,40] Regioselective β–hydride elimination provides conjugated diene byproduct **3e** and regenerates the active PdL_2HI catalyst.



Scheme 3. Derivatization studies concerning pyridinone product **2la**. TBTA = tris(benzyltriazolemethyl)amine, Bz = benzoyl. Tf = trifluoromethanesulfonyl, dppf = 1,1'-bis(diphenylphosphino)ferrocene.

A combined experimental and theoretical approach was taken to better understand the mechanism of the reaction. The proposed hydropalladation via **Path A** and **B**, leading to desired product **2e** and byproducts **3e** and **4e**, respectively, were studied computationally in detail at the IEFPCM (Toluene) M06L/6-311G(d,p)/SDDALL//BP86/6-31G(d,p)/LANL2DZ level of theory.[41] In order to support our proposal for the initial formation of a $HPdL_2I$ species, a homogeneous toluene-d_8 solution of a 1:1 mixture of $Pd(P^tBu_3)_2$ and $Bu_3N{\cdot}HI$ was analyzed by ^1H NMR after 15 minutes. During this experiment, a triplet pattern consistent with a PdL_2HI species was observed at -14.23 ppm. The activation energy for the two possible regioselective alkyne insertions of **I** can be correlated to the experimental ratio of **2e**:(**3e**+**4e**) (Figure 3).

The two corresponding transition states model a rotation of the H−Pd−I fragment to place the H–Pd bond parallel to the C≡C bond.[42] The computed activation energy for the insertion leading to intermediate **II** is slightly lower than that required to form intermediate **V** ($\Delta E^{\ddagger}$ = 2.4 kcal mol^{-1} vs. 3.1 kcal mol^{-1}). Furthermore, the formation of **II** is 4.9 kcal mol^{-1} more favorable than the formation of **V**. These results suggest that insertion leading to β-vinyl–Pd(II) species **II** in Path A is kinetically and thermodynamically favored over the insertion leading to α-vinyl–Pd(II) species **V** in Path B. This result is in agreement with the 1.4:1 ratio measured experimentally for the reaction of **1e** in favor of the formation of **2e** (path A).



Scheme 4. Proposed catalytic cycle for the formation of the hydroiodination product **2e** and the cycloisomerization byproduct **3e** and **4e**. L = P^tBu_3.

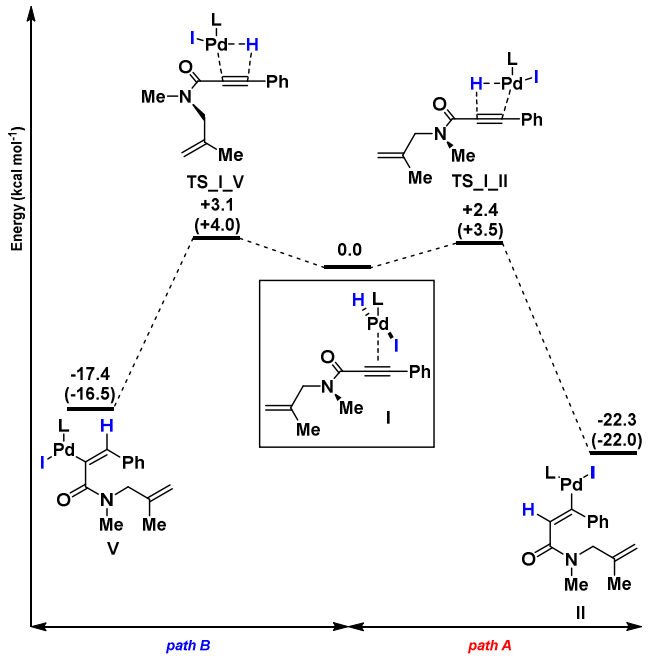


Figure 3. Computed potential energy profile for the insertion of the alkyne moiety into the Pd–H bond (L = P^{t}Bu$_3$). Energies (kcal mol^{-1}) refer to zero-point corrected energies quoted relative to **I** with L = P^{t}Bu$_3$ at the IEFPCM (Toluene) M06L/6-311G(d,p)/SDDALL//BP86/6-31G(d,p)/LANL2DZ level of theory. Gibbs free energies are presented in parentheses.

The isomerization of the vinyl–Pd moiety in intermediate **II** from the *E* to the *Z* configuration is a prerequisite for the subsequent carbopalladation step. There have been several reports describing the isomerization of vinyl–Pd(II),[7h,7i,10,43] however, it is rare that this process occurs as a productive catalytic step. In 2015, Werz and co-workers described an interesting formal *anti*-arylpalladation of alkynes as a key step in a Pd(0)-catalyzed domino cyclization.[44] More recently, Lam and co-workers described a formal *anti* alkyne arylnickelation that was proposed to occur by way of an isomerizing vinyl–Ni(II) intermediates.[45] To the best of our knowledge, our process represents the first *anti*-hydropalladation of alkynes as a productive catalytic step. Isomerization of the *E* conformer **II** to the slightly more stable *Z* conformer **III** requires $\Delta E^{\ddagger}$ = 16.9 kcal mol^{-1} and the corresponding transition state **TS_II_III** models the rotation around the C=C bond placing the C_β–Pd bond almost perpendicular to the carbonyl–C_α bond (Figure 4a). The C_α–C_β distance in the transition state (1.39 Å) is slightly longer than the same distance in the two intermediates **II** and **III** (1.35 Å and 1.36 Å, respectively). Similarly, the C_β–Pd distance in **TS_II_III** (1.91 Å) is slightly shorter than in **II** and **III** (2.01 Å and 1.98 Å, respectively). In order to experimentally support this process, compounds (*E*)-**9** and (*Z*)-**9** were synthesized and subjected to the standard reaction conditions in the absence of the HI surrogate (Figure 4b). Both isomers provided the corresponding product **2la** in 82% and 8% NMR yield, respectively, which supports the feasibility of this seemingly compulsory isomerization step. The marked difference in reactivity of the two isomers is attributed to the bulky palladium catalyst having different oxidative addition aptitudes for the two vinyl iodide isomers. Furthermore, the lack of byproducts **3la** or **4la** formation suggests that the reaction is unidirectional which is further corroborated by the high energy required to produce **I** from intermediate **II** by β-hydride elimination ($\Delta E^{\ddagger}$ = 24.7 kcal mol^{-1}).

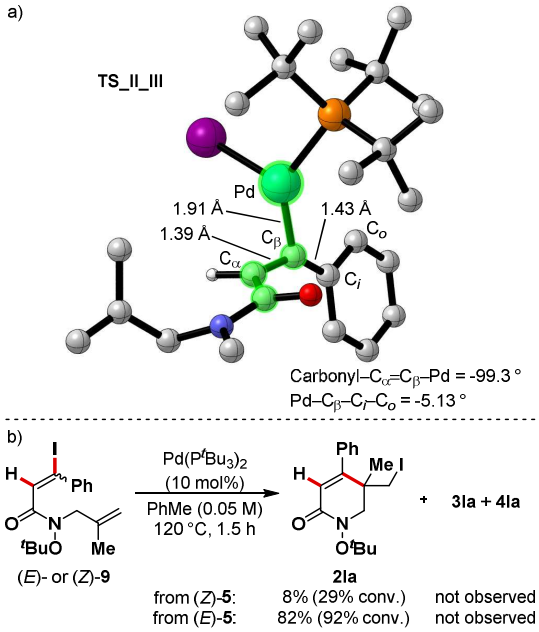


Figure 4. a) Optimized structure of the transition state for the *E*-to-*Z* isomerization process and selected geometrical parameters (H atoms are omitted for clarity with exception of the vinyl proton). b) Control experiments to support the *E*-to-*Z* vinyl-Pd(II) isomerization step.

The computed potential energy surface for Path A is presented in Figure 5.[41] Coordination of the tethered alkene to the palladium atom provides the higher energy intermediate **III'** (ΔE = +16.9 kcal mol). Subsequent intramolecular alkene insertion generates neopentyl–Pd intermediate **IV**. This step requires $\Delta E^{\ddagger}$ = 7.4 kcal mol^{-1} and the corresponding transition state **TS_III'_IV** models a four-centered concerted mechanism. The carbopalladation process from **III** to **IV** requires an overall activation energy of $\Delta E^{\ddagger}$ = 24.3 kcal mol^{-1}, rendering this process the rate determining step. Carbon–iodine bond-forming reductive elimination provides intermediate **2e_Pd** where the Pd atom is coordinated to the product via the halogen atom. The process requires $\Delta E^{\ddagger}$ = 18.1 kcal mol^{-1} and proceeds via **TS_IV_3e**. Final dissociative ligand replacement furnishes the desired product **2e** and regenerates the PdL$_2$ catalyst.[45]

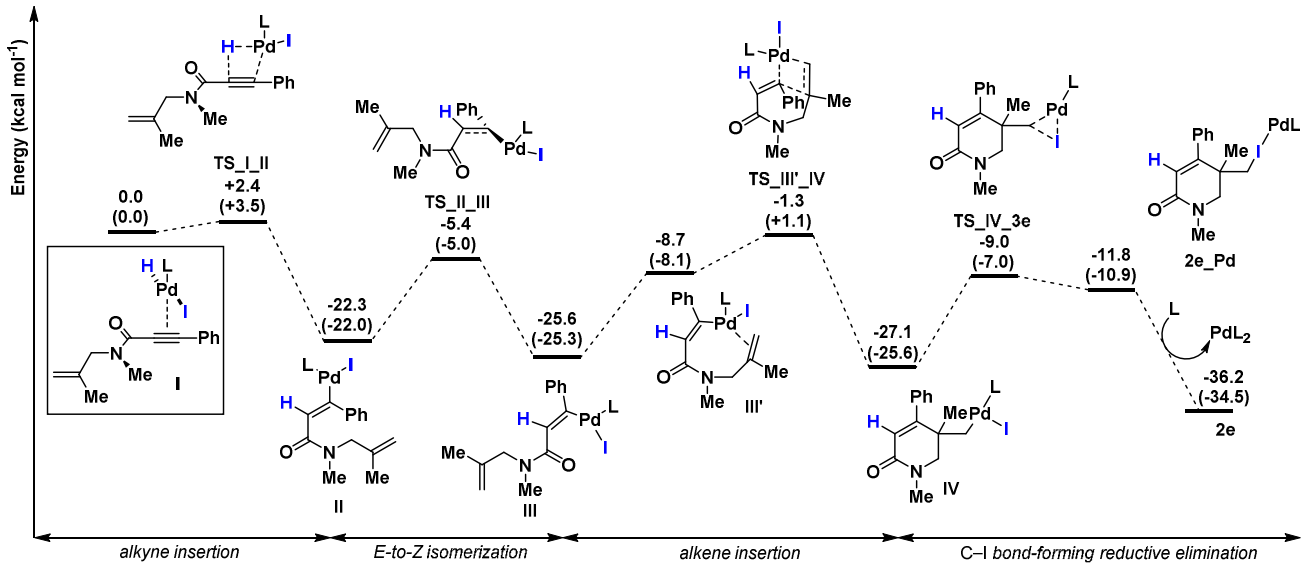


Figure 5. Computed potential energy profile for the Path A (L = P^{t}Bu$_3$). Energies (kcal mol^{-1}) refer to zero-point corrected energies quoted relative to **I** with L = P^{t}Bu$_3$ at the IEFPCM (Toluene) M06L/6-311G(d,p)/SDDALL//BP86/6-31G(d,p)/LANL2DZ level of theory. Gibbs free energies are presented in parentheses.

We next studied the mechanism for the formation of byproducts **3e** and **4e** via Path B (Figure 6).[41] After formation of intermediate **V**, coordination of the tethered alkene and subsequent carbopalladation (overall $\Delta E^{\ddagger}$ = 12.4 kcal mol^{-1}) produces five-membered intermediate **VI**. The structure of **VI** allows a successive intramolecular carbopalladation to produce the cyclopropane-containing intermediate **VII** via a four-centered concerted mechanism. This process only requires $\Delta E^{\ddagger}$ = 3.4 kcal mol^{-1} and is modeled by **TS_VI_VII**. Facile C–C bond rotation in **VII** provides intermediate **VII'** (ΔE = +5.8 kcal mol^{-1}) via a stepwise mechanism.[41] The spatial arrangement in **VII'** allows β-carbon elimination to take place. The overall process requires $\Delta E^{\ddagger}$ = 34.4 kcal mol^{-1} and generates the six-membered intermediate **VIII** (not shown). Stabilization of this intermediate can occur by two separate agostic interactions with the hydrogen atoms attached to the two β–methylene carbons providing structures **VIII'** and **VIII''**. β–hydride elimination can occur from both isomers to generate the corresponding complexes **3e'_Pd** and **3e_Pd** (ΔE = –3.7 kcal mol^{-1}). Of note, diene **3e** was the only isomer detected experimentally and the configuration of the *exo*-double bond was confirmed by NMR spectroscopic analysis after isolation. Final isomerization provides byproduct **4e**.

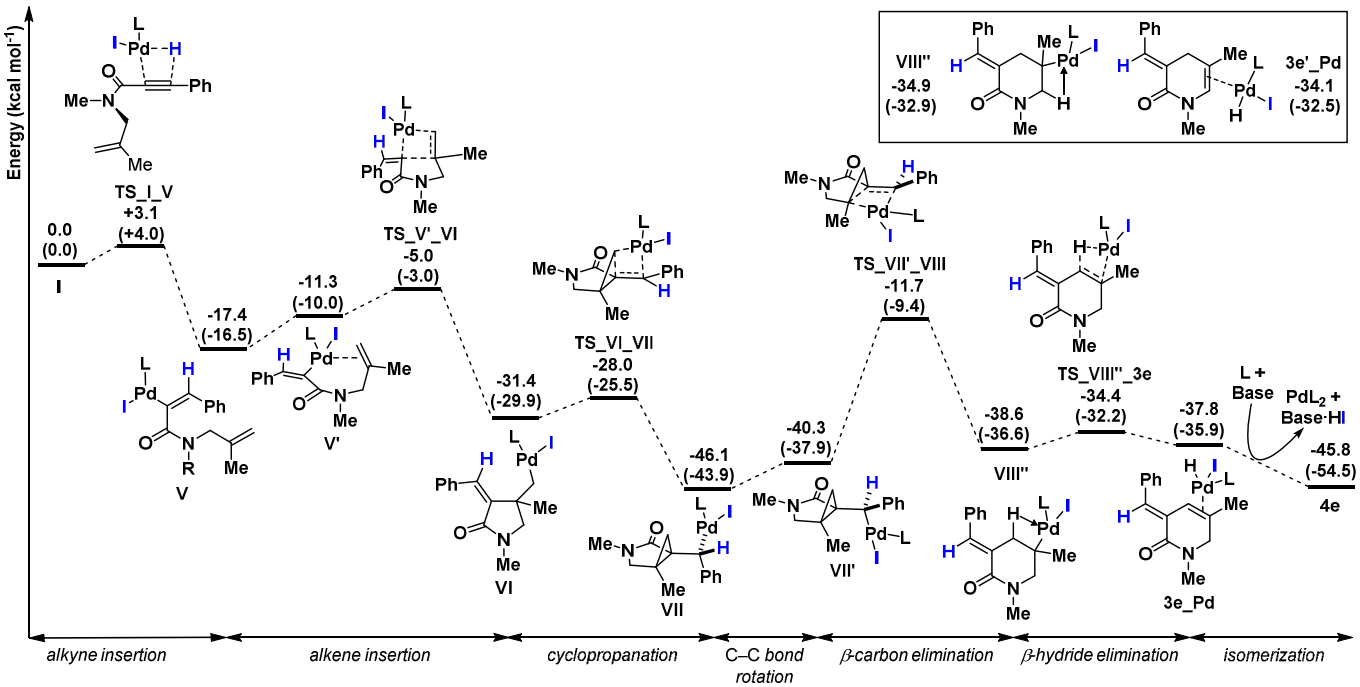


Figure 6. Computed potential energy profile for the Path B (L = P^{t}Bu$_3$). Energies (kcal mol^{-1}) refer to zero-point corrected energies quoted relative to **I** with L = P^{t}Bu$_3$ at the IEFPCM (Toluene) M06L/6-311G(d,p)/SDDALL//BP86/6-31G(d,p)/LANL2DZ level of theory. Gibbs free energies are presented in parentheses.

In analogy to **IV**, we computed the potential energy profile for the C–I bond-forming reductive elimination from the neopentyl–Pd intermediate **VI** (Figure 7). This process requires $\Delta E^{\ddagger}$ = 20.1 kcal mol^{-1} and the corresponding transition state **TS_VI_X** models a three-centered mechanism and an incipient interaction between the Pd atom and the *exo*-double bond. Dissociation of the metal atom from the resulting intermediate **X_Pd** releases the final product **X**. Comparison of the activation energies required for the **VI→VII** ($\Delta E^{\ddagger}$ = 3.4 kcal mol^{-1}) and **VI→X_Pd** ($\Delta E^{\ddagger}$ = 20.1 kcal mol^{-1}) processes and the stability of the corresponding products **VII** (E = -46.1 kcal mol^{-1}) and **X_Pd** (E = -26.8 kcal mol^{-1}) indicated that C–I bond-forming reductive elimination is strongly disfavored with respect to the intramolecular cyclopropanation to form **VII**. This conclusion supports the experimental evidence where product **X** was never detected in the reaction mixture.

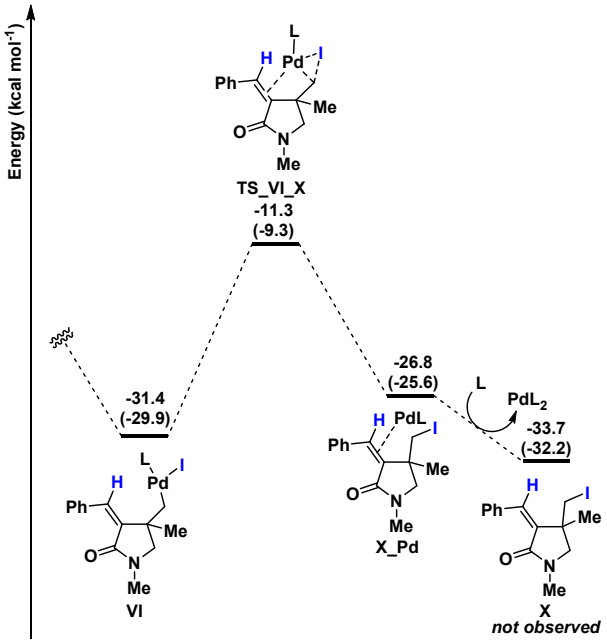
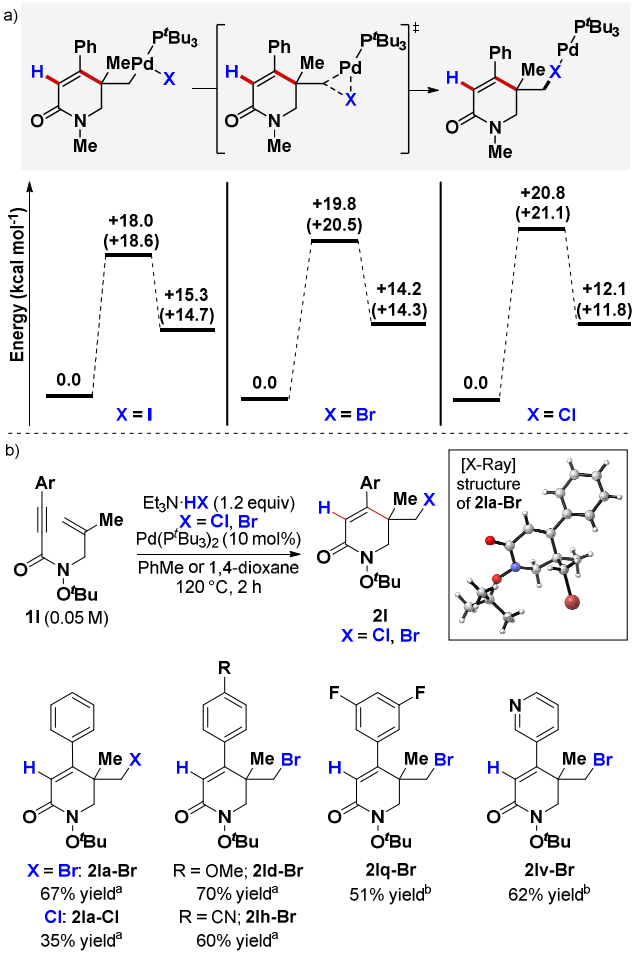


Figure 7. Computed potential energy profile for the C–I bond-forming reductive elimination from intermediate **VI** (L = P^{t}Bu$_3$). Energies (kcal mol^{-1}) refer to zero-point corrected energies quoted relative to **I** with L = P^{t}Bu$_3$ at the IEFPCM (Toluene) M06L/6-311G(d,p)/SDDALL//BP86/6-31G(d,p)/LANL2DZ level of theory. Gibbs free energies are presented in parentheses.

We next computed the activation energies for the carbon−halogen bond-forming reductive elimination step for bromine and chlorine (Scheme 5a). The activation energies required for the formation of the analogous C−Br and the C−Cl bonds are $\Delta E^{\ddagger}$ = 19.8 and 20.8 kcal mol^{-1}, respectively. These values are higher, yet comparable to the activation energy for the C–I case ($\Delta E^{\ddagger}$ = 18.0 kcal mol^{-1}). This observation prompted us to evaluate the reactivity of the corresponding commercially available Et$_3$N·HBr and HCl salts in the reaction. The reaction was successful with both reagents and provided the corresponding products **2la-Br** and **2la-Cl** in 67% and 35% yield, respectively (Scheme 5b). This reactivity trend is in good agreement with the computed activation energies. This represents an exceedingly rare example of a catalytic reaction involving C(sp^3)−X bond-forming (X = Br or Cl) reductive elimination from an alkyl–Pd(II)–X species.[45] The generality of the transformation using Et$_3$N·HBr was evaluated using a number of substrates. The reaction of those containing electron-rich and electron-poor aromatic groups provided the corresponding bromine-containing products **2ld-Br**, **2lh-Br** and **2lq-Br** in moderate to good yields. Pyridine-containing **2lv-Br** could also be obtained in 62% yield.



Scheme 5. Theoretic and experimental studies involving the analogous catalytic hydrobromination and hydrochlorination processes. a) Theoretical comparison between the carbon–iodine, carbon–bromine and carbon–chlorine bond-forming reductive elimination from Pd(II). Energies (kcal mol^{-1}) refer to zero-point corrected energies at the IEFPCM (Toluene) M06L/6-311G(d,p)/SDDALL//BP86/6-31G(d,p)/LANL2DZ level of theory. Gibbs free energies are presented in parentheses. b) Substrate scope for the Pd-catalyzed hydrobromination and hydrochlorination using Et$_3$N·HBr and Et$_3$N·HCl, respectively. Reactions were run on a 0.2 mmol scale. Values represent isolated yields after column chromatography. [a] Reaction was run using PhMe as solvent. [b] Reaction was run using 1,4-dioxane as solvent.

CONCLUSIONS

We have discovered a conceptually and mechanistically novel Pd-catalyzed hydrohalogenation of enynes that affords access to synthetically useful halogenated pyridinones. This process relies on highly practical and crystalline ammonium halides (Et$_3$N·HX) which operate as surrogates to conventional toxic and corrosive hydrogen halide sources. The use of a strategically placed –O^{t}Bu nitrogen protecting group was instrumental in obtaining high selectivity for the desired products containing both a C(sp^3)–halogen motif and an all-carbon quaternary center at the γ-position to the carbonyl. These simple catalytic conditions also enable unprecedented C(sp^3)–Br and –Cl bond-forming reductive

elimination from a Pd(II) species. Therefore, by simply interchanging $Et_3N{\cdot}HX$ sources, iodinated, brominated and chlorinated products can be obtained using non-halogenated substrates. A combination of experiment and theory has provided insight into the unprecedented reaction mechanism that involves a formal *anti* alkyne hydropalladation step resulting from a crucial *E*-to-*Z* vinyl–Pd(II) isomerization. The extension of this concept to the first example of transfer hydroiodination was also realized, whereby a domino Pd-catalyzed release and react strategy enables the use of 1-iodobutane as a non-ionic HI surrogate. We believe that this report will prompt future applications of this class of reagents in other metal-catalyzed processes.

ASSOCIATED CONTENT

The information is available free of charge via the internet at http://pubs.acs.org.

Experimental details of synthetic procedures, X-ray data, and computational details (PDF)
Crystallographic data for **2d**, **4d**, **2la** and **10** (CIF)

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NOTES

The authors declare no competing financial interests.

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