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*J. Am. Chem. Soc.*, **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c03589 • Publication Date (Web): 15 May 2020

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# Development and Mechanistic Interrogation of Interrupted Chain-Walking in the Enantioselective Relay Heck Reaction

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**ABSTRACT:** The formation of alkyl–palladium complexes via the nucleopalladation of alkenes is the entry point for a wide range of diverse reactions. One possibility is that the intermediate alkyl–Pd complexes can undergo a “chain-walking” event, to allow for remote functionalization through various termination processes. However, there are few methods to selectively interrupt the chain-walking process at a prescribed location. Herein we demonstrate that a variety of homoallylic protected amines undergo an interrupted enantioselective relay Heck reaction to give enantioenriched allylic amine products. The selectivity of this process can be diverted to exclusively yield the ene–amide products by virtue of changing the nature of the amine protecting group. To rationalize this observation, we combine experiment and computation to investigate the mechanism of the chain-walking process and termination events. Isotopic labeling experiments and the computed reaction pathways suggest that the system is likely under thermodynamic control, with the selectivity being driven by the relative stability of intermediates encountered during chain walking. These results illustrate that the chain-walking of alkyl–palladium complexes can be controlled through the alteration of thermodynamic processes and provides a roadmap for exploiting these processes in future reaction development.

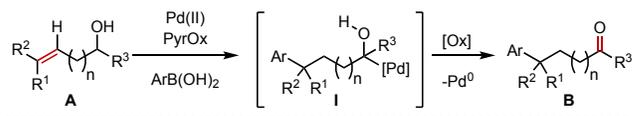
## Introduction:

Alkene functionalization reactions using  $\pi$ -Lewis acidic metals, such as Pd(II), are often initiated by the addition of a nucleophile to the ligated alkene to form a metal-alkyl intermediate.<sup>1</sup> This intermediate can either undergo  $\beta$ -hydride elimination to reform an alkene (e.g., Heck or Wacker type reactions), undergo a subsequent organometallic reaction to ultimately be classified as an alkene difunctionalization reaction,<sup>1-4</sup> or the metal can migrate away from the newly formed bond through iterative  $\beta$ -hydride elimination/migratory insertion processes<sup>5-10</sup> (often referred to as “chain-walking”).<sup>11, 12</sup> Chain-walking strategies allow for either the regeneration of the unsaturation remotely, or incorporation of an external reagent by a terminating organometallic transformation at a site distant from the initial bond forming event.<sup>13-15</sup>

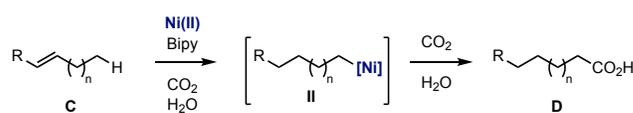
The majority of these termination processes are directed by the innate nature of the substrate.<sup>16-21</sup> As an example, our group,<sup>22-36</sup> as well as others,<sup>37-45</sup> have used redox acceptors to promote the terminating step. In particular, alkenyl alcohols **A** have been widely used wherein the alcohol is ultimately converted into the corresponding carbonyl product **B** through a formal oxidation event (**I** to **B**, Figure 1a). Contrastingly, Martin,<sup>46-48</sup> Marek,<sup>49, 50</sup> Mazet,<sup>51, 52</sup> Zhu,<sup>53-55</sup> and others,<sup>56-63</sup> have used an organometallic step, which often occurs at the termini of the alkyl chain, to trap the chain walking process. As a specific example, the remote functionalization of alkene **C** is initiated by migratory insertion into a Ni–H followed by chain-walking and

ultimate trapping of **II** with CO<sub>2</sub> to yield carboxylic acid **D** (Figure 1b).<sup>47</sup> Clearly, a significant expansion in the scope of remote functionalization would be the ability to intercept the chain walking event at a prescribed position along the alkyl chain.

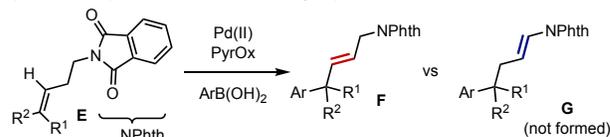
a) remote alcohols terminate the chain-walking process via oxidation



b) Termination of chain-walking by external reagent



c) homoallylic phthalimides give rise to allylic product



**Figure 1.** a) redox acceptors such as alcohols terminate the chain-walking process by oxidation, b) termination of the chain-walking process by external reagent, c) relay Heck reaction to give allylic products using homoallylic phthalimide substrates

In this context, we have discovered that a class of alkenyl substrates, namely homoallylic trisubstituted protected amines (for example, phthalimide **E**), undergo an enantioselective Heck reaction to yield product **F** (Figure

1c). Instead of relaying the unsaturation to form ene amide products of type **G**, akin to the corresponding homoallylic alcohols that form carbonyls, this chain-walking process is interrupted to yield allylic phthalimides in a highly selective manner. This surprising result leads to a range of synthetic and mechanistic questions including: 1) what is the synthetic scope of the process? 2) how does the structure of the protected amine impact product selectivity (ene amide vs interrupted chain-walking), and 3) what is the mechanistic origin for the interrupted Heck process; is it a consequence of thermodynamics or kinetics? Herein, we investigate these questions in detail revealing that the reaction has broad scope in terms of the aryl boronic acid, functional group tolerance, and amine protecting group. Additionally, through a combination of experimental and computational techniques, we have explored the basis for the interruption of the chain-walking process.

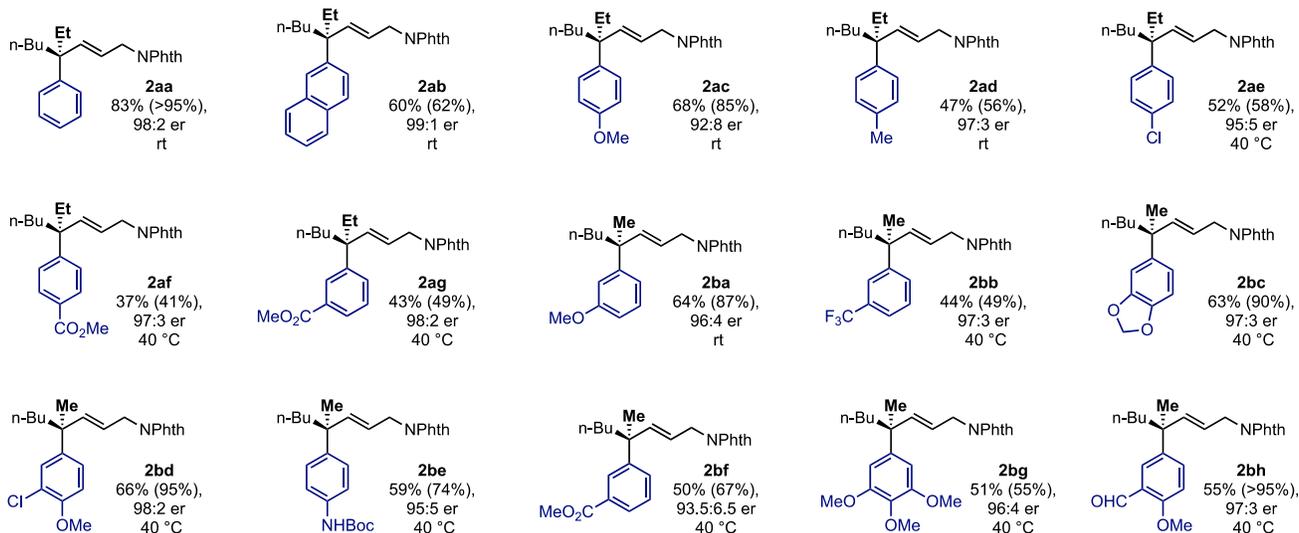
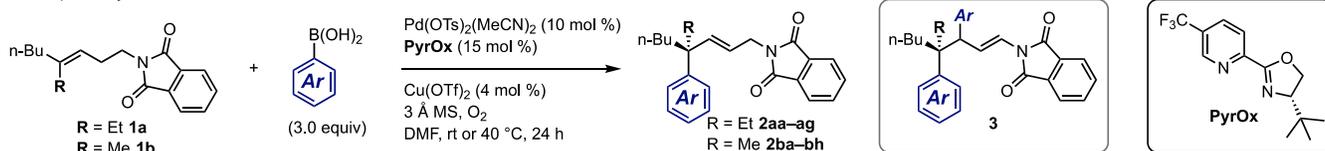
### Results and Discussion:

The optimal conditions for the interrupted enantioselective Heck arylation of trisubstituted homoallylic allylic amine derivatives were found to be similar to those reported for the arylation of homoallylic trisubstituted alcohols<sup>24</sup> with minor modifications (see supporting information (SI) for details). The product of this reaction contains a quaternary carbon center with an appended allylic protected amine. Using these optimized conditions, the scope of the arylboronic acid was explored using homoallylic phthalimides **1a** and **1b** (Table 1a). The reaction tolerates the use of unfunctionalized aromatics

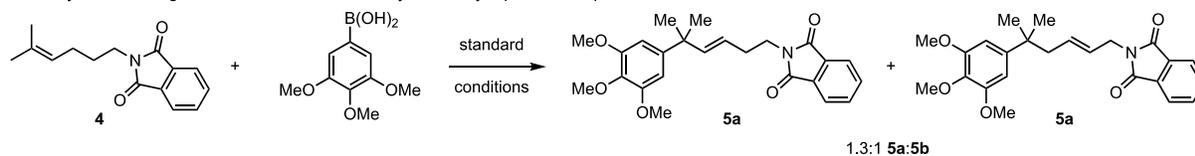
(**2aa–2ab**), electron donating and withdrawing substituents at the 3- and 4- positions (**2ac–g**, **2ba–b**, **2be–f**), and multiply substituted aryl boronic acids (**2bc–d**, **2bg–h**). These results reveal several general trends. First, it was found that the conversion of phthalimide **1b** was higher than **1a** (compare **1ag** and **1bf**) presumably due to the smaller methyl group. Second, the conversion (and subsequently the yield) of the transformation is highly dependent on the electronic nature of the aryl boronic acid used. For example, electron-deficient boronic acids require the reaction to be performed at 40 °C in order to achieve desirable levels of conversion. This is presumably due to the need to overcome the slower migratory insertion as a function of using more electron deficient aryl boronic acids. Fortunately, performing the reaction at elevated temperatures does not cause an observable decrease in enantioselectivity. Alternatively, electron-rich aryl boronic acids were found to add at the newly formed disubstituted alkene to give the 2:1 adduct **3** in low yield (see SI). The absolute configuration of products **2a** and **2b** were established by comparison of the hydrogenated analogue of **2bg** prepared by this route, and via the redox-relay Heck reaction of the alcohol analogue of **1b** (see SI). It should be noted that when the standard conditions were applied to bishomoallylic substrate **4** an inseparable mixture of allylic and homoallylic phthalimides (**5a** and **5b**, respectively) were formed in a 1.3:1 mixture (Table 1b). Lastly, 1,2-disubstituted alkenes were found to give mixtures arising from poor regioselectivity for arylation of the alkene (see SI).

**Table 1. Scope of aryl boronic acid with homoallylic phthalimides 1a and 1b.**

## a. Scope of arylboronic acid



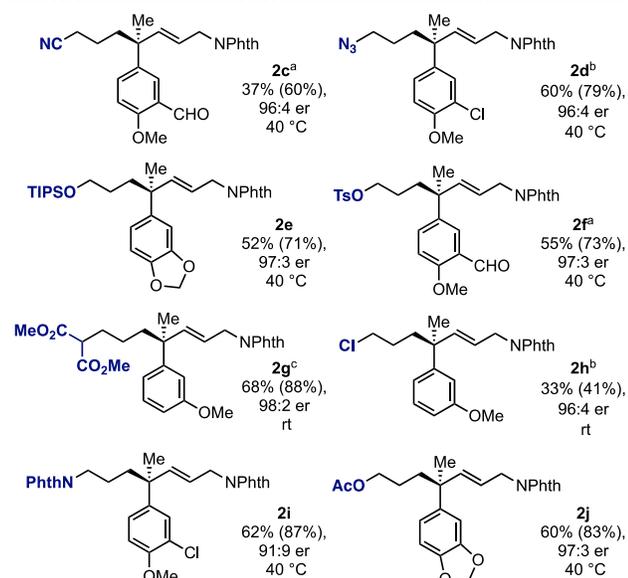
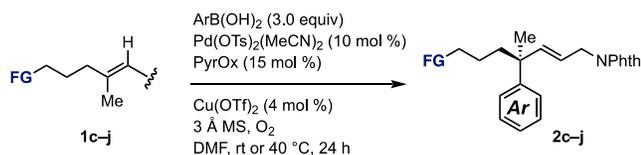
## b. Bishomoallylic substrate gives rise to mixture of homoallylic and allylic phthalimide products



a. For each entry the following notation is used: yield % (conversion %), enantiomeric ratio, reaction temperature. Aryl boronic acid was added batch-wise in either two (room temperature reactions) or three (40 °C reactions) portions. b. ratio of products determined by NMR.

**Scope of functional group on the alkene.** We next turned our attention to probing the effect of functional groups attached to the alkene on the reaction outcome (Table 2). It was found that azides (**2c**), nitriles (**2d**), halides (**2h**), tosylates (**2f**), malonates (**2g**), protected alcohols (**2e**, **2j**), and protected amines (**2i**) are all compatible with the reaction. In general, the yields are modestly diminished when compared to unfunctionalized substrates, but the enantioselectivity remains high. The ability to use electrophiles such as **2e** and **2h** allows for the introduction of a wide scope of additional functionality. Additionally, the use of malonate **2g** highlights the compatibility of this reaction with competing intramolecular nucleophiles. It should be noted that a coeluting isomeric product arising from addition of the aryl group to the internal carbon of the alkene was formed in low yields (up to 15%, see table 2).

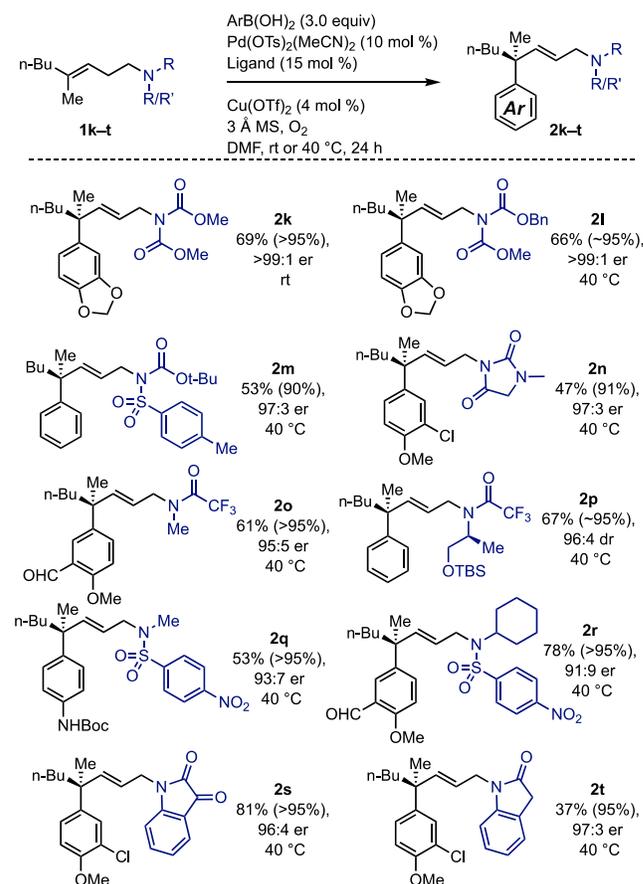
**Table 2. Scope of non-participating functional groups.**



25 For each entry the following notation is used: yield %  
26 (conversion %), enantiomeric ratio, reaction temperature.  
27 Aryl boronic acid was added batch-wise in either two (room  
28 temperature reactions) or three (40 °C reactions) portions. <sup>a</sup>  
29 isolated in 90% purity, <sup>b</sup> isolated in 95% purity, <sup>c</sup> isolated in  
30 85% purity.

31 **Scope of “acceptor” groups.** Having established the  
32 scope of the reaction in terms of aryl boronic acids (Table  
33 1) and attached functional groups on the alkene (Table 2),  
34 we next explored what other amine derivatives at the  
35 termini were capable of selectively forming the allylic  
36 product (Table 3). We focused our attention on groups that  
37 contained useful *N*-protecting groups, or desirable  
38 heterocycles. For example, bisprotected amines (**2k-m**),  
39 monoprotected amines (**2o-2r**), hydantoins (**2n**), isatin  
40 (**2s**), and indolinone (**2t**) are compatible. This greatly  
41 increases the scope of this transformation to include  
42 protected primary amines with or without orthogonal  
43 protecting groups, as well as protected secondary amines.  
44 Alkylated amines with trifluoroacetamide (**2o**, **2p**) and  
45 sulfonamide protecting groups (**2q**, **2r**) are compatible,  
46 which can be readily removed to give rise to allylic  
47 secondary amines. Additionally, the *N*-alkyl substituent  
48 tolerates both primary (**2o**, **2q**) and tertiary (**2p**, **2r**)  
49 substituents. Notably, the remote stereocenter in **2p** does  
50 not influence the enantioselectivity of the transformation.  
51 Finally, the enantioselectivity of these transformations  
52 remains high regardless of the nature of the group at the  
53 amine.

Table 3. Scope of compatible functional groups at the termini.

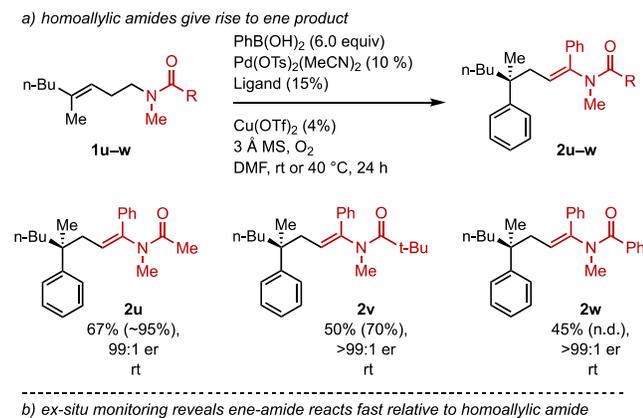


For each entry the following notation is used: yield %  
(conversion %), enantiomeric ratio, reaction temperature.  
Aryl boronic acid was added batch-wise in either two (room  
temperature reactions) or three (40 °C reactions) portions.

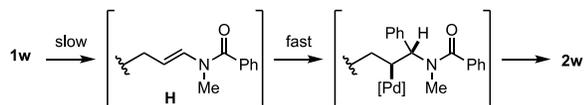
**Formation of ene products.** In each example reported in  
tables 1–3, there was no detectable amount of the isomeric  
ene products. However, when *N*-methyl acetamide **1u** was  
subjected to the standard reaction conditions, the bisarylated  
ene-amide **2u** was unexpectedly formed in moderate yield  
(44%), with none of the isomeric allyl product. Doubling  
the amount of boronic acid to six equivalents in the reaction  
resulted in a significantly improved yield (67%, Table 4a).  
It was reasoned that the cause for this switch in selectivity  
for the formation of the ene amide type product compared to  
the structurally similar trifluoroacetamide could either be  
due to the significantly smaller size of the methyl group  
relative to the trifluoromethyl group, or due to the more  
electron rich carbonyl. To test these hypotheses, the pivaloyl  
amide **1v** and benzamide **1w** were subjected to the reaction  
conditions. In both instances, the ene-amides **1v** and **2v**  
were formed exclusively in comparable yields and high  
enantioselectivity. These results suggest that the difference  
in the electron density of the amide carbonyl is responsible

for this observed change in selectivity. To further probe the origin of the addition of two aryl groups, the formation of **2w** was investigated at early time points using ex-situ monitoring (Table 4b). If the initially formed ene-amide **H** reacts at a comparable rate with **1w**, then at early time points only a small amount of **2w** should be present. However, at early conversions (<10%) only a trace amount of a 1:1 adduct presumed to be **H** was evident, with the primary product being **2w**. This result suggests that the ene-amide **H** reacts significantly faster than **1w**.

**Table 4. Scope of amide substrates**



b) ex-situ monitoring reveals ene-amide reacts fast relative to homoallylic amide



For each entry the following notation is used: yield % (conversion %), enantiomeric ratio, reaction temperature. Aryl boronic acid was added batch-wise in two portions.

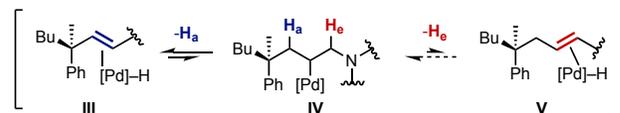
**Mechanistic investigations.** Above it is demonstrated that a wide variety of alkenyl amine derivatives selectively undergo the redox relay Heck reaction to form allylic products (Tables 1–3), while alkyl and aryl amides selectively form ene products (Table 4). This observed disparity led us to explore the mechanism by which the terminal group imparts selectivity in the chain walking process. Importantly, a detailed mechanistic understanding could guide the future development of site-selective termination of chain-walking processes. Therefore, we employed a combination of experimental and computational approaches to interrogate these observations.

We reasoned that the selectivity of these processes could be a result of either the thermodynamics or kinetics of the chain-walking process (Figure 2a). If the system is under thermodynamic control, then the alkene ligated Pd–H species **III**, alkyl–Pd complex **IV**, and alkene ligated Pd–H species **V** could establish an equilibrium (Figure 2a). If this were the case, then the selective formation of the allylic products would be a result of the relative stability of **III** compared to **V**. Alternatively, the selectivity could be driven by the kinetics of the migratory insertion and  $\beta$ -hydride elimination processes. For example, if the barrier for migratory insertion of the Pd–H to form **IV**, or the  $\beta$ -hydride elimination of Pd–H<sub>e</sub> to form **V** were prohibitively

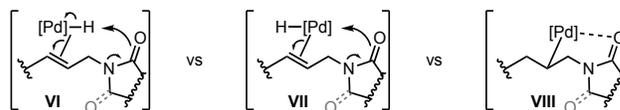
high, then the selective formation of the allylic product would be under kinetic control. Differentiating between these two scenarios could allow for insight into how to design future systems.

Alternatively, the selective formation of the allyl product could arise from direct involvement of the carbonyl (Figure 3b). For example, the carbonyl could deprotonate the alkene bound Pd–H intermediate **VI**, displace the alkene through ligand exchange (**VII**), or stabilize the intermediate Pd–alkyl species (**VIII**) (Figure 2b). In each case, the selective formation of the allylic product could arise from the ability of each of these processes to occur through a proposed six-membered palladacycle transition state (**VI** and **VII**), or intermediate (**VIII**).

a) governed by thermodynamics or kinetics?



b) is the carbonyl directly involved in the product determining step?



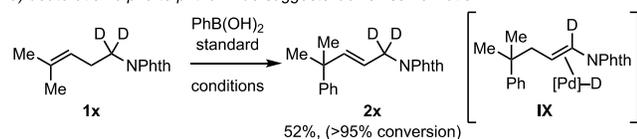
**Figure 2.** Mechanistic hypotheses for the interrupted chain-walking: a) kinetic and/or thermodynamic driven, b) direct involvement of the carbonyl

**Deuterium labeling experiments.** On the basis of previous mechanistic investigations from our group using deuterium labeling studies to probe the chain-walking process,<sup>64</sup> we investigated the outcome of the reaction when either of the two methylene subunits of the homoallylic chain were deuterated (Figure 3). We began with dideuterated substrate **1x**, which would allow us to probe whether the reaction proceeds through the intermediacy of Pd–D intermediate **IX** (Figure 3a). Subjecting **1x** to the standard reaction conditions resulted in the formation of **2x** with no observable deuterium scrambling, as well as a small amount of the double arylation product (see SI). This suggests that if Pd–D alkene intermediate **IX** is formed, that it exists in equilibrium amounts and no dissociation of the Pd–D occurs from **IX**.

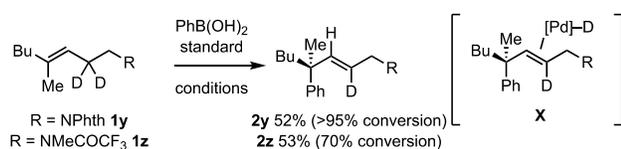
To confirm the dehydrogenation process occurs from the allylic carbon, substrates **1y** and **1z** were subjected to the reaction conditions (Figure 3b). This resulted in the formation of monodeuterated products **2y** and **2z** with no detection of deuterium scrambling, or dideuterated products. This result suggests that the reaction is proceeding through Pd–D alkene complex **X**, and the final product is formed via dissociation of the ligated Pd–D or deprotonation of the Pd–D. The formation of **2y** and **2z** also rule out the possibility of an E<sub>2</sub>-type elimination occurring from the alkyl–Pd complex **IV** (Figure 3c). Because the migratory insertion and  $\beta$ -hydride elimination processes are stereospecific, the alkyl–Pd complex **IV-DD** would be formed from **1y** or **1z**. The exclusive formation of the monodeuterated alkene **III-HD** rules out an E<sub>2</sub>

elimination via deprotonation of the hydrogen anti to the Pd to form **III-DD**.

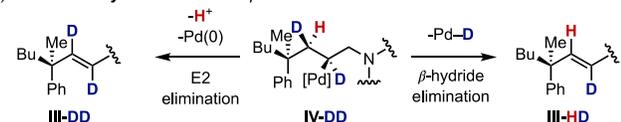
a) deuteration alpha to phthalimide suggests lack of isomerization



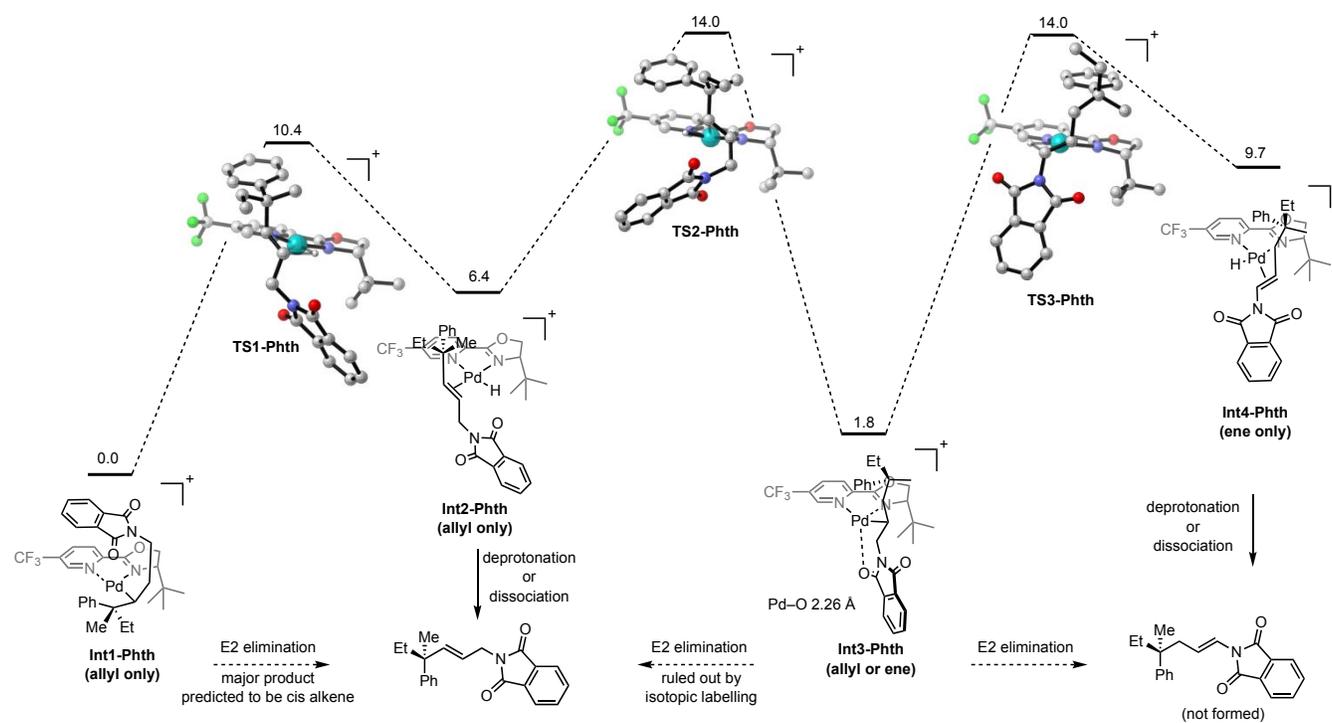
b) deuteration beta to phthalimide suggests facile removal of Pd-D



c) formation of **2y** and **2z** rule out a possible E2 elimination



### Scheme 1. Computed reaction pathway of homoallylic phthalimides



DFT studies were performed at the IEFPCM(DMF)-Mo6/6-31+G(d)//Mo6/SDD-6-31+G(d,p) level of theory. All energies listed are reported in kcal/mol. See the supporting information for details

**DFT studies.** In order to further understand the factors that differentiate between the formation of the allyl and ene products, we next turned to DFT calculations. The reaction pathway was calculated for simplified substrate analogues of phthalimide (Phth) **1a** and *N*-methyltrifluoroacetamide (TFA) **10**, both of which showed high selectivity for formation of the allyl product, and *N*-methylacetamide (Acet) **10**, which showed high selectivity for formation of the ene product. Geometry optimizations were performed with the SDD effective core potential (ECP) for Pd and Mo6 functional and 6-31+G(d) basis set for all other atoms. Solvent effects were added as energy correction using the IEFPCM (DMF) implicit solvation

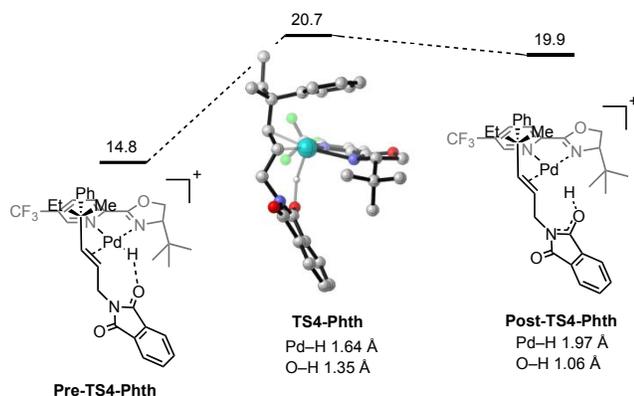
**Figure 3.** Deuterium labeling studies: a) deuteration  $\alpha$  to phthalimide, b) deuteration  $\beta$  to phthalimide, and c) formation of monodeuterated product rules out an E2 elimination.

model at the Mo6/6-31+G(d,p) level (see SI). Since the selectivity determining step would be determined after the initial migratory insertion of the aryl-Pd complex, all stationary points beyond this step were computed. The results of these calculations are detailed in Schemes 1-5.

**Potential energy surface of the relay Heck reaction with homoallylic phthalimides.** We began our investigation with the homoallylic phthalimide (Scheme 1). The phthalimide complex **Int1-Phth** was calculated to be the most stable intermediate along the pathway. This is in contrast to previous studies with an alcohol redox acceptor in which the C-Pd and alkene-Pd-H complexes were found to be more stable as the Pd migrated towards the redox

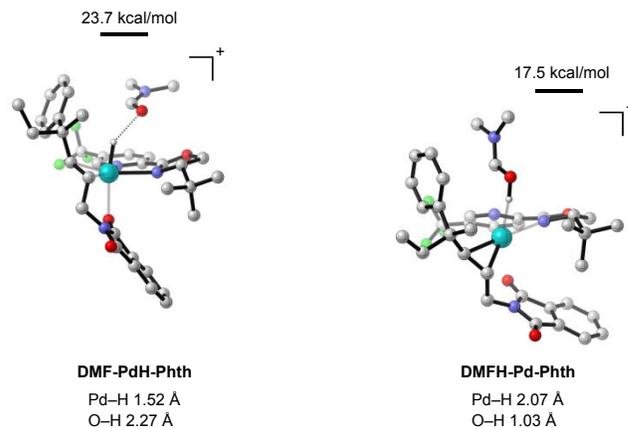
acceptor.<sup>64</sup> The calculated energy barriers of the following  $\beta$ -hydride elimination and migratory insertion steps (**TS1-3-Phth**) are relatively low, which suggests that the system is under thermodynamic control. Notably, the allyl Pd-H complex **Int2-Phth** and the ene Pd-H complex **Int4-Phth** are relatively high energy intermediates, with low barriers leading to either **Int1-Phth** or **Int3-Phth**. A possible mechanism to account for the formation of the allyl product is an E2 elimination to form Pd(o) from either **Int1-Phth** or **Int3-Phth**. The lowest energy conformer of **Int1-Phth** has a favorable anti-periplanar arrangement for an E2 elimination to occur. However, this geometry would lead to the formation of the unobserved cis alkene product. Alternatively, an E2 elimination from **Int3-Phth** can be ruled out by the isotopic labelling experiments discussed in Figure 3c. Therefore, we computationally investigated the possible mechanisms for loss of Pd-H from **Int2-Phth**.

### Scheme 2. Intramolecular deprotonation of Pd-H



We envisioned that the Pd-H complex **Int2-Phth** could undergo either deprotonation of the Pd-H to directly generate Pd<sup>0</sup>, ligand exchange of the alkene with the phthalimide carbonyl, or dissociation of the ligated Pd-H through an associative mechanism with DMF.<sup>64</sup> To determine the feasibility of intra- or intermolecular deprotonation of the Pd-H by either the phthalimide carbonyl (Scheme 2) or DMF (Scheme 3), respectively, the reaction pathways for these two processes were calculated. For the phthalimide to deprotonate the Pd-H, **Int2-Phth** must first adopt a conformation in which the carbonyl is in close contact to the hydride (**Pre-TS4-Phth**). The intramolecular deprotonation of the Pd-H from this high energy intermediate occurs with a relatively high barrier of 20.7 kcal/mol. The resulting protonated phthalimide **Post-TS4-Phth** would likely undergo rapid deprotonation by trace water or DMF to yield the corresponding neutral Pd(o) complex. To investigate whether DMF could serve as a competent base to deprotonate the Pd-H of **Int2-Phth**, the solvate **DMF-PdH-Phth** and protonated DMF adduct **DMFH-Pd-Phth** were calculated (Scheme 3). This process was found to be thermodynamically favorable, which suggests that this is a viable pathway for the formation of the allyl product (see SI for details).

### Scheme 3. Intermolecular deprotonation of Pd-H



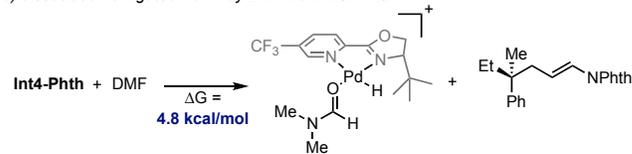
However, a reasonable alternative mechanism is direct dissociation of the ligated Pd-H by DMF. To test this hypothesis, the energetics for the displacement of **Int2-Phth** and **Int4-Phth** by DMF were calculated (Figure 4). Previous reports have shown that the transition state for these similar processes could not be located.<sup>65</sup> In line with these, the dissociation process was found to be endergonic for both **Int2-Phth** and **Int4-Phth** (Figure 4). Importantly, the process is less endergonic from **Int4-Phth**. If we assume that the transition states for these two process show the same trend, this data suggests that the selectivity is likely not driven by the relative rates of the dissociation of the ligated Pd-H from **Int2-Phth** and **Int4-Phth** by DMF.

Overall, these results suggest that the preferential formation of the allylic product is likely a result of the thermodynamics of the system. Additionally, the results presented in Schemes 2–3 suggest that if the final product determining step is deprotonation, it is occurring intermolecularly by DMF or trace water. Alternatively, the results in Figure 4 show that dissociation of the alkene from the ligated Pd-H by DMF is also an energetically viable pathway.

a) dissociation of ligated Pd-H by DMF from **Int2-Phth**



b) dissociation of ligated Pd-H by DMF from **Int4-Phth**



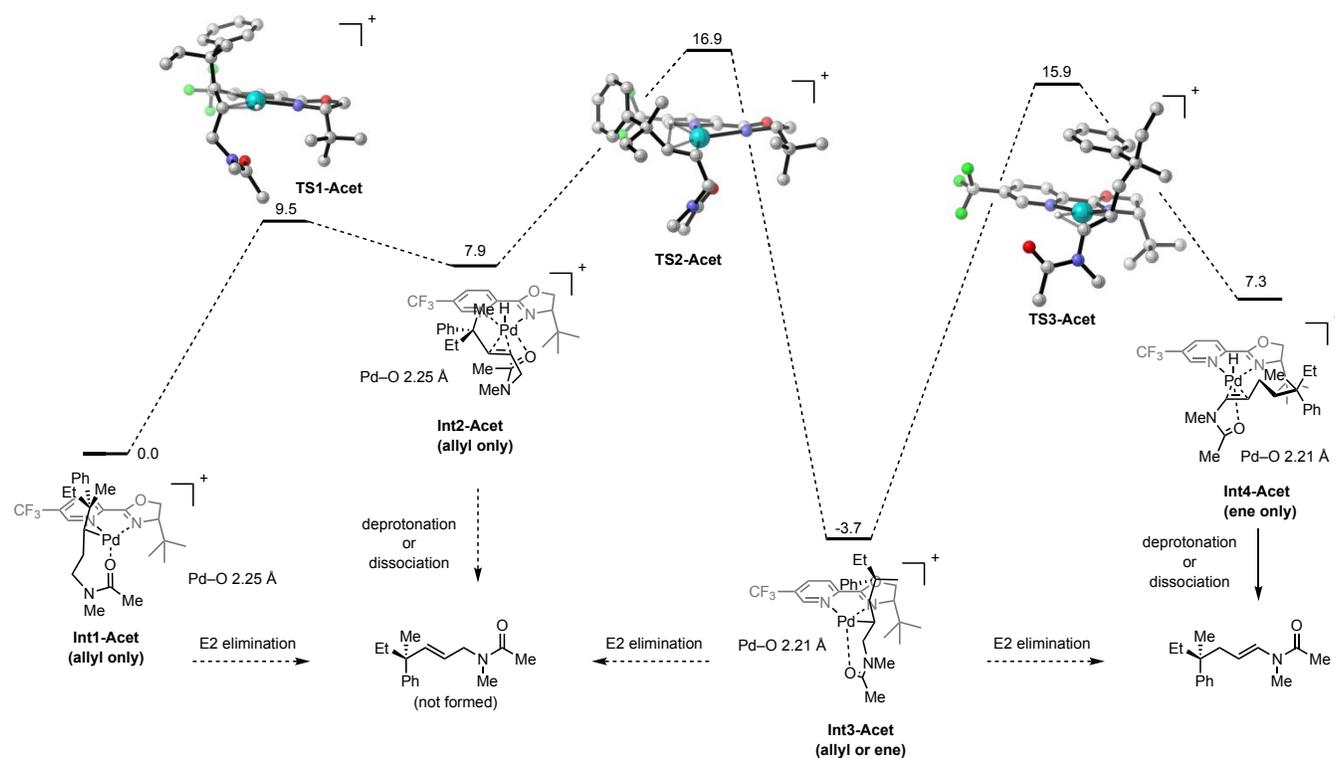
**Figure 4.** Dissociation of ligated Pd-H by DMF: a) dissociation from **Int2-Phth**, b) dissociation from **Int4-Phth**

**Potential energy surface of the relay Heck reaction with homoallylic acetamides and trifluoroacetamides.** We next carried out a similar analysis for the acetamide (Acet) acceptor group (Scheme 4). In contrast to the phthalimide, the carbonyl of the acetamide shows a significant amount of ligation to the cationic Pd center throughout the reaction pathway

consistent with the amides enhanced Lewis basicity. In particular, the degree of ligation of the carbonyl to the Pd center destabilizes **TS2-Acet**, and stabilizes **Int3-Acet** and **Int4-Acet**. This results in the formation of **Int3-Acet** being essentially irreversible. These two factors combined presumably lead to the preferential formation of the ene-product.

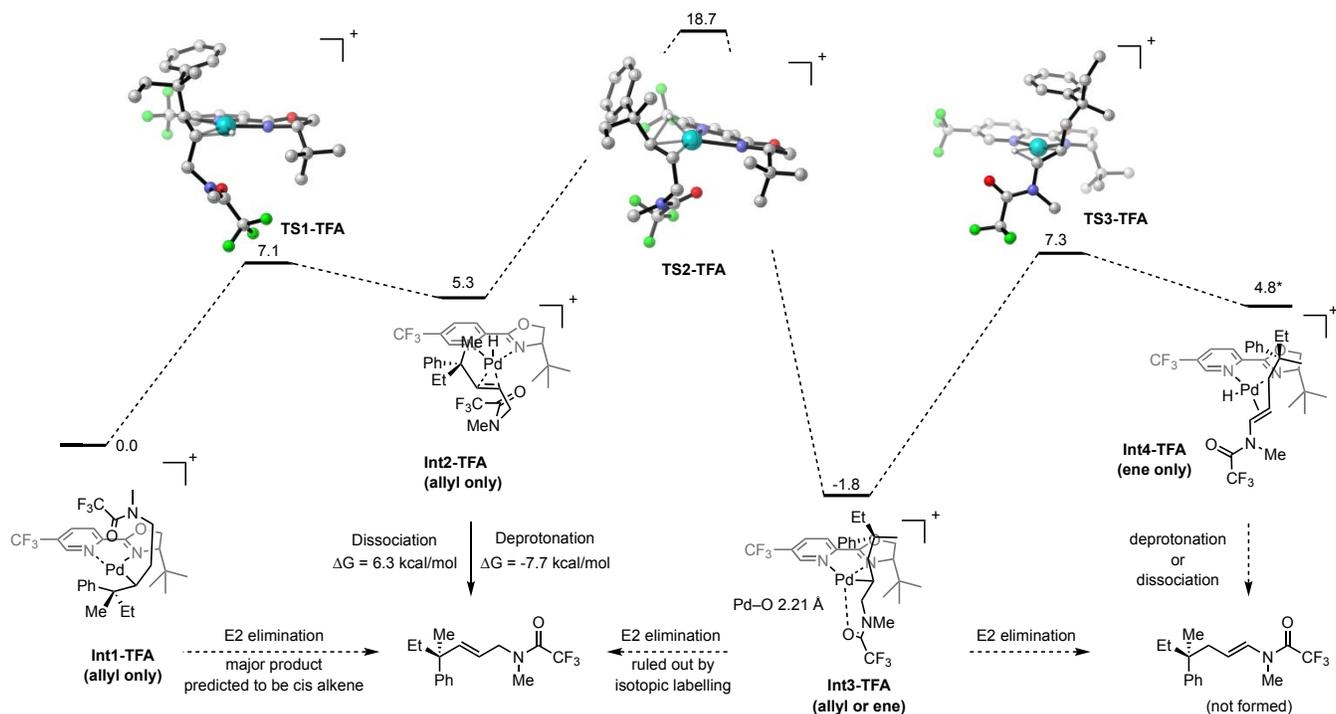
Conversely, the potential energy surface of the trifluoroacetamide (TFA, Scheme 5) is similar to that of the phthalimide (Phth). One notable difference is **Int3-TFA** is the lowest energy species along the pathway. However, the relative stabilities of **Int2-TFA** relative to reversion back to **Int1-TFA** combined with the relatively high barrier of **TS2-TFA** suggests that this system is potentially under kinetic control. This would require that the barrier for either deprotonation of **Int2-TFA** or dissociation of **Int2-TFA** by **Scheme 4. Computed reaction pathway of N-methylacetamides**

DMF be lower than conversion to **Int3-TFA**. The DMF adduct **DMF-PdH-TFA** was found to be significantly lower in energy compared to the phthalimide analogue (15 kcal/mol vs. 24 kcal/mol, Scheme 5) and the deprotonation of the Pd-H by DMF was found to be energetically favorable (see SI for details). Additionally, the dissociation by DMF was found to be more favorable in the case of **Int2-TFA** (6 kcal/mol vs. 9 kcal/mol, Scheme 5). Ultimately, these results suggest that the decomposition of **Int2-TFA** to product may preferentially occur via a dissociation or deprotonation pathway that has a lower barrier than the formation of **Int3-TFA**. Importantly, this is consistent with the experimentally observed allyl selectivity of the trifluoroacetamide substrates.



DFT studies were performed at the IEFPCM(DMF)-Mo6/6-31+G(d)//Mo6/SDD-6-31+G(d,p) level of theory. All energies listed are reported in kcal/mol. See the supporting information for details

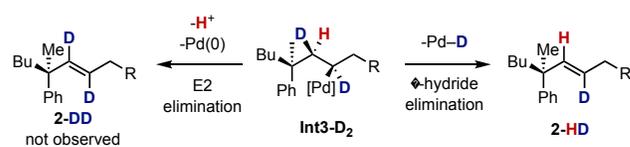
#### Scheme 5. Computed reaction pathway of N-trifluoromethylacetamides



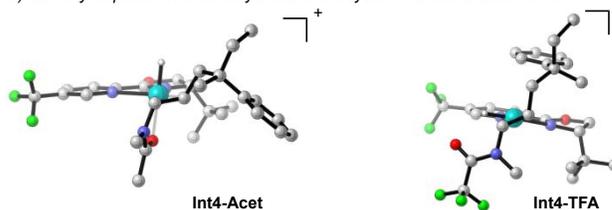
DFT studies were performed at the IEFPCM(DMF)-Mo6/6-31+G(d)//Mo6/SDD-6-31+G(d,p) level of theory. All energies listed are reported in kcal/mol. \*Minimum using loose convergence criteria. See the supporting information for details

**Summary of mechanistic studies.** The mechanistic studies presented here have demonstrated that the selective formation of the allyl and ene products is driven primarily by thermodynamics (Figure 5). Additionally, deuterium labeling studies showed that an E2 elimination from **Int3-D<sub>2</sub>** does not occur based on the exclusive formation of **2-HD** without any evidence for the formation of **2-DD** (Figure 5a). The computational studies revealed that the nature of the carbonyl has a direct impact on the relative stabilities of **Int2**, **Int3**, and **Int4**, with the electron rich amide carbonyl serving to stabilize **Int3** and **Int4** (Figure 5b). Importantly, the stabilization of these intermediates likely results in the preferential formation of the ene product. Lastly, the computations revealed that the allyl selective pathways greatly favor the formation of **Int1** and **Int3** through the intermediacy of **Int2** (Figure 5c). Overall, the results suggest that the selective formation of the allyl product is a result of deprotonation of the Pd-H of **Int2** or direct dissociation of Pd-H from **Int2**.

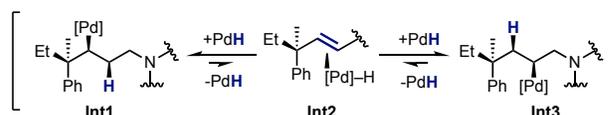
a) deuterium labeling rules out E2 elimination from **Int3**



b) carbonyl impacts the thermodynamics of the system via coordination to Pd



c) allyl selective substrates establish equilibrium between **Int1**, **Int2**, and **Int3**



**Figure 5.** Summary of mechanistic studies: a) **Int3** does not undergo E2 elimination, b) ligation of the carbonyl to the Pd effects the selectivity, and c) system is under thermodynamic control

### Conclusion

In summary, we have demonstrated that a variety of homoallylic imides, biscarbamates, sulfonamides, and trifluoroacetamides are capable of engaging in the relay Heck reaction to form enantiomerically enriched allylic amines containing a quaternary center. The scope of this process is broad with modest to good yields and high enantioselectivity for all examples. Alternatively, we have found that homoallylic amides give rise to related ene-

amides products. To explain the observed difference in selectivity between these two substrate classes, isotopic labeling experiments were combined with DFT calculations. These studies demonstrated that the preferential formation of the allylic products is governed by a combination of the reversible nature of the chain-walking process and the instability of intermediates that would lead to ene amide type products. In contrast, the formation of the ene-amide is governed by the stability imparted by the general Lewis basicity of the amide carbonyl. The underlying strategies of using modest changes to substrate structure to control chain-walking termination events should impact the discovery and development of new synthetically attractive remote functionalization reactions.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures for all reactions; spectroscopic characterization data for all new compounds; detailed computational methods; copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra; copies of SFC chromatograms. (PDF)

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## ACKNOWLEDGMENT

M.S.S. thanks the National Institute of Health (NIGMS R01GM063540), S.P.R thanks the National Institute of Health for financial support through a F32 Ruth L. Kirschstein NRSA fellowship (F32 GM128354-01A1). The computational portion of this work was supported by the National Science Foundation's Extreme Science and Engineering Discovery Environment (XSEDE, CHE190028) and the Center for High Performance Computing (CHPC) at the University of Utah. NMR results included in this report were recorded at the David M. Grant NMR Center, a University of Utah Core Facility. Funds for construction of the Center and the helium recovery system were obtained from the University of Utah and the National Institutes of Health awards 1Co6RR017539-01A1 and 3R01GM063540-17W1 respectively. NMR instruments were purchased with support of the University of Utah and the National Institutes of Health award 1S10OD25241-01.

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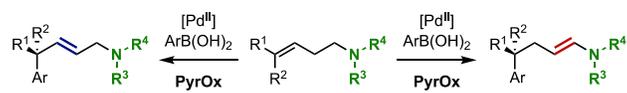
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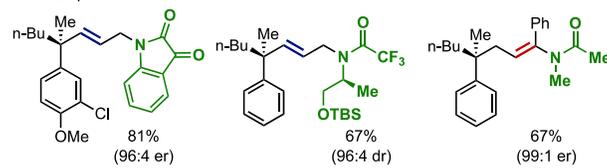
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For example:



◆ >30 examples ◆ Mechanistic experiments ◆ DFT studies on the chain-walking process