

# Gold-Catalyzed Interrupted Relay Heck Reaction

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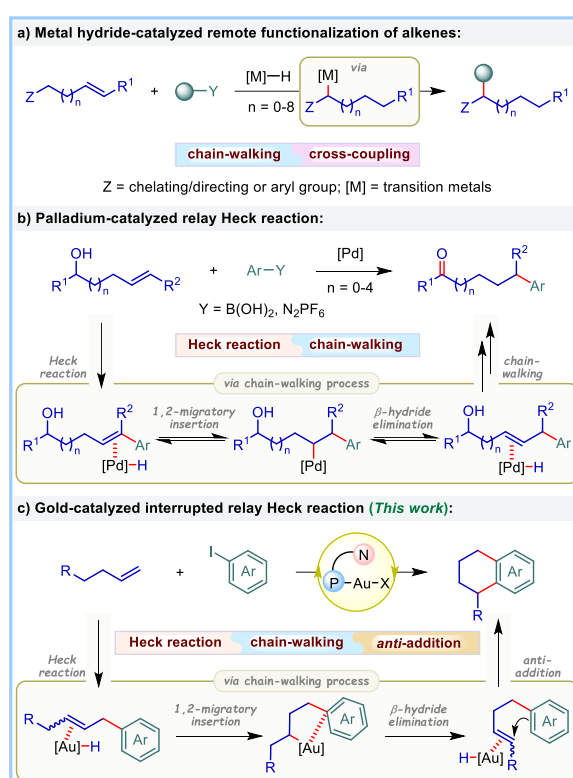
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**ABSTRACT:** Herein, we disclose the gold-catalyzed interrupted relay Heck reaction successfully demonstrating the implementation of a chain-walking process for the first time in a catalytic fashion. The reaction involves the merging of three distinct reactivities such as the Heck reaction, chain-walking, and anti-addition *via*  $\pi$ -activation to provide direct access to tetrahydronaphthalenes and octahydrophenanthrenes with high diastereoselectivity. We have also demonstrated the application of the interrupted chain-walking reaction in the development of 1,3-diarylation and 1,*n*-hydroarylation (*n* = 3, 4) of alkenes.

The Heck reaction has made a significant impact on organic synthesis and has been used in the synthesis of many important compounds, including natural products, pharmaceuticals, and materials.<sup>1</sup> However, this reaction is limited to the use of specialized substrates such as styrene, vinyl ethers, or  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>2</sup> The use of simple long-chain aliphatic alkenes results in the formation of a mixture of regioisomers through an iterative migratory insertion and  $\beta$ -hydride elimination process known as “chain walking”.<sup>3</sup>

The transition metal-catalyzed chain-walking processes have emerged as a state-of-the-art technique for the selective remote functionalization of unreactive C–H bonds.<sup>4</sup> This strategy allows the installation of functional groups at distant positions from the initial reaction center. For instance, Zhu,<sup>5</sup> He,<sup>6</sup> Engle,<sup>7</sup> Yuan/Zhang,<sup>8</sup> and others<sup>9</sup> developed the metal hydride-catalyzed remote C–H functionalization of alkenes by combining the chain-walking with the cross-coupling reactivity (Scheme 1a). The presence of chelating/directing or aryl group on the alkenes is necessary to control the regioselectivity as these groups impart the stabilization of the metal alkyl intermediate at a specific position along the alkyl chain. In parallel, the pioneering work from Sigman's research group disclosed a palladium-catalyzed relay Heck reaction of alkenyl alcohols with aryl boronic acids or aryl diazonium salts by merging the Heck reaction with the chain-walking process (Scheme 1b).<sup>10</sup> The use of redox acceptor groups on the alkene undergoing re-functionalization typically serves as a thermodynamic driving force for the formation of carbonyl compounds. In both cases (Schemes 1a and 1b), the requirement of preinstalled directing/chelating, aryl, or redox acceptor groups on the alkenes substrates is necessary.

Over the last two decades, Au(I)/Au(III) redox catalysis has emerged as an important topic of research for accessing various cross-coupling and 1,2-difunctionalization reactions of C–C multiple bonds.<sup>11</sup> The field has experienced remarkable growth, with significant advancements, including the development of enantioselective Au(I)/Au(III) redox catalysis, as reported by our<sup>12</sup> group and Shi's<sup>13</sup> group.<sup>14</sup> In spite of such significant progress in Au(I)/Au(III) redox catalysis, the development of fundamental elementary steps such as migratory insertion and  $\beta$ -hydride elimination that are



**Scheme 1.** Transition Metal-Catalyzed Chain-Walking Reactions for Remote Functionalization of Alkenes: General Overview and Present Work

required for the Heck reaction and chain-walking process to occur remain elusive.<sup>15</sup> A few theoretical<sup>16</sup> and stoichiometric experimental investigations have been carried out to show the feasibility of migratory insertion and  $\beta$ -hydride elimination steps in gold complexes. In a stoichiometric study, the feasibility of migratory insertion and  $\beta$ -hydride elimination steps in gold has been shown by the research group of Toste,<sup>17</sup> Bochmann,<sup>18</sup> Bourissou,<sup>19</sup> Nevado,<sup>20</sup> Tilset,<sup>21</sup> and Bower/Russell.<sup>22</sup> Notably, Bourissou and co-workers showcased the feasibility of the chain-walking process in the Au(III)-*n*-butyl complex.<sup>19c</sup> Our group recently discovered the gold-catalyzed Heck reaction, in which the fundamental organometallic steps such as migratory insertion and  $\beta$ -hydride elimination occurred in a catalytic fashion for the

first time.<sup>23</sup> Later, the Xie group showcased the feasibility of the migratory insertion in gold-catalyzed iodo-alkynylation of benzyne.<sup>24</sup> Despite these advances, until now there is no report on the gold-catalyzed chain-walking reactions.

In this manuscript, we report the gold-catalyzed interrupted relay Heck reaction successfully demonstrating the implementation of the chain-walking process for the first time in a catalytic manner (Scheme 1c). The reaction involves the merging of three distinct reactivities within a single transformation: 1) Heck reaction, 2) chain-walking, and 3) chain-walking interruption *via anti*-attack of the pendant aryl group on alkene. The chain-walking process is interrupted due to the inherent  $\pi$ -activation ability of gold catalyst enabling the activation of alkenes and facilitating nucleophilic attack from the pendant aryl ring. This distinctive feature sets this reaction apart from the other transition metal-catalyzed chain-walking reactions and relay Heck reactions.<sup>25</sup> Interestingly, the present methodology utilizes simple long-chain aliphatic alkenes as a substrate without the requirement of any preinstalled directing/chelating, aryl, or redox acceptor group. Apart from this, we also demonstrate the application of interrupted chain-walking reaction in the development of 1,3-diarylation and 1,*n*-hydroarylation ( $n = 3, 4$ ) of alkenes.

We initiated our study by exploring our previously developed optimized reaction conditions of the gold-catalyzed Heck reaction.<sup>23</sup> Pleasingly, the reaction between 1-hexene **1a** and 2-iodo-1-methoxy-4-methylbenzene **2a** as coupling partner in the presence of MeDalPhosAuCl (10 mol%), AgOTf (1.1 equiv) and pyridine (0.7 equiv) in DCE (0.1 M) at 80 °C for extended hours of reaction time (48 h) delivered the desired cyclized product **3a** in 78% yield (Table 1). With this excellent reaction outcome, we turned our attention to explore the scope of alkenes **1** by using 2-iodo-1-methoxy-4-methylbenzene **2a** as a model substrate. To our delight, a wide range of alkenes **1a-1p** reacted smoothly to afford the desired cyclized products **3a-3p** in up to 87% yield. For instance, alkenes **1b-1f** reacted smoothly under the standard reaction conditions to afford the corresponding products **3b-3f** in 51-71% yield. Besides, the alkene tethered with phenoxide groups reacted with **2a** to afford the desired product **3g** and **3h** in 51% and 55% yield, respectively. Furthermore, the alkene tethered with sulfone, dimethyl malonates, phthalimide, indole, and protected aniline also reacted smoothly with **2a** to deliver the products **3i-3m** in 44-59% yield. Notably, a single *cis*-diastereomer of product **3n** was obtained in 74% yield when 1-vinyl-cyclohexane was used as an alkene source.

**Table 1.** Scope of the Gold-Catalyzed Interrupted Relay Heck Reaction<sup>a,b</sup>

**scope of alkenes 1**

<b>3a</b> , 78% 48 h	<b>3b</b> , 71% 48 h	<b>3c</b> , 65% 48 h	<b>3d</b> , 51% 48 h	<b>3e</b> , 51% 48 h	<b>3f</b> , 59% 48 h	<b>3g</b> , 51% 48 h	<b>3h</b> , 55% 48 h	<b>3i</b> , 46% 48 h
<b>3j</b> , 57% 48 h	<b>3k</b> , 53% 48 h	<b>3l</b> , 59% 48 h	<b>3m</b> , 44% 48 h	<b>3n</b> , 74% 24 h	<b>3o</b> , R = Et, 60%, 24 h	<b>3p</b> , R = <sup>n</sup> Pr, 87%, 36 h	<b>3o</b> , CCDC = 2254613	

**scope of aryl iodides 2**

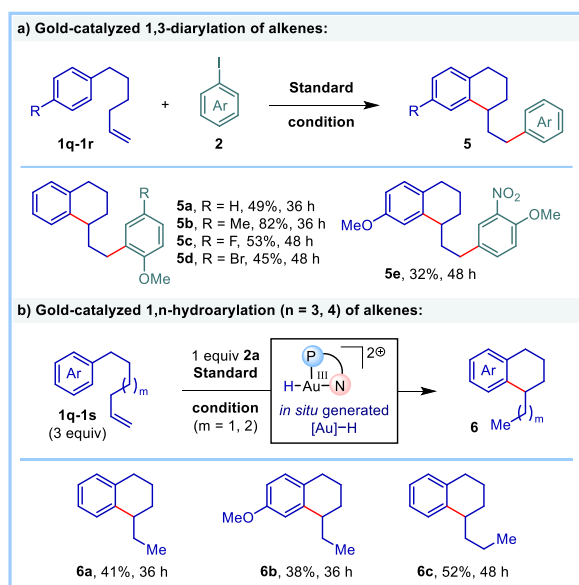
<b>4b</b> , 60%, 48 h	<b>4c</b> , 80%, 36 h	<b>4d</b> , 82%, 48 h	<b>4e</b> , 69%, 48 h	<b>4f</b> , 72%, 36 h	<b>4g</b> , 96%, 36 h	<b>4h</b> , 56%, 48 h	<b>4i</b> , 65%, 48 h
<b>4j</b> , 87%, 36 h	<b>4k</b> , 58%, 48 h	<b>4l</b> , 87%, 48 h	<b>4m</b> , 65%, 40 h	<b>4n</b> , 53%, 24 h	<b>4o</b> , 47%, 48 h	<b>4p</b> , 30%, 14 h	

CCDC = 2246572

<sup>a</sup>Reaction conditions: 0.6 mmol **1**, 0.2 mmol **2**, 0.02 mmol MeDalPhosAuCl, 0.22 mmol AgOTf, 0.14 mmol pyridine, DCE (0.1 M), 80 °C. <sup>b</sup>Isolated yields.

Additionally, 4-substituted-1-vinyl-cyclohexane derivatives (**1o-1p**) also reacted efficiently to deliver the desired products **3o-3p** in 60-87% yield as a single diastereomer. The structure of product **3o** was unambiguously confirmed by X-ray crystallographic analysis.

Next, we turned our attention to the scope of aryl iodides **2** (Table 1). Gratifyingly, a series of aryl iodides (**2b-2o**) having different substituents at *ortho*, *meta*, and *para* positions reacted smoothly to deliver the products **4b-4p** in up to 96% yield as a single *cis*-diastereomer. For instance, iodobenzene (**2b**) reacted smoothly under standard reaction conditions to deliver the desired product **4b** in 60% yield. Besides, *para*-substituted aryl iodides (**2c-2h**) reacted efficiently to afford the products **4c-4h** in 56-96% yield. Further, mesyl-protected *para*-iodo-N-methylaniline **2i** also reacted nicely to deliver the product **4i** in 65% yield. Moreover, the products **4j** and **4k** were obtained in 87% and 58% yield when *ortho*-iodoanisole (**2j**) and *meta*-iodoanisole (**2k**) were used as substrates. Additionally, *para*-iodoanisole bearing halo (Br, Cl) or electron-donating substituents also reacted smoothly under the standard reaction conditions, furnishing the corresponding products **4l-4o** in 47-87% yield with excellent chemoselectivity for the C(sp<sup>2</sup>)-I bond over other C(sp<sup>2</sup>)-X bonds (X = Br, Cl; see entries **4l**, **4m**, **4o**). The structure of product **4o** was unambiguously confirmed by X-ray crystallographic analysis.

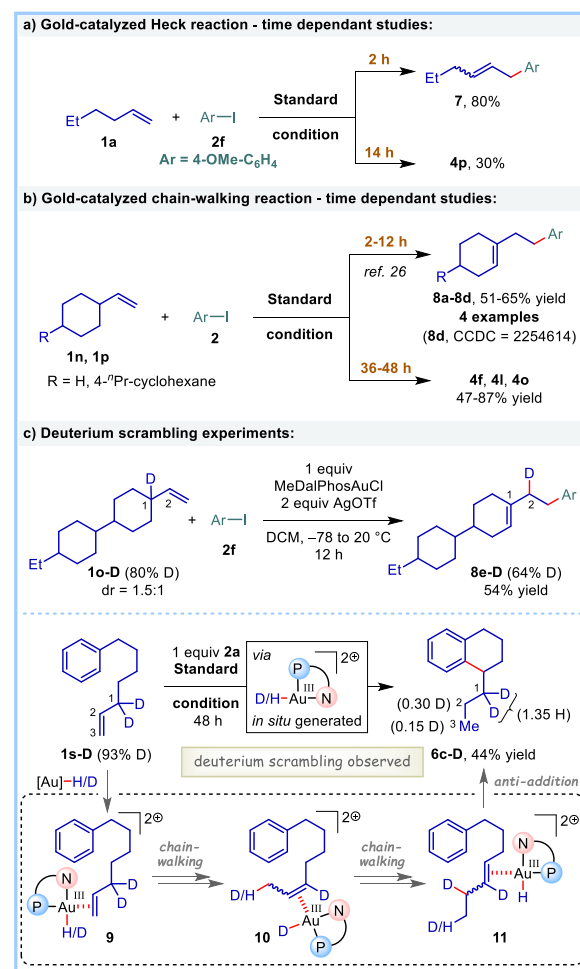


**Scheme 2.** Application of Gold-Catalyzed Interrupted Chain-Walking Reactions

Further, the application of an interrupted chain-walking process has also been demonstrated in the development of 1,3-diarylation of alkenes, wherein a chain-walking process has been terminated by the tethered aryl group on the alkene (Scheme 2a). For instance, the hex-5-en-1-ylbenzene (**1q**) reacts with aryl iodides **2** under the standard reaction conditions giving the corresponding products **5a-5d** in 45-82% yield. Further, 1-(hex-5-en-1-yl)-4-methoxybenzene (**1r**) was reacted with 4-iodo-1-methoxy-2-nitrobenzene giving the 1,3-diarylated product **5e** in 32% yield.

Interestingly, the present methodology can also be applied for the 1,n-hydroarylation (n = 3, 4) of alkenes *via* the *in situ* generated Au(III)-hydride-catalyzed chain-walking process followed by cyclization (Scheme 2b). For instance, alkenes **1q-1s** were treated with **2a** under the standard reaction conditions, the 1,n-hydroarylated products **6a-6c** were obtained in 38-52% yield.

To gain a deeper understanding into the reaction mechanism, a few mechanistic investigations were carried out (Scheme 3). To begin, time-dependent experiments were performed to thoroughly understand the plausible reaction intermediates for the formation of products **3** or **4**. In particular, when alkene **1a** was treated with **2f** under the standard reaction conditions, the allylic Heck product **7**<sup>23</sup> was obtained in 80% yield in just 2 h; however, prolonged reaction time (14 h) resulted in the formation of **4p** in 30% yield (Scheme 4a). Similarly, when alkenes **1n** and **1p** were reacted with aryl iodides **2**, the chain-walking products **8a-8d** were formed in 51-65% yield in 2-12 h,<sup>26</sup> while, further extending the reaction time to 36-48 h resulted in the formation of cyclized products **4f**, **4l**, and **4o** in 72%, 87%, and 47% yields, respectively (Scheme 4b). These two control experiments (Schemes 4a and 4b) suggest that the allylic Heck product **7** and the chain-walking product **8** serve as intermediates in the formation of products **3** or **4**. Next, when the deuterated alkene **1o-D** was treated with **2f** in the

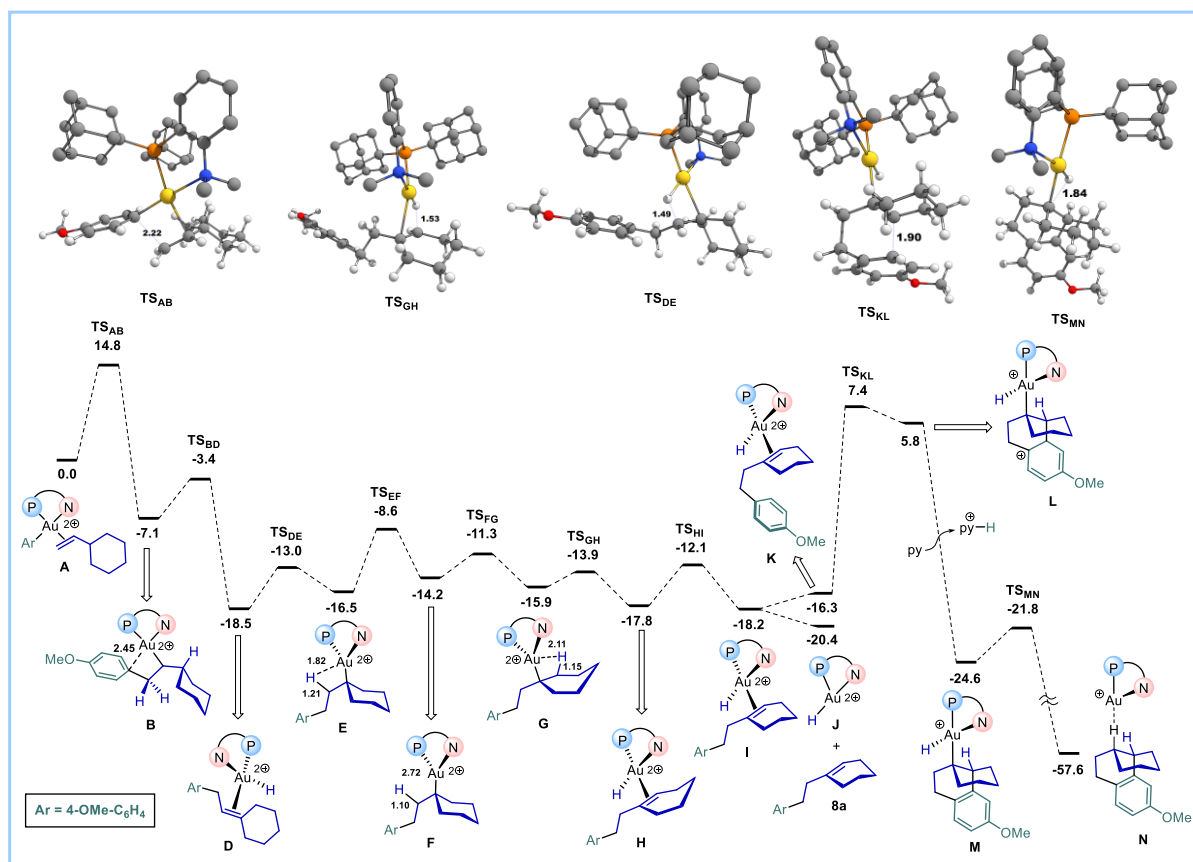


**Scheme 3.** Mechanistic Investigations

presence of MeDalPhosAuCl (1 equiv) and AgOTf (2 equiv), the product **8e-D** was obtained in 54% yield (Scheme 4c). The migration of deuterium from the C1 (80% D) to C2 (64% D) position in product **8e-D** suggests that the chain-walking process is operative in the reaction. Further, when deuterated alkene **1s-D** was treated with **2a** under standard reaction conditions, the deuterium scrambling product **6c-D** was obtained in 44% yield (Scheme 4c). The scrambling of deuterium (0.15 D at C3 and 0.30 D at C2) and loss of D at C1 (1.35 H) in the product clearly suggests that the chain-walking process is operational. Furthermore, the formation of 1,*n*-hydroarylated products **6a-6c** (Scheme 3b) and incorporation of deuterium at the C3 position (0.15 D) in product **6c-D** (Scheme 4c) indicate that the chain-walking process follows a dissociative pathway. Additionally, the *cis* ring fusion of compounds **3** and **4** (Scheme 2) indicates that the cyclization follows an *anti*-nucleophilic attack through a  $\pi$ -activation mode.

Based on the literature precedence<sup>23,24</sup> and the gathered experimental evidences, we initially proposed a plausible mechanism for the gold-catalyzed interrupted relay Heck reaction.<sup>26</sup> In order to provide additional support for the proposed reaction mechanism, DFT computations were performed with the Gaussian 16 set of program using 1-vinylcyclohexane and 4-iodoanisole as model substrates (Figure 1).<sup>27</sup> The study revealed that insertion of the alkene into the Au–Ar bond requires 14.8 kcal/mol free energy of activation (**TS<sub>AB</sub>**) and is exergonic by 7.1 kcal/mol. As discussed in our previous study,<sup>23</sup> the resulting complex **B** shows a  $\kappa^1$ -C

coordination between gold and the *ipso* aryl carbon, making the benzylic hydrogen inaccessible for a *cis*  $\beta$ -H elimination. Lengthening of the *ipso*C–Au distance followed by  $\beta$ -H elimination resulted in the formation of the alkene complex **D** (-18.5 kcal/mol) through **TS<sub>BD</sub>** (-3.4 kcal/mol). Next, the insertion of the alkene moiety into the Au–H bond can provide the agostic complex **E** (-16.5 kcal/mol) through **TS<sub>DE</sub>** (-13.0 kcal/mol). Lengthening of the Au–H distance revealed **TS<sub>EF</sub>** (-8.6 kcal/mol), leading to the non-agostic complex **F** (-14.2 kcal/mol). Flipping of the chair *via* **TS<sub>FG</sub>** (-11.3 kcal/mol) proved necessary to reach the agostic complex **G** (-15.9 kcal/mol). The endocyclic alkene complex **H** (-17.8 kcal/mol) could be connected to **G** after  $\beta$ -H elimination through **TS<sub>GH</sub>** (-13.9 kcal/mol). Back-flipping of the pseudo-chair *via* **TS<sub>HI</sub>** (-12.1 kcal/mol) provided the more stable conformer **I** (-18.2 kcal/mol). Complex **I** is less stable than **D** by 0.3 kcal/mol, but once the gold hydride moiety is removed and the free alkenes optimized, the endocyclic one is more stable by 1.6 kcal/mol.<sup>27</sup> It is also worthy of note that the dissociation of **I** into the gold hydride **J** and the experimentally-observed alkene **8a** is exergonic by 2.2 kcal/mol (-20.4 kcal/mol). This is consistent with the fact that the formation of products **8** (Scheme 4b) is independent from that of the hydroarylation products (dissociative pathway). Hydroarylation was modeled from **K** (-16.3 kcal/mol), which is simple conformer of **I** preorganized for the *anti*-nucleophilic attack of the anisole fragment on the endocyclic alkene. A free energy of 23.7 kcal/mol must be overcome to reach **TS<sub>KL</sub>** (25.9 kcal/mol from **D**). The Wheland intermediate **L** (5.8 kcal/mol) is, of course, obtained in a



**Figure 1.** M11L/SDD+f(Au):6-311+G(d,p) free energy profile ( $\Delta G_{298}$ , kcal/mol; some hydrogen atoms have been omitted for clarity; selected distances in Å).

markedly endergonic fashion. Its deprotonation by pyridine would lead to **M** (-24.6 kcal/mol). Its reductive elimination through **TS<sub>MN</sub>** (-21.8 kcal/mol) requires only 2.8 kcal/mol of free energy of activation. The experimentally observed *cis* product **N** (-57.6 kcal/mol) is finally obtained in a strongly exergonic manner. Various other modes of approach, as well as another Lewis acid ((P,N)Au(I)<sup>+</sup>), were tested, but these options proved more energetically demanding or ineffective.<sup>27</sup>

In conclusion, we have developed the gold-catalyzed interrupted relay Heck reaction. The key features of this transformation are the Heck reaction, chain-walking, and *anti*-addition *via*  $\pi$ -activation. Further, the present methodology provides direct access to synthetically challenging tetrahydronaphthalenes and octahydrophenanthrenes which are otherwise difficult

to access *via* existing means. The mechanism of this reaction was supported by several control experiments involving time-dependent studies and deuterium scrambling experiments. Further, the mechanism of the reaction is corroborated with the DFT studies. The realization of “chain-walking” in gold catalysis should open up several opportunities for discovering new reactions that are not possible by other transition metals.

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