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Experimental and Computational Studies of Palladium-Catalyzed Spirocyclization via a Narasaka–Heck/C(sp^3 or sp^2)–H Activation Cascade Reaction

Wan-Xu Wei,‡ Yuke Li,‡ Ya-Ting Wen, Ming Li, Xue-Song Li, Cui-Tian Wang, Hong-Chao Liu, Yu Xia, Bo-Sheng Zhang, Rui-Qiang Jiao, and Yong-Min Liang*

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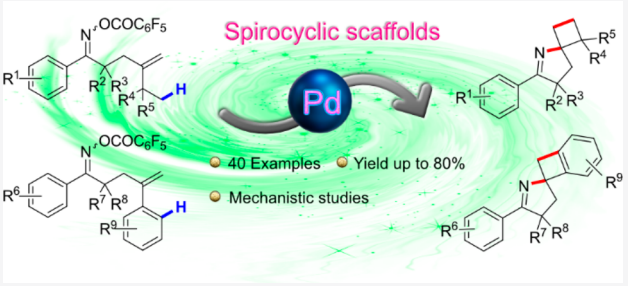
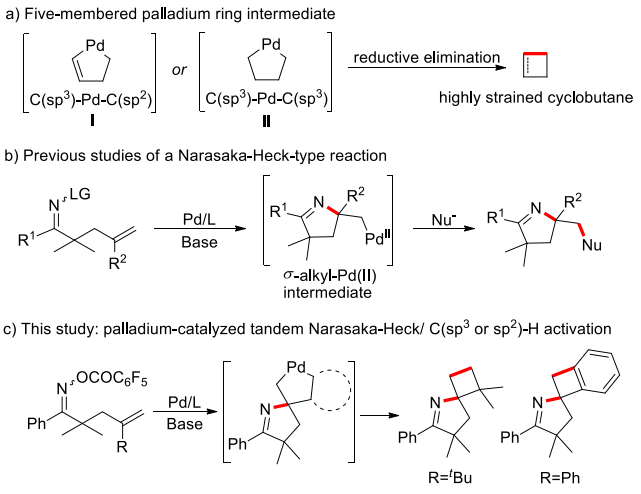
ABSTRACT: The first synthesis of highly strained spirocyclobutane-pyrrolines via a palladium-catalyzed tandem Narasaka–Heck/C(sp^3 or sp^2)–H activation reaction is reported here. The key step in this transformation is the activation of a δ-C–H bond via an in situ generated σ-alkyl-Pd(II) species to form a five-membered spiropalladacycle intermediate. The concerted metalation-deprotonation (CMD) process, rate-determining step, and energy barrier of the entire reaction were explored by density functional theory (DFT) calculations. Moreover, a series of control experiments was conducted to probe the rate-determining step and reversibility of the C(sp^3)–H activation step.



INTRODUCTION

Tremendous developments over the past few decades have exploited the high atom and step economies of palladium-catalyzed C–H bond activation,[1] which has become a powerful tool for fabricating useful compounds,[2] including medicines, industrial materials, and natural products.[3] Numerous pioneering palladium-catalyzed directing-group-(DG)-assisted C–H bond activations have been widely reported.[4] Palladium-catalyzed intramolecular Heck-type cyclization/C–H bond activation reactions have also been extensively studied as a complementary strategy for remote C–H activation.[5] This efficient strategy consists of using a transient σ-alkyl-Pd(II) species generated in situ during Heck cyclization to remotely activate a C–H bond for the effective one-step preparation of complex heterocyclic and carbocyclic molecular skeletons from well-designed starting materials.[6] Grigg and co-workers[7] reported the first example of utilizing the σ-alkyl-Pd(II) intermediate of Heck cyclization for intramolecular C–H bond activation. A wide range of spirocyclic compounds have since been produced via Heck cyclization, C–H activation, and direct reductive elimination or migratory insertion through five-membered palladacycle intermediate **I** (Scheme 1a).[8] In 2017, Lautens and co-workers successfully implemented this protocol to activate C(sp^2)–H groups in alkene-tethered aryl iodides to obtain spiro-fused benzocyclobutenes via five-membered palladacycle intermediate **I** (Scheme 1a).[9] In sharp contrast to these achievements, C(sp^3)–H bond activation by a σ-alkyl-Pd(II) intermediate has been significantly less exploited[10] because of its low acidity, high bond dissociation energy, and lack of stabilizing orbital interactions with the metal center.[11] In most cases, oxidative addition of aryl halogens has been used to trigger domino reactions that form σ-alkyl-Pd(II) intermediates, and other generation mechanisms

Scheme 1. Previous Studies and This Study



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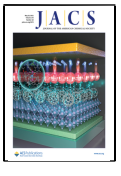

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remain underexplored.[10c] To the best of our knowledge, the five-membered palladacycle intermediate **II** (Scheme 1a) formed by δ-C(sp^3)−H activation by a σ-alkyl-Pd(II) intermediate has not been reported to date, and its direct reductive elimination would be an effective route to build highly strained cyclobutane.

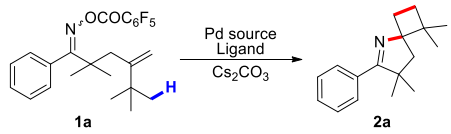
In 1999, Narasaka and co-workers first reported that pyrrole could be efficiently synthesized by the palladium-catalyzed cyclization of a γ,δ-unsaturated oxime ester,[12] a process known as the Narasaka−Heck reaction. Since then, this type of reaction has been widely used to synthesize structurally diverse *N*-heterocyclic compounds,[13] such as imidazoles,[14] indoles,[15] pyridines,[16] and isoquinolines.[17] Bower,[18] Tong,[19] Zhu,[20] and other groups[21] have used the σ-alkyl-Pd(II) intermediate of Narasaka−Heck cyclization in many nucleophile-trapping reactions to complete the acylation, carboxylation, arylation, vinylation, alkynylation, and halogenation of pyrrolines (Scheme 1b). In addition, in 2019, our group reported the first polyfluorophenylation of the σ-alkyl-Pd(II) intermediate of Narasaka−Heck cyclization, in which a $C_6F_5^-$ source was produced via the decarboxylation of a $C_6F_5CO_2^-$ leaving group.[22] Altogether, a series of functionalized pyrrolines and *N*-heterocyclic compounds have been built by this type of reaction, but the synthesis of spiropyrrolines, which are regarded as significant scaffolds in drug development and discovery,[23] remains a challenge. In addition, previous Narasaka−Heck reactions mainly focused on the nucleophile-trapping and β-hydrogen elimination of its σ-alkyl-Pd(II) intermediate; tandem intramolecular C−H activation had not been developed until now.

Domino Heck/C(sp^2)−H activation reactions of alkene-tethered aryl halogens have been well-documented over the years; in contrast, C(sp^3)−H activation of the transient C(sp^3)-Pd species is challenging and has rarely been reported. Nevertheless, our group has been studying domino C(sp^3)−H activation by a σ-alkyl-Pd(II) intermediate. We designed a novel palladium-catalyzed domino intramolecular Narasaka−Heck/C(sp^3)−H activation reaction (Scheme 1c) to synthesize spirocyclobutane-pyrrolines from γ,δ-unsaturated oxime esters via the new five-membered palladacycle intermediate **II** which is formed by δ-C(sp^3)−H activation. The reaction is triggered by oxidative addition to the N−O bond, which is different from the domino Heck/C−H activation reaction of an alkene-tethered aryl halogen.

RESULTS AND DISCUSSION

Reaction Optimization. To meet the above-mentioned challenges, we first employed γ,δ-unsaturated oxime ester **1a** as a substrate to verify the feasibility of the well-designed domino process (Table 1). The introduction of a tertiary butyl group ensures the formation of a σ-alkyl-Pd(II) species without a β-hydrogen atom and provides a suitable site for C(sp^3)−H activation. The anticipated domino reaction was conducted in the presence of $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, and Cs_2CO_3 in 1,4-dioxane at 140 °C for 12 h under an argon atmosphere, generating the desired product **2a** in 41% yield (Table 1, entry 1). Next, various solvents (Table 1, entries 1−4) were carefully screened, and toluene was identified as the optimal choice because it resulted in an improved isolated product yield of 70%. Further studies were used to determine that the electron-rich monophosphine $PCy_3{\cdot}HBF_4$ was the most suitable phosphine ligand for this system (Table 1, entries 5−8). The bisphosphine ligand was also suitable for this process but less

Table 1. Optimization of the Tandem Narasaka−Heck/C(sp^3)−H Activation Reaction Conditions[a]



entry	Pd source	ligand	solvent	yield (%)
1	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	dioxane	41
2	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	toluene	70
3	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	MeCN	trace
4	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	DMSO	23
5	$Pd(OAc)_2$	PPh_3	toluene	34
6	$Pd(OAc)_2$	$P^tBu_3{\cdot}HBF_4$	toluene	31
7	$Pd(OAc)_2$	P(o-Tol)$_3$	toluene	56
8	$Pd(OAc)_2$	$PCyp_3{\cdot}HBF_4$	toluene	68
9	$Pd(OAc)_2$	L1	toluene	38
10	$Pd(PPh_3)_4$	$PCy_3{\cdot}HBF_4$	toluene	60
11	$Pd(TFA)_2$	$PCy_3{\cdot}HBF_4$	toluene	63
12	$Pd(PCy_3)_2$	–	toluene	43
13[b]	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	toluene	75
14[b,c]	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	toluene	72
15[b,d]	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	toluene	64
16[b]	–	$PCy_3{\cdot}HBF_4$	toluene	0

[a]Reaction conditions unless otherwise noted: **1a** (0.2 mmol), Pd source (10 mol %), ligand (20 mol %), Cs_2CO_3 (2.0 equiv), solvent (2 mL), 140 °C, 12 h, Ar; isolated yields. [b]150 °C. [c]24 h. [d]K_2CO_3 used instead of Cs_2CO_3; L1 = 1,2-bis(dicyclohexylphosphino)ethane; $PCyp_3{\cdot}HBF_4$ = tricyclopentylphosphine tetrafluoroborate.

effective than $PCy_3{\cdot}HBF_4$ (Table 1, entry 9). Using other palladium sources, such as $Pd(PPh_3)_4$, $Pd(TFA)_2$, and $Pd(PCy_3)_2$, did not improve the yield (Table 1, entries 10−12). However, elevating the temperature to 150 °C improved the isolated yield of **2a** to 75% (Table 1, entry 13). Prolonging the reaction time did not further increase the yield (Table 1, entry 14). Replacing Cs_2CO_3 with K_2CO_3 (Table 1, entry 15) resulted in an isolated yield of **2a** of 64% (see Supporting Information for the further screening of bases). A control experiment showed that palladium is necessary for the transformation (Table 1, entry 16).

Investigation of the Substrate Scope. Having optimized the reaction conditions (Table 1, entry 13), we examined the generality of the reaction. As shown in Table 2, the smooth reactions of many γ,δ-unsaturated oxime ester substrates **1** produced moderate to good yields of the corresponding spirocyclobutane-pyrroline products **2**. First, the influence of the aromatic ring subunit on the reaction outcome was evaluated. Notably, γ,δ-unsaturated oxime esters with electron-donating groups, including methyl (**2b**), methoxy (**2c**), dimethylamino (**2d**), and phenyl (**2e**) groups, at the *para*-position of the aryl rings showed high reactivity in this reaction. Furthermore, substrates with electron-withdrawing substituents, such as fluoro (**1f**), trifluoromethoxy (**1g**) and trifluoromethyl (**1h**) groups, at the *para*-position were transformed into **2f**, **2g**, and **2h** in 64%, 79%, and 67% yields, respectively. Both electron-donating (methyl, **2i**) and electron-withdrawing (fluoro, trifluoromethyl, **2j**−**2l**) groups in the *meta*-position were well tolerated, and good yields of the corresponding spirocyclobutane-pyrrolines were obtained. Only a 20% yield was achieved for the transformation of substrate **1l** bearing Me in the *ortho*-position of the aryl ring,

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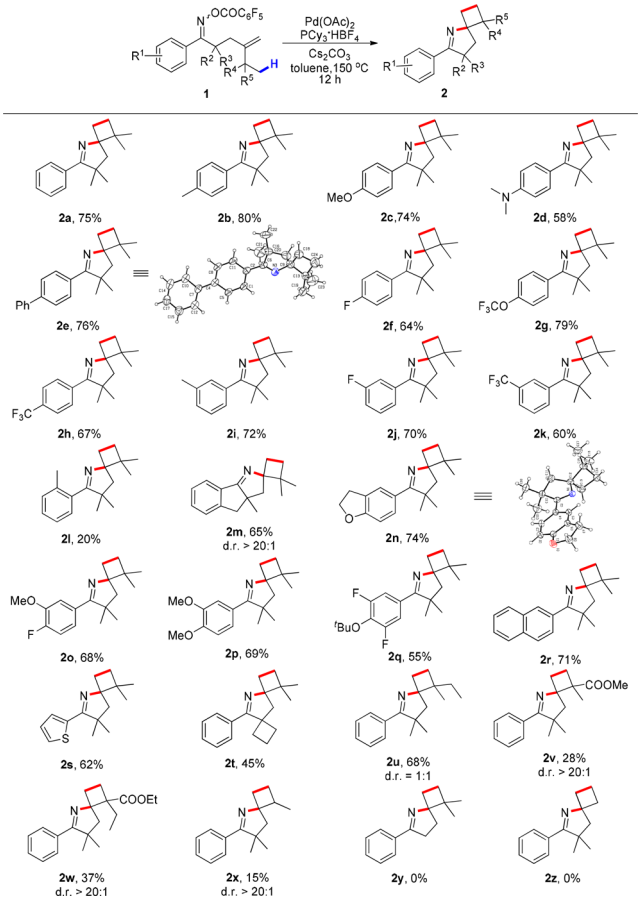
Table 2. Substrate Scope of the Tandem Narasaka–Heck/C(sp^3)–H Activation Reaction[a]



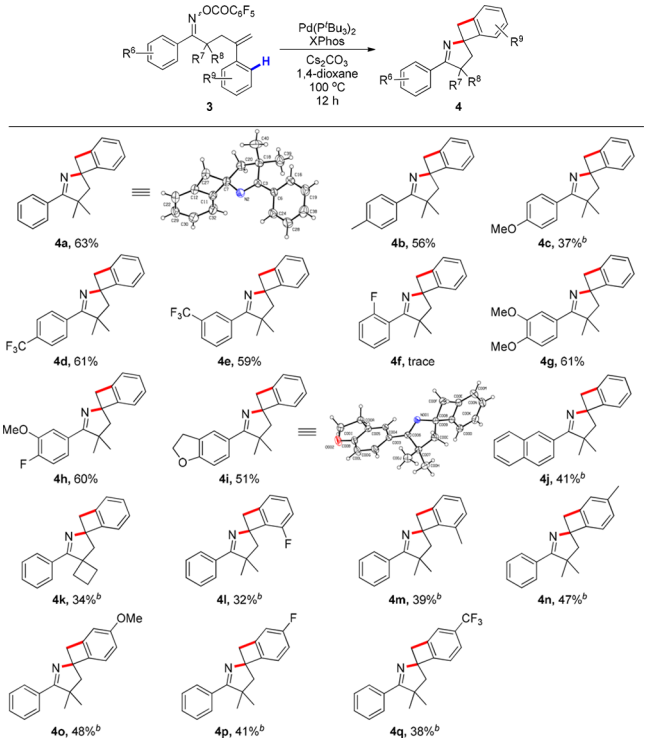
[a]Reaction conditions unless otherwise noted: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $PCy_3{\cdot}HBF_4$ (20 mol %), Cs_2CO_3 (2.0 equiv), toluene (2 mL), 150 °C, 12 h, Ar; isolated yields. The diastereomeric ratio was determined by ^1H NMR.

presumably because of steric congestion, whereas substrate **1m** with a tethered *ortho*-substituent gave **2m** in a satisfactory yield of 65%. Polysubstituted reactants **1n**-**1q** were successfully transformed, affording **2n**–**2q** in 74%–55% yields. Similarly, electron-rich naphthalene oxime ester **1r** could participate in the process. The 2-thiophene-substituted product **2s** was generated in a 62% yield, indicating the compatibility of the heterocycle. Substrate **1t** bearing spirocyclobutane at the alkyl chain moieties was also transformed by this reaction to give **2t** in 41% yield. However, substrate **1y** was poorly tolerated and failed to give the corresponding product, probably because of the absence of the *gem*-dimethyl effect. The structures of **2e** and **2n** were definitively elucidated by X-ray crystal structure analysis (see the Supporting Information).

Next, we explored the scope of *γ*,*δ*-unsaturated oxime ester substrates without *tert*-butyl groups. As expected, substrates (**2v** and **2w**) with esters on the quaternary carbon were tolerated under the optimized conditions. Substrate **1u** bearing an ethyl group cyclized smoothly and satisfactorily at the methyl group to generate the desired product **2u** in 68% yield with a 1:1 diastereomeric ratio. Note that substrate **1x** bearing an isopropyl group instead of a *tert*-butyl group also afforded the target product **2x**, indicating that a quaternary carbon is not essential for this cascade C(sp^3)–H bond activation. Unfortunately, substrate **1z** failed to give the corresponding product, possibly because the freely rotating methyl group was less accessible to the palladium center and there were fewer reactive C–H bonds.

The above-mentioned results showed that the *σ*-alkyl-Pd(II) intermediate of Narasaka–Heck cyclization can be used for intramolecular *δ*-C(sp^3)–H activation. Inspired by these results, we explored the tandem Narasaka–Heck/C(sp^2)–H activation reaction using substrate **3a**. Considerable investigation (see the Supporting Information) led to the following optimized conditions, under which **4a** was produced in 63% yield: a catalytic system consisting of $Pd(P^tBu_3)_2$, XPhos, and Cs_2CO_3 in 1,4-dioxane at 100 °C for 12 h under an argon atmosphere. We then explored the substrate scope of this reaction. The alkyl moiety and the two aromatic rings of the substrate could be changed, thus providing a new class of spirocyclobutane-pyrrolines (**4a**–**4q**) (Table 3). The aryl ring

Table 3. Substrate Scope of the Tandem Narasaka–Heck/C(sp^2–H) Activation Reaction[a]



[a]Reaction conditions unless otherwise noted: **3** (0.2 mmol), $Pd(P^tBu_3)_2$ (10 mol %), XPhos (20 mol %), Cs_2CO_3 (2.0 equiv), 1,4-dioxane (2 mL), 100 °C, 12 h, Ar; isolated yields. [b]24 h.

on the oxime ester could be substituted at the *meta*- or *para*-position with a wide scope of functional groups, including electron-donating methyl (**4b**) and methoxy (**4c**) groups and electron-withdrawing trifluoromethyl (**4d** and **4e**) groups. Unfortunately, the reaction of the sterically hindered substrate **3f** did not proceed smoothly, and the expected cascade product **4f** was detected only in trace amounts. However, several polysubstituted reactants (**3g**–**3i**) were perfectly tolerated, affording **4g**–**4i** in 61%, 60%, and 51% yields, respectively. A substrate containing electron-rich naphthalene (**3j**) could also be transformed into the corresponding product. Remarkably, substrate **3k** with spirocyclobutane as the R^7 and R^8 substituents could also cyclize. Substituting the aryl ring on

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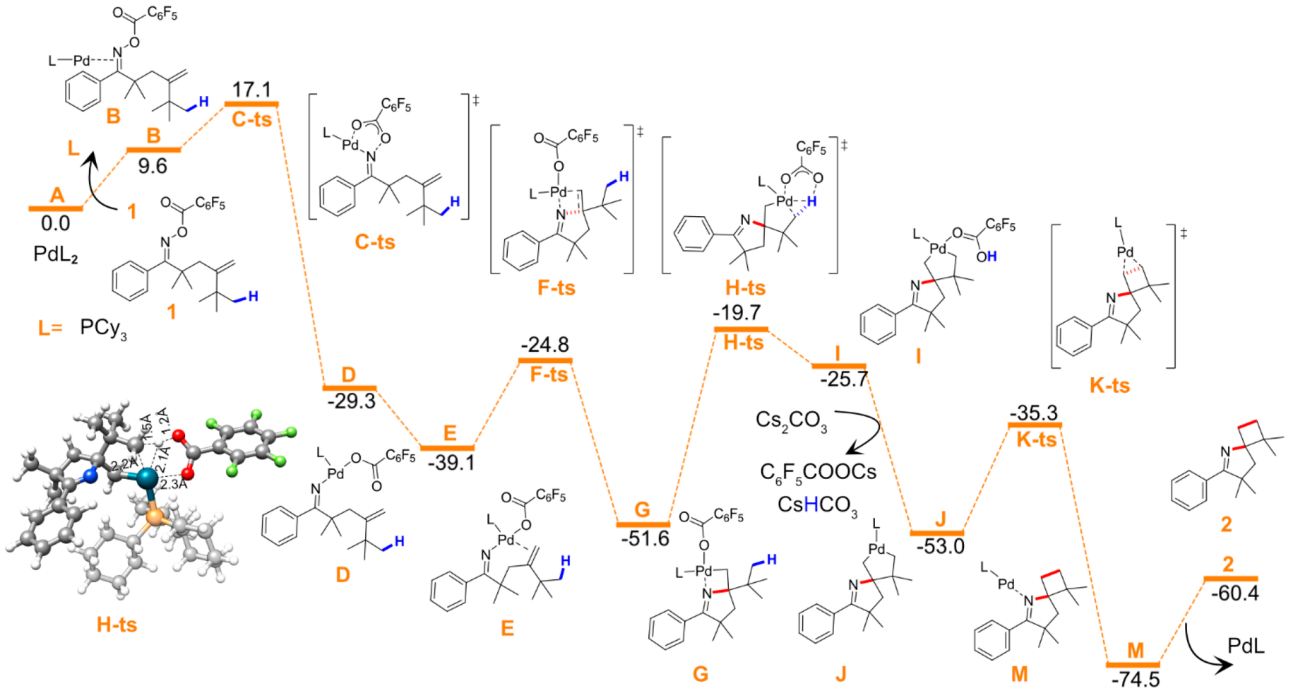


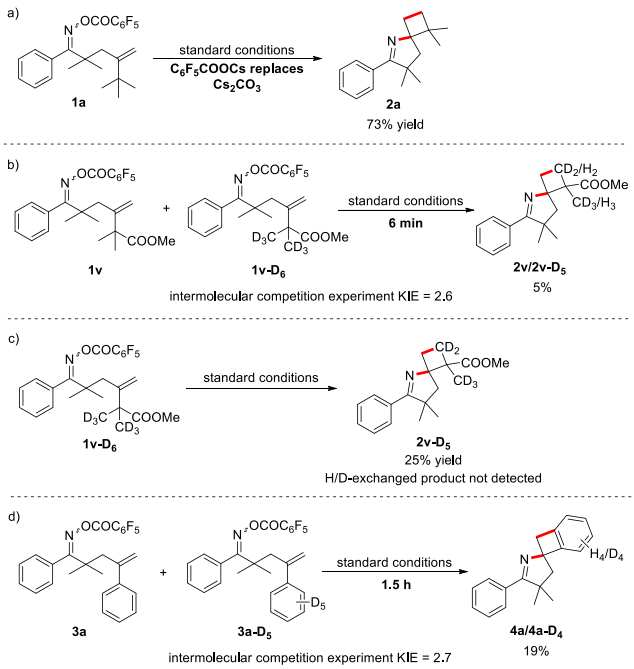
Figure 1. Computed Gibbs free energy profile of the tandem Narasaka–Heck/C(sp^3)–H activation reaction. The relative free energies are presented in kcal mol^{-1}.

the alkene with electron-rich or electron-deficient groups, such as fluoro (**3l** and **3p**), methyl (**3m** and **3n**), methoxy (**3o**) and trifluoromethyl (**3q**) groups, afforded the desired products **4l**–**4q** of the cascade reaction. Subsequently, the structures of **4a** and **4i** were definitively elucidated by X-ray crystal structure analysis (see the Supporting Information).

Computational Studies and Control Experiments. Figure 1 shows the results of DFT calculations that were performed to gain insight into the mechanism of the tandem Narasaka–Heck/C(sp^3)–H activation reaction (see the Supporting Information for details).[24] As shown in Figure 1, coordination of the palladium catalyst to γ,δ-unsaturated oxime ester **1** provides intermediate **B**, which undergoes an oxidative addition process to generate intermediate **D**. Steric hindrance prevents $C_6F_5CO_2^-$ in intermediate **D** from chelating with the palladium center. Subsequently, intermediate **E** undergoes Narasaka–Heck cyclization through transition state **F-ts** with an energy barrier of 14.3 kcal mol^{-1} to form the σ-alkyl-Pd(II) intermediate **G**. Intermediate **G** undergoes concerted metalation-deprotonation (CMD) via transition state **H-ts** with an energy barrier of 31.9 kcal mol^{-1} to produce five-membered spiro-palladacycle intermediate **J**. Then, the reductive elimination of intermediate **J**, which has an energy barrier of 17.7 kcal mol^{-1}, generates intermediate **M**, and the desired product **2** is obtained via the dissociation of complex **M**. In summary, the DFT calculation results indicated that the energy barrier of the entire reaction is 31.9 kcal mol^{-1}, and C(sp^3)–H bond cleavage during CMD is the rate-determining step.

To gain further insight into the reaction mechanism, a series of control experiments was performed (Scheme 2). Considering that CO_3^{2-} from Cs_2CO_3 is also likely to function during the CMD process, we used C_6F_5COOCs instead of Cs_2CO_3 under the standard conditions, and substrate **1a** could be transformed into **2a** in 73% yield (Scheme 2a), which indicated that it might be $C_6F_5COO^-$ rather than CO_3^{2-} that functions as a ligand during the CMD process. Next, an

Scheme 2. Control Experiments



intermolecular competition experiment using equimolar amounts of **1v** and **1v-D_6** gave an intermolecular KIE value of 2.6 (Scheme 2b), suggesting that the cleavage of the C(sp^3)–H bond during the CMD step of the tandem Narasaka–Heck/C(sp^3)–H activation reaction might be the rate-determining step, which is consistent with the results of the computational studies. To probe whether the C(sp^3)–H activation step (intermediate **G** to **I** via **H**-ts) is reversible, which seems possible based on the DFT-calculated energies, a well-designed H/D scrambling experiment was performed with

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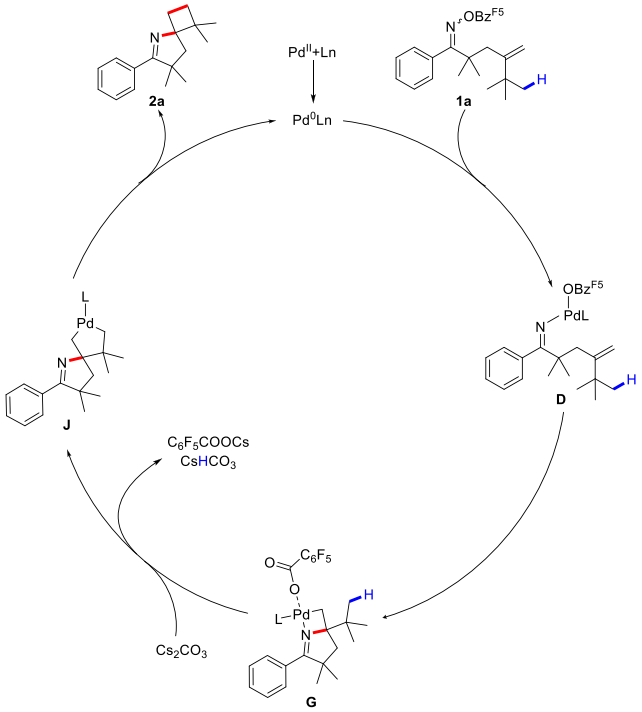
1v-D_6 (Scheme 2c). However, no H/D-exchanged products were detected in the NMR spectrum (see the Supporting Information), probably because the subsequent steps are easier for intermediate **I**. Similarly, intermolecular kinetic experiments with substrates **3a** and **3a-D_5** revealed that C(sp^2)−H bond cleavage is most likely the rate-determining step in the tandem Narasaka−Heck/C(sp^2)−H activation reaction (Scheme 2d).

We proposed a mechanism for the palladium-catalyzed tandem Narasaka−Heck/C(sp^3)−H activation reaction (see Scheme 3) based on the above experimental results and

Scheme 3. Proposed Mechanism of the Palladium-Catalyzed Tandem Narasaka−Heck/C(sp^3)−H Activation Reaction



mechanistic studies, as well as results reported in the literature.[25] Initially, imino-Pd(II) intermediate **D** is formed through the oxidative addition of the in situ generated Pd(0) to γ,δ-unsaturated oxime ester **1**. Then, σ-alkyl-Pd(II) intermediate **G** is generated by an intramolecular Heck cyclization, which cannot undergo β-hydrogen elimination because of the presence of the angular tertiary butyl group. Instead, intermediate **G** undergoes CMD via transition state **H-ts** to produce five-membered spiro-palladacycle intermediate **J**, thus completing the activation of the C(sp^3)−H bond, and the desired product **3** is produced through subsequent reductive elimination.

CONCLUSIONS

In summary, we developed a palladium-catalyzed intramolecular Narasaka−Heck/C(sp^3 or sp^2)−H activation cascade reaction, which is an economically efficient protocol for assembling highly strained spirocyclobutane-pyrrolines. This reaction represents the first case of using the σ-alkyl-Pd(II) intermediate of Narasaka−Heck cyclization for intramolecular C(sp^3 or sp^2)−H activation. Remarkably, the key step of this reaction requires the activation of δ-C(sp^3 or sp^2)−H bonds by the in situ-generated σ-alkyl-Pd(II) species to form a five-membered spiro-palladacycle intermediate. The reaction has a wide substrate scope, and the product yield is as high as 80%. A series of computational studies and control experiments provided some insights into the reaction mechanism, which should facilitate the development of novel catalytic domino reactions for challenging diverse C−H functionalization procedures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04114.

Experimental procedures, compound characterization, and NMR spectra (PDF)

Accession Codes

CCDC 2050684, 2050686, and 2050688−2050689 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Yong-Min Liang − *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China;* orcid.org/0000-0001-8280-8211; Email: liangym@lzu.edu.cn

Authors

Wan-Xu Wei − *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

Yuke Li − *Department of Chemistry and Centre for Scientific Modeling and Computation, Chinese University of Hong Kong, Shatin, Hong Kong, China*

Ya-Ting Wen − *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

Ming Li − *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

Xue-Song Li − *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

Cui-Tian Wang − *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

Hong-Chao Liu − *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

Yu Xia − *Urumqi Key Laboratory of Green Catalysis and Synthesis Technology, College of Chemistry, Xinjiang University, Urumqi 830046, P.R. China*

Bo-Sheng Zhang − *College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, P.R. China;* orcid.org/0000-0003-1148-0065

Rui-Qiang Jiao − *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c04114

Author Contributions

‡W.-X.W. and Y.L. contributed equally to this work.

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Notes

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