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Regioselective synthesis of spirocyclic pyrrolines *via* a palladium-catalyzed Narasaka–Heck/C–H activation/[4 + 2] annulation cascade reaction†

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A novel palladium-catalyzed spirocyclization through sequential Narasaka–Heck cyclization, C–H activation and [4 + 2] annulation has been developed. In this reaction, cheap and readily available 2-chlorobenzoic acid or ethyl phenylpropiolate was employed as the C2 insertion unit to react with γ,δ-unsaturated oxime ester. The key step in this transformation is the regioselective insertion of the C2 synthon into the spiro-palladacycle intermediate that is formed by the δ-C–H activation process, thereby efficiently assembling a series of spirocyclic pyrrolines with high regiocontrol. Furthermore, density functional theory (DFT) calculations and control experiments were performed to gain some insights into the reaction mechanism.

Introduction

In the past few decades, palladium-catalyzed inert C–H bond activation, as an extremely powerful tool for constructing useful compounds, including industrial materials, pharmaceuticals and natural products, has experienced tremendous developments due to its high atom- and step-economy.[1–11] Many of the pioneering studies on palladium-catalyzed directing-group-assisted C–H activation have been widely investigated.[12–18] Moreover, palladium-catalyzed intramolecular Heck-type cyclization/C–H activation cascade reactions, as a complementary strategy for the remote C–H bond activation, were also extensively reported.[19,20] In 1994, Grigg and co-workers for the first time discovered that the *in situ* generated transient σ-alkyl-Pd(II) intermediate of Heck cyclization could activate the remote C–H bond to construct palladacycle, and its direct reductive elimination forms spiro-heterocycles.[21,22] This efficient strategy represents an elegant means to complex carbocyclic and heterocyclic molecular frameworks in one step from well-designed starting materials.[23–30] Afterward, other conversion methods of palladacycle, including [1,4]-Pd shift[31–35] and coupling reagent capture,[36–42] have also been developed to furnish various polycyclic compounds. However, direct reductive elimination and [1,4]-Pd shift conversions of palladacycle rely on the inherent C–H bonds as the terminal functional group, thus leading to poor product diversity. The palladacycle capture strategy has been drawing significant attention because various external reagents could be introduced by trapping palladacycle. Despite great progress, such domino reactions of the capturing strategy are usually initiated by the oxidative addition of palladium to aryl halogens in most cases; in contrast, other triggering modes remain underdeveloped. To the best of our knowledge, the regioselective insertion of unsymmetrical synthons into the palladium center is difficult to control, yielding mainly inseparable isomeric mixtures.[43–50]

In 1999, Narasaka and co-workers for the first time reported a palladium catalyzed cyclization of γ,δ-unsaturated oxime ester, namely the Narasaka–Heck reaction,[51–53] which is an efficient method for synthesizing pyrrole. Subsequently, this kind of reaction was widely used to establish structurally diverse N-heterocyclic compounds,[54–57] such as imidazoles,[58] pyridines,[59–61] indoles[62] and isoquinolines.[63,64] What is more, Bower,[65–69] Zhu,[70] Tong[71] and other groups[72–75] extensively synthesized functionalized pyrrolines by using nucleophiles to trap the σ-alkyl-Pd(II) intermediate of the Narasaka–Heck cyclization. In addition, our group reported the synthesis of polyfluorophenylated pyrrolines by using the $C_6F_5CO_2^-$ leaving group as the $C_6F_5^-$ source *via* its decarboxylation.[76] Altogether, previous reports about the Narasaka–Heck reaction mainly focused on σ-alkyl-Pd(II) intermediate nucleophile trapping and β-hydrogen elimination. Recently, our group made a significant breakthrough, synthesizing a series of highly strained spirocyclobutane-pyrrolines through a Narasaka–Heck/C–H

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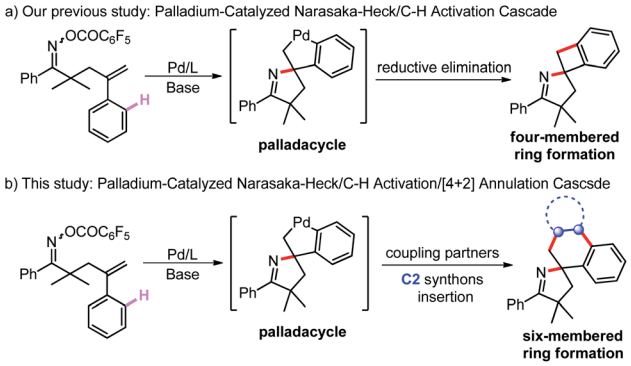


Scheme 1 (a) Our previous study; (b) this study.

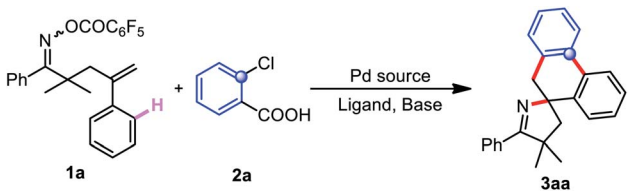
activation cascade reaction (Scheme 1a), which is the first case of using the σ-alkyl-Pd(II) intermediate from Narasaka–Heck cyclization for intramolecular C–H activation.[77] Despite numerous achievements, the ring size of spirocyclic pyrrolines is limited. Consequently, methods to obtain more diverse spirocyclic pyrrolines are highly desirable, which can be accomplished *via* employing external reagents to capture the palladacycle from Narasaka–Heck/C–H activation cascade.

While the efficient synthesis of various spirocyclic pyrrolines through the domino Narasaka–Heck/C–H activation reaction has been reported, the ring size is limited to a four-membered ring. There is an urgent need for methods to access more diverse spirocyclic products, which are regarded as significant scaffolds in drug discovery and development.[78–82] Inspired by these causes and our interest in tandem reactions involving palladacycles, we envisioned that a spiropalladacycle formed by the Narasaka–Heck/C–H activation cascade could be trapped by the C2 synthon (Scheme 1b), and its insertion leads to the formation of a six-membered ring.

Results and discussion

For the insertion of an aromatic ring, cheap and readily available 2-chlorobenzoic acid, in sharp contrast to the unselective insertion of aryne or aryl halide, inserts into palladacycle with high regioselectivity because the palladacycle reacts with 2-chlorobenzoic acids through two sequential C–C cross-couplings, and two C–C bonds are formed with excellent chemoselectivity.[83–90] Consequently, we commenced our initial investigation by employing γ,δ-unsaturated oxime ester **1a** and 2-chlorobenzoic acid **2a** as the model substrates (Table 1). Fortunately, the anticipated domino reaction of **1a** and **2a** was conducted in the presence of $Pd(OAc)_2$, P(*p*-Tol)$_3$ and K_2CO_3 in DMF at 140 °C for 12 h under an argon atmosphere, generating the desired product **3aa** in 15% yield (Table 1, entry 1). Given the previous literature reporting that *n*-Bu_4NCl probably activate and stabilize palladium complexes,[91–94] we added *n*-Bu_4NCl (2.0 equiv.) to the reaction system and found that the extra addition of *n*-Bu_4NCl do have a positive effect on the conversion (Table 1, entry 2). Further examination of the bases, such as Cs_2CO_3, Rb_2CO_3 and K_3PO_4, showed that Rb_2CO_3 was the most

Table 1 Condition optimization for the reaction of γ,δ-unsaturated oxime ester and 2-chlorobenzoic acid[a]



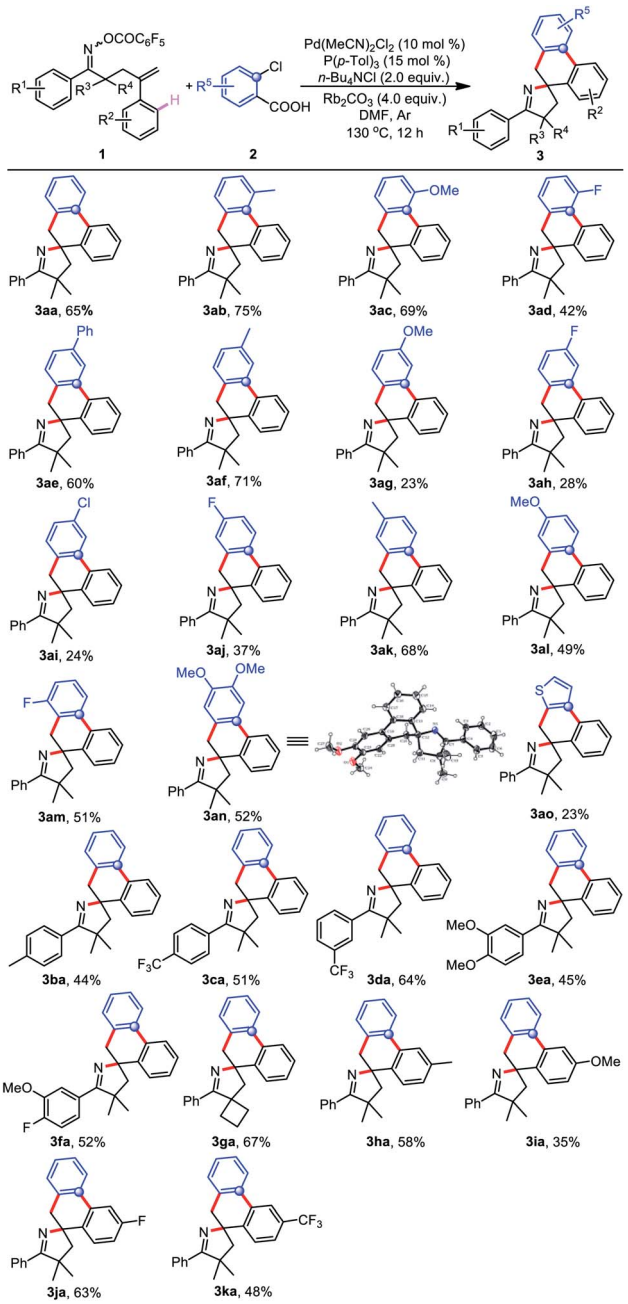
Entry	Pd	Ligand	Base	Yield (%)
1[b]	$Pd(OAc)_2$	P(*p*-Tol)$_3$	K_2CO_3	15
2	$Pd(OAc)_2$	P(*p*-Tol)$_3$	K_2CO_3	31
3	$Pd(OAc)_2$	P(*p*-Tol)$_3$	Cs_2CO_3	34
4	$Pd(OAc)_2$	P(*p*-Tol)$_3$	Rb_2CO_3	40
5	$Pd(OAc)_2$	P(*p*-Tol)$_3$	K_3PO_4	7
6	$Pd(OAc)_2$	P(*o*-Tol)$_3$	Rb_2CO_3	Trace
7	$Pd(OAc)_2$	P(4-OMe-Ph)$_3$	Rb_2CO_3	39
8	$Pd(OAc)_2$	PPh_3	Rb_2CO_3	21
9	$Pd(OAc)_2$	P(2-furan)$_3$	Rb_2CO_3	Trace
10	$Pd(PPh_3)_2Cl_2$	P(*p*-Tol)$_3$	Rb_2CO_3	36
11	$Pd(dba)_2$	P(*p*-Tol)$_3$	Rb_2CO_3	34
12	$Pd(MeCN)_2Cl_2$	P(*p*-Tol)$_3$	Rb_2CO_3	52
13	$Pd(TFA)_2$	P(*p*-Tol)$_3$	Rb_2CO_3	31
14[c]	$Pd(MeCN)_2Cl_2$	P(*p*-Tol)$_3$	Rb_2CO_3	64
15[c,d]	$Pd(MeCN)_2Cl_2$	P(*p*-Tol)$_3$	Rb_2CO_3	65

[a] Reaction conditions unless otherwise noted: **1a** (0.2 mmol), **2a** (0.3 mmol), Pd (10 mol%), ligand (15 mol%), base (4.0 equiv.), *n*-Bu_4NCl (2.0 equiv.), DMF (2 mL), 140 °C, 12 h, Ar; isolated yields. [b] No *n*-Bu_4NCl. [c] **1a** (0.3 mmol), **2a** (0.2 mmol). [d] 130 °C.

effective in terms of yield (Table 1, entries 3–5). Using other ligands, including P(*o*-Tol)$_3$, P(4-OMe-Ph)$_3$, PPh_3, and P(2-furan)$_3$, did not improve the yield (Table 1, entries 6–9). Next, after careful screening of palladium sources (Table 1, entries 10–13), $Pd(MeCN)_2Cl_2$ turned out to be the optimal choice. Gratifyingly, the yield was dramatically improved by meticulous fine-tuning of the substrate stoichiometry (Table 1, entry 14). Eventually, reducing the reaction temperature displayed better efficiency, improving the isolated yield of **3aa** to 65% (Table 1, entry 15).

With the optimized reaction conditions in hand (Table 1, entry 15), we examined the generality of this reaction (Table 2). The regioselectivity was initially investigated by testing a variety of 2-chlorobenzoic acid derivatives. As shown in Table 2, the reactions of a series of 2-chlorobenzoic acids **2b–o** with 1a yielded the desired products **3ab–3ao** with complete regioselectivity. Substrates with a methyl (**2b**), methoxy (**2c**) or fluoro (**2d**) group at the 3-position could efficiently couple with **1a**, despite steric hindrance, yielding the corresponding products (**3ab–3ad**) with perfect regiocontrol. Furthermore, a range of functional groups at the 4-position of 2-chlorobenzoic acid could all survive, furnishing spirocyclic products **3ae–ah**. It is worth noting that the second chloro group of substrate **2i** remained intact during this conversion, albeit with a decreased yield (**3ai**). This protocol was also applicable to 5-substituted 2-chlorobenzoic acids to afford products **3aj–al**. To our delight,

Table 2 Substrate scope for the reaction of γ,δ-unsaturated oxime esters and 2-chlorobenzoic acids[a]

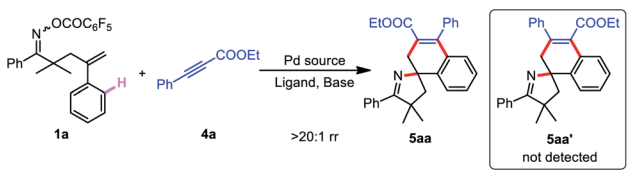


[a] Reaction conditions unless otherwise noted: **1** (0.3 mmol), **2** (0.2 mmol), $Pd(MeCN)_2Cl_2$ (10 mol%), P(*p*-Tol)$_3$ (15 mol%), Rb_2CO_3 (4.0 equiv.), *n*-Bu_4NCl (2.0 equiv.), DMF (2 mL), 130 °C, 12 h, Ar; isolated yields.

the reaction of the sterically hindered substrates **2m** with **1a** successfully gave **3am** in 51% yield. Pleasingly, di- and thiophen-substituted reactants were converted into **3an** and **3ao** *via* this protocol, respectively; the spirocyclic structure of **3an** was definitively elucidated by X-ray crystal structure analysis (see the ESI†). Subsequently, the scope of γ,δ-unsaturated oxime esters **1** was evaluated. The γ,δ-unsaturated oxime esters **1b–d** substituted with electron-donating methyl or electron-withdrawing trifluoromethyl groups at the *para*- or *meta*-position of the aromatic ring on the oxime ester showed good reactivity in this conversion, and provided the corresponding products (**3ba–3da**) in 44–64% yields. As expected, disubstituted substrates **1e** and **1f** could also be subjected to the tandem cyclization with **2a**. In addition, the reactant **1g** bearing a spirocyclobutyl moiety also exhibited high reactivity, and **3ga** was obtained in 67% yield. Similarly, substituting the aryl ring on the alkene with electron-rich or electron-deficient groups, such as methyl (**1h**), methoxy (**1i**), fluoro (**1j**) and trifluoromethyl (**1k**), delivered the desired products **3ha–3ka** of the cascade reaction with **2a**.

Inspired by the above results, we next turned our attention to probing the feasibility of employing cheap and readily accessible ethyl phenylpropiolate as the C2 synthon.[95,96] We began our studies by investigating the reaction of γ,δ-unsaturated oxime ester **1a** and ethyl phenylpropiolate **4a**. It is satisfactory that the target product **5aa** was obtained in 53% yield and more than 20 : 1 ratio of regioisomers (rr) in a catalytic system consisting of $Pd(PPh_3)_4$ and Cs_2CO_3 in dioxane at 100 °C for 22 h (Table 3, entry 1). Further exploration of the solvent showed that toluene was the optimal choice (Table 3, entries 2–4). Next, various combinations of palladium sources and ligands were carefully screened (Table 3, entries 5–7), and $Pd(PPh_3)_4$ was identified as the most suitable catalyst. Using other bases, such as K_2CO_3, Na_3PO_4, K_3PO_4, NaOAc and PhCOOK, did not improve the yield (Table 3, entries 8–12). Subsequently, the structure of **5aa** was definitively elucidated by X-ray crystal structure analysis (see the ESI†).

Table 3 Condition optimization for the reaction of γ,δ-unsaturated oxime ester and ethyl phenylpropiolate[a]

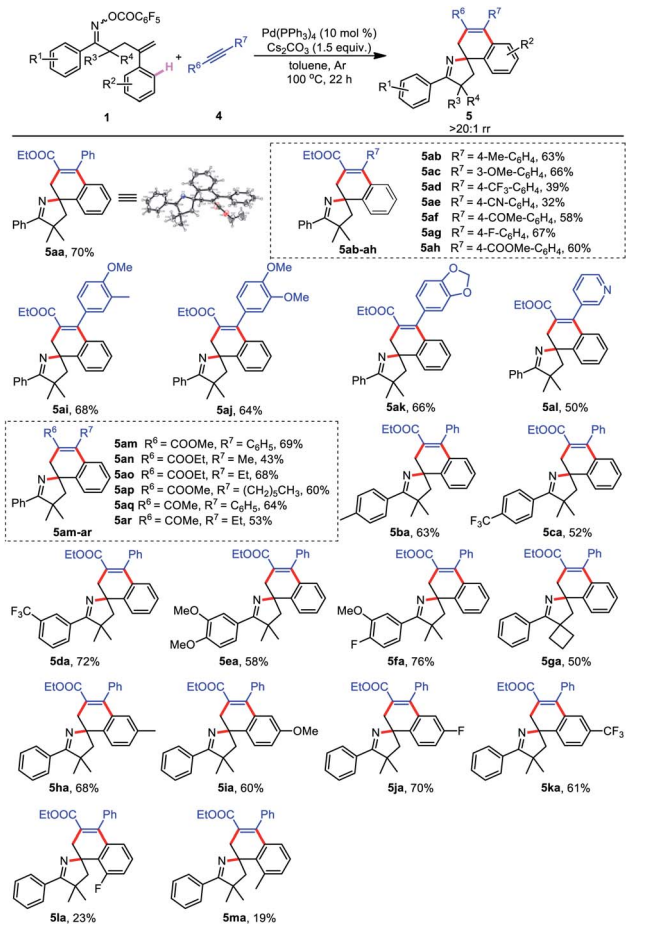


Entry	Pd/ligand	Base	Solvent	Yield (%)
1	$Pd(PPh_3)_4$/—	Cs_2CO_3	Dioxane	53
2	$Pd(PPh_3)_4$/—	Cs_2CO_3	MeCN	37
3	$Pd(PPh_3)_4$/—	Cs_2CO_3	DCE	Trace
4	$Pd(PPh_3)_4$/—	Cs_2CO_3	Toluene	70
5	$Pd(OAc)_2$/PPh_3	Cs_2CO_3	Toluene	47
6	$Pd(OAc)_2$/XPhos	Cs_2CO_3	Toluene	33
7	$Pd(PPh_3)_4$/$PCy_3 \cdot HBF_4$	Cs_2CO_3	Toluene	68
8	$Pd(PPh_3)_4$/—	K_2CO_3	Toluene	45
9	$Pd(PPh_3)_4$/—	Na_3PO_4	Toluene	33
10	$Pd(PPh_3)_4$/—	K_3PO_4	Toluene	44
11	$Pd(PPh_3)_4$/—	NaOAc	Toluene	38
12	$Pd(PPh_3)_4$/—	PhCOOK	Toluene	25

[a] Reaction conditions unless otherwise noted: **1a** (0.2 mmol), **4a** (0.4 mmol), Pd (10 mol%), ligand (20 mol%), base (1.5 equiv.), solvent (2 mL), 100 °C, 22 h, Ar; isolated yields; rr values were determined by ^1H NMR.

After identifying the optimal reaction conditions, we set out to investigate the substrate scope of this cascade reaction. As shown in Table 4, both substrates **1** and **4** can be changed, thus constructing a new class of spirocyclic pyrrolines (**5aa–ma**). To assess the influence of **4a** electronic effects on the reaction outcomes, a wide scope of functional groups, including electron-donating methyl (**4b**) and methoxy (**4c**) groups and electron-withdrawing trifluoromethyl (**4d**), cyano (**4e**), acetyl (**4f**), fluoro (**4g**), and ester (**4h**) groups were introduced into the aryl ring of **4a**, and all were well tolerated. In addition, several disubstituted substrates (**4i–k**) also performed well. The pyridine-substituted product **5al** was generated in 50% yield, indicating the compatibility of the heterocycle. Moreover, methyl phenylpropiolate **4m** was also a viable coupling partner of **1a** to provide **5am** in 69% yield. When R^7 was not an aromatic ring but an alkyl group, spirocyclic products **5an–ap** were still successfully synthesized. Gratifyingly, substitution of the ester with ketone did not impede the generation of **5aq** and **5ar**. Satisfactorily, both single and double substituents of the aryl ring on oxime ester were subjected to the optimal conditions, delivering the target products **5ba–fa** in 52–76% yield. Remarkably, substrate **1g** with spirocyclobutane as the R^3 and R^4 substituents could also cyclize with **4a**. Furthermore, reactants (**1h–m**) bearing various functional groups of the aryl ring on the alkene could participate in the spirocyclization with **4a**.

Table 4 Substrate scope for the reaction of γ,δ-unsaturated oxime esters and alkynes[a]



[a] Reaction conditions unless otherwise noted: **1** (0.2 mmol), **4** (0.4 mmol), $Pd(PPh_3)_4$ (10 mol%), Cs_2CO_3 (1.5 equiv.), toluene (2 mL), 100 °C, 22 h, Ar; isolated yields.

A series of mechanistic studies were then conducted. First, to probe the regioselective insertion of ethyl phenylpropiolate **4a** into spiropalladacycle **C** and the potential side reaction of intermediate **C**, DFT calculations were performed (see the ESI† for details).[97] As shown in Fig. 1, the energy barrier for the direct reductive elimination of spiropalladacycle **C** is much higher than that for the migratory insertion of **4a**, so the direct reductive elimination of **C** would not occur in this reaction. In addition, the calculated energy-difference between the corresponding transition states (**J-TS** and **J-TS′**) for the two insertion patterns of ethyl phenylpropiolate favors the formation of **5aa** other than **5aa′**, which is responsible for the high rr value of **5aa**. What is more, a series of control experiments were performed to explore whether the C–H activation process is the rate-determining step in this transformation. The intermolecular competition reaction (Scheme 2a) of equimolar **1a** and **1a-D_5** with **2a** gave an intermolecular KIE value of 4.4, suggesting that the cleavage of the C–H bond during the CDM step of the tandem Narasaka–Heck/C–H activation/decarboxylation reaction is the rate-determining step. Similarly, the intermolecular competition experiment (Scheme 2b) of **1a**, **1a-D_5** and **4a** also revealed that the C–H bond cleavage might be the rate-determining step for the reaction of γ,δ-unsaturated oxime esters and alkynes.

On the basis of our experimental results and previous reports, a plausible catalytic cycle of this cascade reaction is illustrated in Scheme 3. Initially, oxidative addition of the Pd(0) to γ,δ-unsaturated oxime ester **1a** followed by Narasaka–Heck type cyclization forms the σ-alkyl-Pd(II) intermediate **B**, which

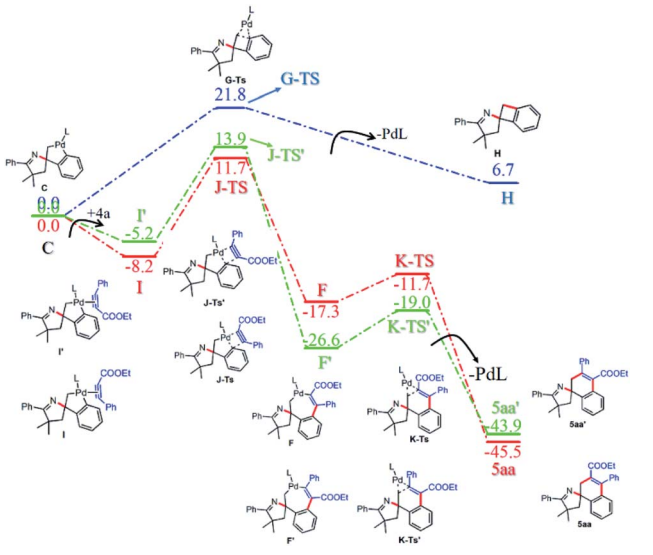
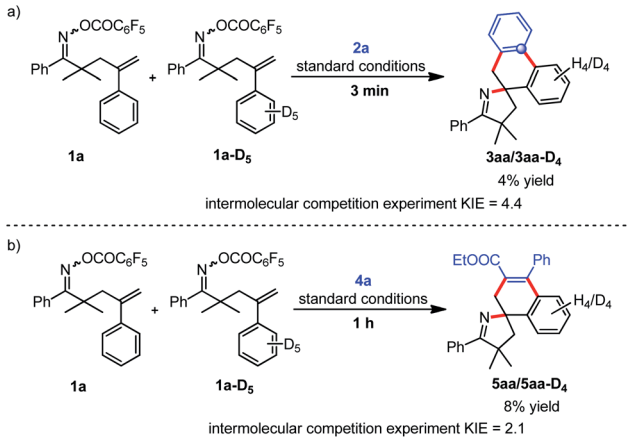
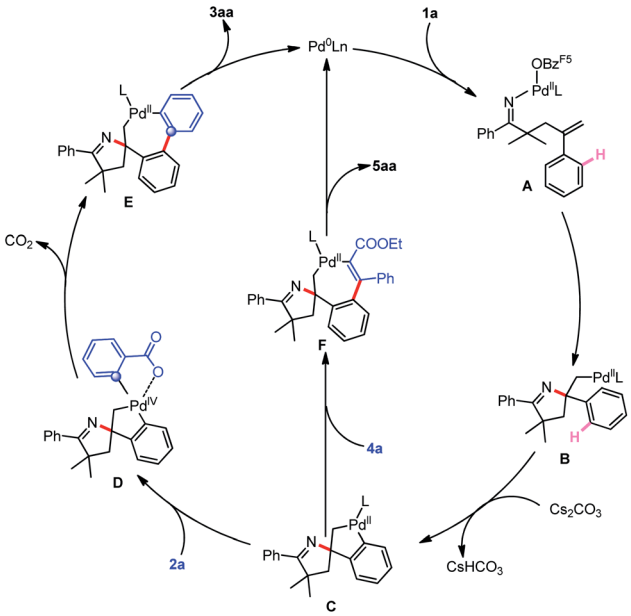


Fig. 1 Free energy profile for the migratory insertion step with ethyl phenylpropiolate **4a** and the direct reductive elimination of spiropalladacycle **C** (L = PPh_3). The relative free energies are presented in kcal mol^{-1}.



Scheme 2 Control experiments, (a) kinetic isotope effect experiment of **1a** and **1a-D$_5$** with **2a**; (b) kinetic isotope effect experiment of **1a** and **1a-D$_5$** with **4a**.



Scheme 3 Proposed mechanism.

undergoes intramolecular C–H activation to generate spiropalladacycle(II) **C**. Then, when 2-chlorobenzoic acid **2a** is employed as the C2 synthon, spiropalladacycle(II) **C** transforms into palladacycle(IV) species **D** by the second oxidative addition to the C–Cl bond of **2a** with the assistance of an *ortho*-chelating carboxyl group, whose sequential reductive elimination and decarboxylation produces intermediate **E**, and the two sequential C–C cross-couplings are the key to the regioselective introduction of an aromatic ring. Eventually, target product **3aa** and Pd(0) species are delivered by the reductive elimination of intermediate **E**. Alternatively, for the reaction with ethyl phenylpropiolate **4a**, the regioselective migratory insertion of **4a** into spiropalladacycle **C** forms intermediate **F**, and its reductive elimination generates the final product **5aa** and Pd(0).

Conclusions

In conclusion, we developed a palladium-catalyzed Narasaka–Heck/C–H activation/[4 + 2] annulation cascade reaction, in which cheap and readily available 2-chlorobenzoic acid or ethyl phenylpropiolate is employed as the C2 insertion unit to react with γ,δ-unsaturated oxime ester. Remarkably, the highly regioselective insertion of the C2 synthon into the spiropalladacycle intermediate that is formed by δ-C–H activation is the key step in this transformation, thus providing a novel means for efficiently assembling a range of spirocyclic pyrrolines with high regiocontrol. What is more, DFT calculations revealed that the energy-difference between the corresponding transition states for the two insertion patterns of ethyl phenylpropiolate is the reason for the high rr value of **5aa**. And further control experiments suggested that the cleavage of the C–H bond is the rate-determining step in this reaction.

Data availability

All data associated with this study are available in the article and ESI.†

Author contributions

W.-X. W. performed the methodology, synthesis, characterization, and analysis, and wrote the manuscript. X. K. and Y. L. carried out the calculation studies. R.-Q. J., X.-S. L., and C.-T. W. revised the manuscript. Y.-M. L. designed the project and supervised the whole experiment. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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