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Pd-Catalyzed Intramolecular C−N Bond Cleavage, 1,4-Migration, sp^3 C−H Activation, and Heck Reaction: Four Controllable Diverse Pathways Depending on the Judicious Choice of the Base and Ligand

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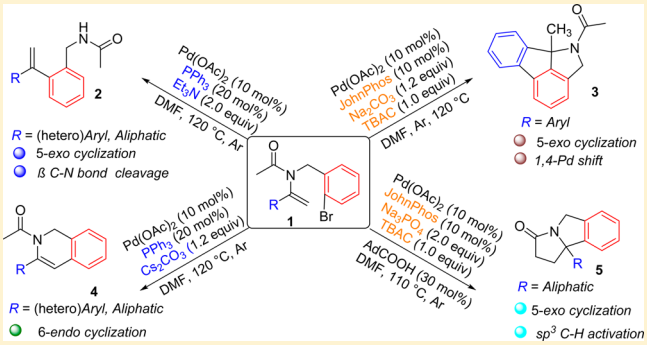
Supporting Information

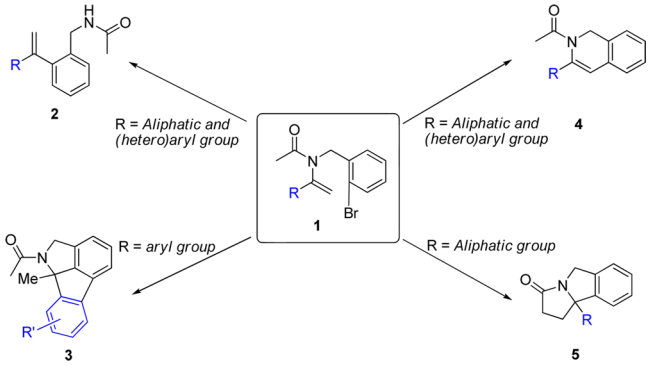
ABSTRACT: Diverse and controllable pathways induced by palladium-catalyzed intramolecular Heck reaction of *N*-vinylacetamides for the synthesis of nitrogen-containing products in reasonable to high yields via tuning the phosphine ligands and bases are reported. Domino reactions including unique *β*-N−Pd elimination, 1,4-Pd migration, or direct acyl C−H bond functionalization were found to be involved forming different products, respectively. Given the ability of using the same starting material to generate diverse products via completely different chemoselective processes, these current methodologies offer straightforward access to valuable nitrogen-containing products under mild reaction conditions as well as inspire the discovery of novel reactions.



INTRODUCTION

Due to their diverse and efficient catalytic performance, palladium catalysts have been used widely in various coupling reactions to forge new C−C or C−heteroatom bonds for rapid access to complex and useful molecules.[1] In recent years, there has been a great interest in the use of transient palladium complexes generated in a Heck reaction for domino reactions to construct complex polycycles.[2] This transient palladium complex may be involved in *β*-elimination,[3] sp^3 or sp^2 C−H bond functionalization,[4] 1,4-migration,[5] to yield complex structures. In light of our interest in the use of transient palladium intermediates for domino reactions and our previously reported works on direct functionalization of *N*-vinylacetamides,[6] we studied the palladium-catalyzed transformation of vinylacetamide derivative **1**. To our surprise, we found that the reaction can furnish either the 1,1′-disubstituted ethylene derivative **2**, the 2-azabicyclo[3,3,0]octadiene derivative **3**, isoquinoline derivatives **4** or 5/5/6-membered pyrroloisoindolone derivative **5** depending on the ligand and base used in the reaction (Scheme 1). Therefore, the realization of a very rare *β*-N−Pd elimination pathway and the divergent routes leading to different products from the same starting material with high selectivity is the subject of current work.

Scheme 1. Palladium-Catalyzed Diverse Synthetic Pathways from *N*-(2-Bromobenzyl)-*N*-(1-phenylvinyl)acetamide 1



RESULTS AND DISCUSSION

Optimization of Palladium-Catalyzed Controllable Diverse N-Containing Compounds. Initially, we examined the reaction of *N*-(2-bromobenzyl)-substituted vinylacetamide **1a** under Heck reaction conditions by using $Pd(OAc)_2$ and triphenylphosphine catalytic system with K_2CO_3. It was found that products **2a** and **3a** were obtained (determined by ^1H NMR spectrum) along with the formation of 6-*endo* product **4a** (Table 1, entry 3).[7] However, the direct use of $Pd(PPh_3)_4$ or the combination of $Pd(PhCN)_2Cl_2$ with PPh_3 (Table 1, entry 4 and 5, respectively) did not yield any of the desired products.

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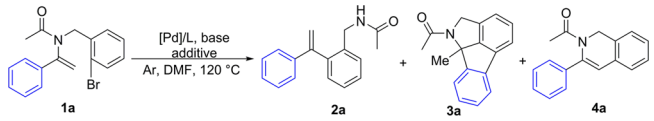
Table 1. Optimization of Catalytic Conditions[a]



entry	catalyst (10 mol %)	ligand (mol %)	base (equiv)	additive (equiv)	2a[b] (%)	3a[b] (%)	4a[b](%)
1	none	PPh_3 (20)	K_2CO_3(1.2)	none	0	0	0
2	$Pd(OAc)_2$	PPh_3 (20)	none	none	0	0	0
3	$Pd(OAc)_2$	PPh_3 (20)	K_2CO_3(1.2)	none	4	40	56
4	$Pd(PPh_3)_4$	none	K_2CO_3(1.2)	none	0	0	0
5	$Pd(PhCN)_2Cl_2$	PPh_3 (20)	K_2CO_3(1.2)	none	trace	trace	10
6[c]	$Pd(OAc)_2$	PPh_3 (20)	Et_2NH (2.0)	none	20	0	0
7[c]	**$Pd(OAc)_2$**	**PPh_3** (20)	**Et_3N (2.0)**	**none**	**90(80)**	**0**	**0**
8[c]	$Pd(OAc)_2$	PPh_3 (20)	DBU (2.0)	none	16	0	0
9[c]	$Pd(OAc)_2$	PCy_3(20)	Et_3N (2.0)	none	11	0	0
10[c]	$Pd(OAc)_2$	dppb(10)	Et_3N (2.0)	none	23	0	0
11	$Pd(OAc)_2$	dppb(10)	K_2CO_3(1.2)	none	4	38	54
12	$Pd(OAc)_2$	XantPhos(10)	K_2CO_3(1.2)	none	3	43	52
13	$Pd(OAc)_2$	Johnphos (20)	K_2CO_3(1.2)	none	5	45	50
14	$Pd(OAc)_2$	Johnphos (30)	K_2CO_3(1.2)	none	4	47	47
15	$Pd(OAc)_2$	Johnphos (10)	K_2CO_3(1.2)	none	3	54	43
16	$Pd(OAc)_2$	Johnphos (10)	K_3PO_4(1.2)	none	18	48	33
17	$Pd(OAc)_2$	Johnphos (10)	Ag_2CO_3(1.2)	none	0	0	0
18	$Pd(OAc)_2$	Johnphos (10)	Na_2CO_3(1.2)	none	19	55	9
19	$Pd(OAc)_2$	Johnphos (10)	Na_2CO_3(1.2)	PivOH(0.3)	16	62	18
20	**$Pd(OAc)_2$**	**Johnphos (10)**	**Na_2CO_3(1.2)**	**TBAC(1.0)**	**10**	**76 (75)**	**trace**
21	$Pd(OAc)_2$	Johnphos (10)	Na_2CO_3(1.2)	TBAB(1.0)	16	62	18
22	**$Pd(OAc)_2$**	**PPh_3** (20)	**Cs_2CO_3(1.2)**	**none**	**10**	**trace**	**71(68)**

[a]Reaction conditions: To a mixture of 0.2 mmol **1a**, catalyst, ligand, base, and additive was added anhydrous DMF (2 mL) and allowed to stir for 24 h at 120 °C under argon atmosphere. [b]Yield was determined by ^1H NMR using phenyltrimethylsilane as internal standard; isolated yields are shown in parentheses. [c]Reaction conditions: To a mixture of 0.3 mmol **1a**, catalyst, ligand, base and additive was added DMF (5 mL).

Different bases were tested to adjust the chemoselectivity of this reaction. To our delight, when triethylamine was applied, product **2a** was exclusively obtained (Table 1, entry 7).

Next, we sought for appropriate reaction conditions to improve the yield of product **3a**. It was found that organic bases do not favor the latter transformation even though different phosphine ligands were tested. In the presence of the inorganic base K_2CO_3 and bulky phosphine ligands, the formation of **3a** was facilitated (Table 1, entries 11−15). When Na_2CO_3 was used as base, the yield of **3a** was increased to 55% along with the formation of **2a** and **4a** as the side products (Table 1, entry 18). After much screening, product **3a** could be isolated in 75% yield when *tetra*-butyl-ammonium chloride (TBAC) was introduced as additive (Table 1, entry 20). Other additives such as *tetra*-butyl-ammonium bromide (TBAB) or PivOH did not improve the efficiency of this transformation (Table 1, entries 19 and 21). Finally, it was found that the combination of PPh_3 and Cs_2CO_3 would greatly favor the formation of product **4a** (Table 1, entry 22).

***β*-N−Pd Elimination for the Synthesis of 1,1′-Disubstituted Ethylene Derivatives.** The difficulty of controlling the regioselectivity of traditional Mizoroki−Heck reactions between common alkenes and organic (pseudo)-halides for the synthesis of 1,1′-disbstituted ethylenes has been known to be a challenging task.[8] Only few examples for highly regioselective intermolecular Mizoroki−Heck reactions have been successfully achieved.[9] However, to the best of our knowledge, there has been no example reported on the intramolecular Heck coupling pathway to access 1,1′-disubstituted alkenes via a vinyl C−N bond cleavage. With the optimal reaction conditions in hand (Table 1, entry 7), the scope of the palladium-catalyzed intramolecular Heck reaction-induced domino reaction for the synthesis of 1,1′-disubstituted ethylenes was investigated. Various 1,1′-disubstituted alkenes products are summarized in Table 2. As shown, the tolerance scope of R^1 group was first examined. The reaction of phenyl-substituted *N*-vinylacetamides with an electron-donating or electron-withdrawing group at *meta*- or *para*-position could all afford the desired products in good yields (Table 2, entries **2a**−**2j**). Especially, halogen substituents on the benzene ring do not affect the Heck reaction's selectivity which permits further functionalization of products (Table 2, entries **2f**−**2h**). However, only a 40% yield was obtained when a methyl group was installed at the *ortho*-position (Table 2, entry **2b**). Heteroaryl such as furyl or thioenyl substituted *N*-vinyl-acetamides both performed well in this reaction, giving the products in 61 and 67% yields, respectively (Table 2, entries **2k** and **2l**), while the product was obtained in 49% yield when benzofuran-substituted *N*-vinylacetamide was used in the reaction (Table 2, entry **2m**). When the *para*-toluenesulfonyl protected indole-substituted substrate was employed, the desired product was generated in a 31% yield (Table 2, **2n**). Notably, R^1 group could be extended to aliphatic substituents, the more bulky cyclohexyl- and *tert*-butyl-substituted *N*-vinylacetamides also worked well in this reaction to give the corresponding products in moderate yields (Table 2, entries **2o** and **2p**). Subsequently, we turned our attention to test the scope of bromo-substituted groups. It was observed that the substrate with electron-donating group favors a higher yield of the product than that with Cl-substituent (Table 2, entries **2q**-

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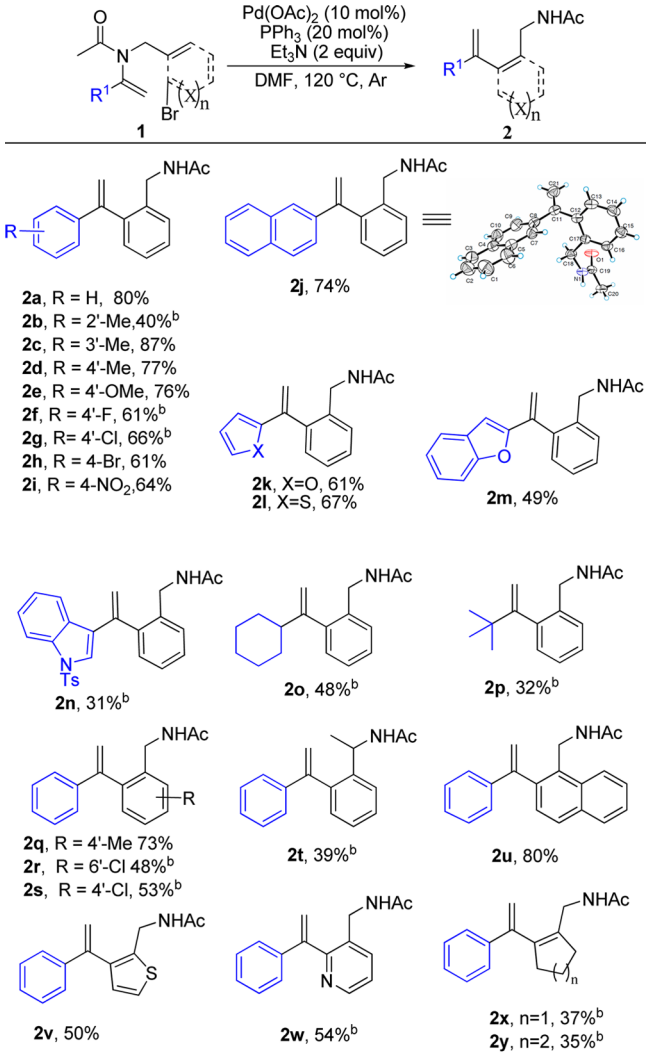
Table 2. Synthesis of 1,1′-Disubstituted Ethylene Derivatives from *N*-Vinylacetamides Catalyzed by Palladium[a]

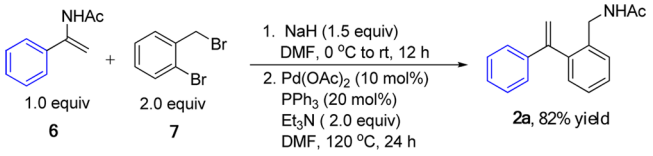


[a]Unless noted, the reaction was conducted with **1** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), PPh_3 (0.06 mmol), Et_3N (0.6 mmol) in DMF (5 mL) for 24 h at 120 °C under argon atmosphere. [b]Reaction time was extended to 48 h.

2s). In addition, substitution on the benzylic position had a dramatic effect on the product yield; only 39% **2t** was obtained (Table 2, entry **2t**). Bromo-substituted naphthyl and heteroaryl groups were also tolerated in this reaction, and the substrates were smoothly transformed to the corresponding products in good yields (Table 2, entries **2u**-**2w**). To our delight, when cyclic alkenyl bromides were applied as the coupling initiator, the conjugated diene products could also be obtained in acceptable yields (Table 2, entries **2x** and **2y**). It is to be noted that, we have successfully achieved the synthesis of 1,1′-disubstitued ethylene derivatives via the intramolecular pathway which exclude the formation of 1,2-disubstitued ethylene products commonly observed in the Heck coupling reaction. Moreover, a one-pot reaction between vinylacetamide **6** and 2-bromobenzyl bromide **7** was also carried out. The desired product **2a** could be isolated in 82% yield (Scheme 2).

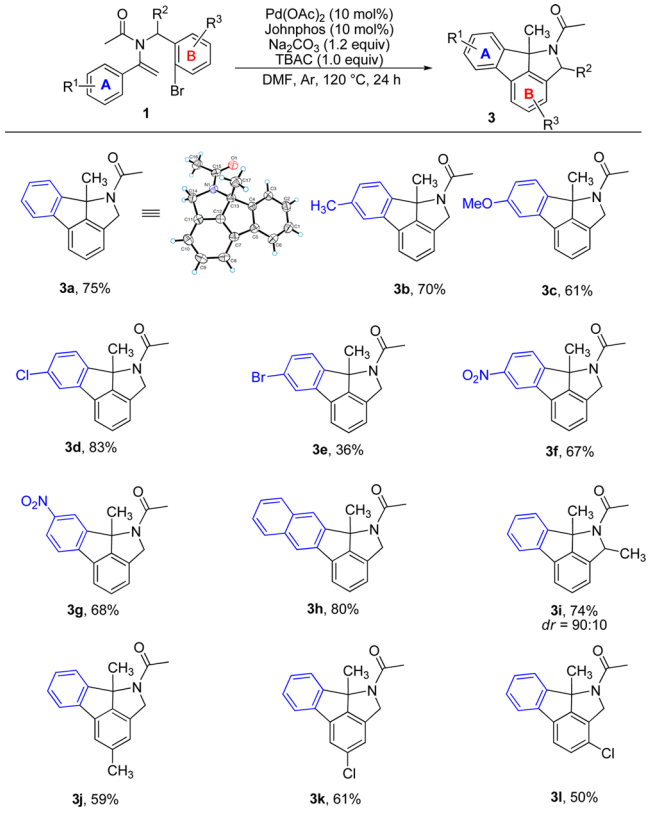
Palladium-Catalyzed 5-*exo*-Heck, 1,4-Palladium Migration and Aryl−Aryl Coupling Domino Reactions. On the other hand, the reaction leading to **3a** can be rationalized by

Scheme 2. One-Pot Reaction between *N*-Vinylacetamide 6 and 1-Bromo-2-(bromomethyl)benzene 7



invoking a 1,4-palladium shift as previously proposed by Larock,[10] Catellani,[11] Lautens,[12] Gallagher,[13] Cámpora,[14] Buchwald,[15] Dyker,[16] Pan,[17] Jia,[18] Kim[19] et al. for the synthesis of 6/5-, 6/6- or 5/6-membered[3] polycyclic compounds, while examples for the formation of 5/5-membered heterocyclic compounds has been rarely reported. In the presence of TBAC and Na_2CO_3, various bisannelated 2-azabicyclo[3,3,0]octadiene derivatives were obtained in moderate to good yields (Table 3).

Table 3. Palladium-Catalyzed Domino Coupling Reactions for the Synthesis of 2-Azabicyclo[3,3,0]octadiene Derivatives[a,b]



[a]Unless noted otherwise, the reaction was conducted with 1 (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), JohnPhos (0.02 mmol), Na_2CO_3 (0.24 mmol), TBAC (0.2 mmol) in anhydrous DMF (2 mL) for 24 h at 120 °C under argon atmosphere. [b]Isolated yield.

The influence of the electronic property of the phenyl ring **A** was first investigated. Both electron-donating groups (such as methoxyl and methyl groups) and strong electron-withdrawing group (such as nitro group) on the phenyl ring **A** could all drive the reaction to form the desired products in good yields (Table 3, **3b**, **3c** and **3f**, respectively). It was found that a Cl-substituent was well tolerated in this reaction to afford the product in an excellent yield (Table 3, **3d**). In addition, the

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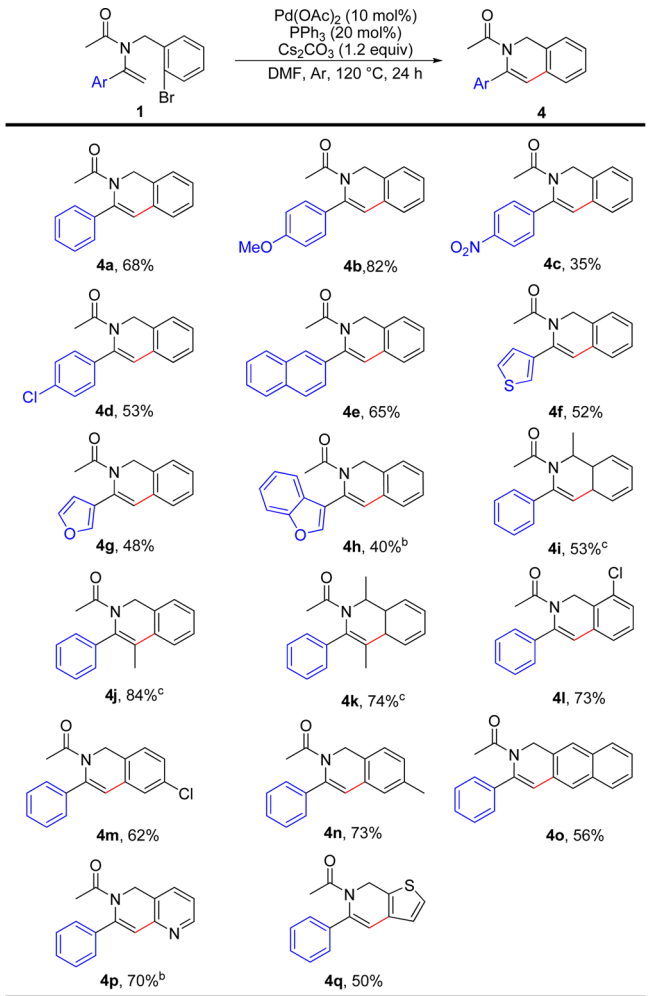
naphthyl-group substituted *N*-vinylacetamide also gave the product in a high yield (Table 3, **3h**). However, the yield of **3e** decreased sharply when bromine was installed on the benzene ring due to side reactions. Surprisingly, the steric hindrance of a methyl group at the benzylic position could be completely ignored; **3i** could be obtained in 74% yield (dr = 90:10, determined from the crude ^{1}H NMR spectrum of the crude product). With regards to ring **B**, methyl- or Cl-substituted *N*-vinylacetamides both provided the products in good yields (Table 3, **3j**, **3k** and **3l**).

Palladium-Catalyzed 6-*endo*-Heck Coupling Reaction for the Synthesis of Isoquinoline Derivatives. Highly selective 6-*endo* Heck cyclization reaction for the synthesis of dihydroisoquinoline derivatives is always challenging due to competitive 5-*exo* pathway. In our reaction system, we found that when the base used in the coupling reaction was changed into Cs_2CO_3, then various 3-(hetero)aryl-substituted 1,2-dihydroisoquinoline derivatives could be smoothly generated via a 6-*endo* Heck cyclization process (Table 4). It is important to note that different functional groups such as nitro-, halides, etc. could be tolerated at the (hetero)aryl rings which will permit the products to be further functionalized in sequence steps (Table 4, **4c**, **4d**, **4f**, **4g** and **4h**). Moreover, the *N*-acetyl-7-phenyl-5,6-dihydro-1,6-naphthyridine **4p** and *N*-acetyl-5-phenyl-6,7-dihydrothieno[2,3-*c*]pyridine **4q** also could be prepared in reasonable yields under the optimized reaction conditions.

Neopentylpalladium Species Catalyzed Amide's α-C−H Bond Direct Functionalization for the Synthesis of Pyrroloisoindolone Derivatives. Finally, inspired by the good reactivity of neopentyl-type σ-alkylpalladium(II) species in reaction (as proposed in Scheme 1) and limited previously reported examples on C(sp^3)−C(sp^3) formation through σ-alkylpalladium induced C(sp^3)−H activation,[4g] we embarked on the development on the synthesis of pyrroloisoindolone derivatives via α direct C−H functionalization of amide. With careful optimization of the reaction conditions (see the details in Supporting Information section), we found that the combination of Na_3PO_4, TBAC (tributylammonium chloride), adamantane acid (AdCOOH) with the JohnPhos ligand would facilitate the desired product's formation in good yields (Table 5). Regardless of its bulky or electron-deficient character, various aliphatic substituents could be tolerated at the 9-position of the final products. However, a significant decrease of product yield with good stereoselectivity was observed when the acetamide group was replaced by propionamide group (Table 2, **5l**).

Proposed Mechanistic Pathways for the Synthesis of Diverse N-Containing Products. Similar to the synthesis of products **2**, **3** and **5**, a 5-*exo*-trig Heck reaction gave the transient palladium complex **B** (Scheme 3), which undergoes a β-N−Pd elimination to afford 1,1′-disubstituted ethylene derivatives **2a**.[21] Pd(0) was regenerated with the aid of triethylamine which serves as a reductant.[20] Though β-hydride,[22] oxygen,[23] halide[24] or carbon[25] elimination are common in palladium chemistry, the β-N−Pd elimination has rarely been reported.[26] On the other hand, the reaction leading to **3a** can be rationalized using the 1,4-palladium shift and C(aryl, sp^2)−C(aryl, sp^2) coupling. The formation of 5/5/6-membered pyrroloisoindolone derivative **5a** could be achieved by cross-coupling between acyl sp^3 carbon with neopentyl-type σ-alkylpalladium(II) species generated via 5-*exo*-trig Heck reaction. The formation of 3-aryl-substituted dihydroisoquinoline **4a** was caused by the highly selective 6-*endo* Heck cyclization reaction.

Table 4. Palladium-Catalyzed Domino Coupling Reactions for the Synthesis of Isoquinoline Compounds[a]



[a]Reaction conditions: The mixture of 0.3 mmol **1a**, 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, and 1.2 equiv Cs_2CO_3 in the dry DMF (3 mL) under argon atmosphere was heated at 120 °C for 24 h. [b]Reaction conditions: The mixture 0.3 mmol **1a**, 10 mol % $Pd(OAc)_2$, 10 mol % Johnphos, 1.2 equiv Na_2CO_3, and 1 equiv TBAC in the dry DMF (3 mL) under argon atmosphere was heated at 120 °C for 24 h. [c]The ligand used in reaction was PCy_3.

The Possible Effect of the Used Bases and Ligands in Control of the Diverse Selectivities. As proposed in Scheme 3, the synthesis of the four different products could be achieved via a 5-*exo*−*trig* or a 6-*endo*−*trig* pathway, respectively. First, with the use of Cs_2CO_3 as base in the presence of $Pd(OAc)_2$ and PPh_3, a rare 6-*endo* Heck cyclization product could be observed.[27] While changing the base to triethylamine (Et_3N), a 5-*exo* cyclization product was obtained. Although the real reason for the diverse pathways (6-*endo* vs 5-*exo*) is not clear, the difference in regioselectivity caused by these two bases was possibly attributed to their difference in coordination abilities. The difference in the coordination sphere as well as the steric effect of the palladium complex may be the reasons for this result. Further investigation into this is still in progress. As for the 5-*exo* selective process which results in the formation of neopentyl σ-alkylpalladium species **B**, the ring strain of this intermediate promotes β-C−N bond cleavage

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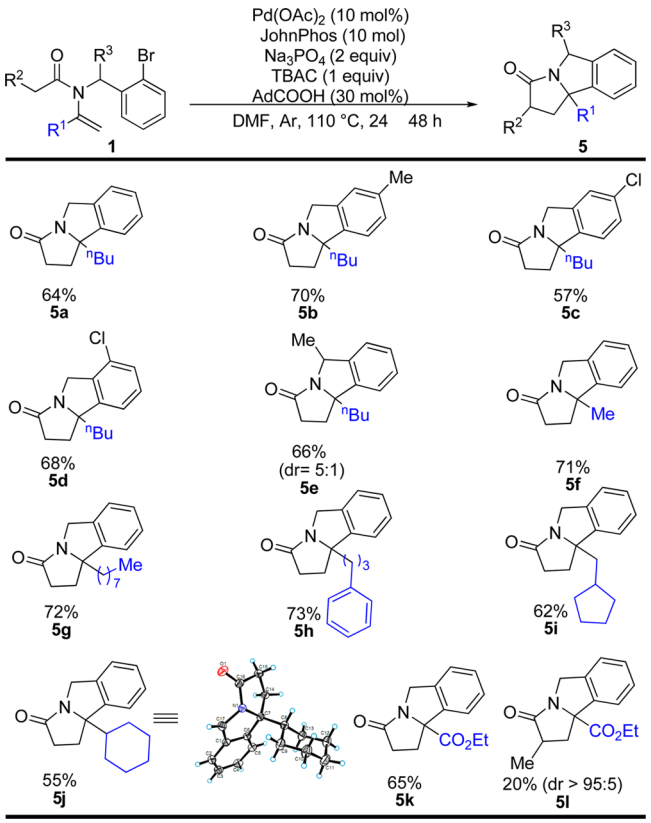
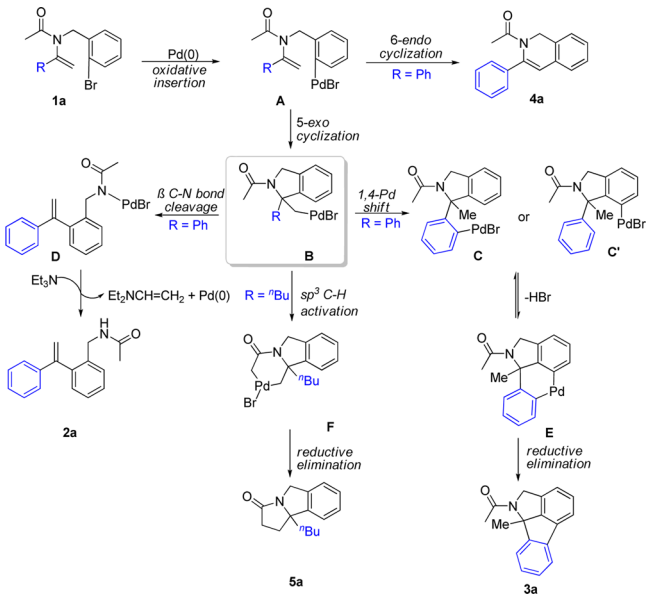
Table 5. Palladium-Catalyzed Domino Coupling Reactions for the Synthesis of Pyrroloisoindolone Derivatives[a,b]



[a]Unless noted otherwise, the reaction was conducted with **1** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), JohnPhos (0.02 mmol), Na_3PO_4 (0.4 mmol), TBAC (0.2 mmol), and AdCOOH (0.06 mmol) in anhydrous DMF (2 mL) for 24 h at 110 °C under argon atmosphere. [b]Isolated yield.

Scheme 3. Proposed Mechanistic Pathways for the Synthesis of Diverse and Controllable Products Using *N*-Vinylacetamides



which after protonation by Et_3N results in the formation of the desired product **2**.

Previous studies by Lautens,[28] Larock,[10e] Hartwig,[29] and Zhu[30] et al. have demonstrated that the electron-rich and bulky phosphine ligands could stabilize the neopentyl-type σ-alkylpalladium intermediate (resulted from the 5-*exo* pathway) and suppress the direct elimination reaction. For substrates containing two aryl groups, the 1,4-palladium migration from σ-alkylpalladium to aryl group takes place to form an arylpalladium species **C** or **C′** which could further react with another aryl group to give the product **3** in the presence of strong organic ionic bases generated *in situ*.[31] On the other hand, replacing the aryl substituent with an alkyl group to prevent the 1,4-palladium migration reaction and the use of stronger ionic base resulted in the sp^3 C–H bond direct functionalization which then undergoes the sp^3–sp^3 coupling reaction (Scheme 3, **F** → **5a**).

CONCLUSION

We have successfully developed a new and efficient strategy using a simple starting material for selective syntheses of four types of products by tuning the ligands and bases used in the reactions. (i) Under basic condition, an unprecedented β-N–Pd elimination occurred after an intramolecular Heck 5-*exo*–*trig* cyclization reaction leading to the formation of 1,1′-disubstituted ethylene derivatives. (ii) 1,4-Palladium shift and intramolecular oxidative diaryl cross-coupling reactions following intramolecular Heck cyclization can furnish unusual bisbenzo-annelated 2-azabicyclo[3,3,0]octa-4,7-diene products. (iii) Another pathway via highly selective direct 6-*endo* Heck cyclization reaction can give isoquinoline products. (iv) Finally, an intramolecular Heck 5-*exo*–*trig* cyclization reaction followed by $C(sp^3)$–$C(sp^3)$ coupling reaction can provide 5/5/6-membered pyrroloisoindolone compounds. Moreover, these methods provide simple and diverse ways for the synthesis of nitrogen-containing molecules. Given the knowledge of these results, the discovery of interesting and novel reactions and their applications are in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds (^1H NMR, ^{13}C NMR, IR, HRMS), and crystallographic data (CIF) of compounds **2j** and **3a** in CCDC numbers: 988450 and 988325. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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