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Palladium-Catalyzed Cyclization-Heck Reaction of Allenamides: An Approach to 3-Methylene-5-phenyl-1,2,3,4-tetrahydropyridine Derivatives

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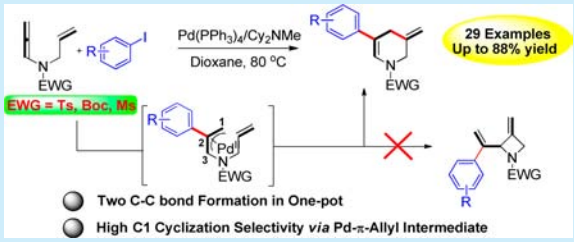
Supporting Information

ABSTRACT: An efficient one-pot construction of functionalized 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivatives via palladium-catalyzed cyclization-Heck reaction of allenamides has been described. The 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivatives feature a nonconjugated diene, including one *endo*-enamine and one exocyclic double bond, which could be used for further transformation. Both aryl and vinyl halides performed very well under the standard conditions, delivering the corresponding products efficiently.



Functionalized 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivatives represent a prevalent structural motif among natural products and pharmaceuticals with numerous bioactivities, such as (±)-preclamol (the first autoreceptor-selective agonist), mesulergine (for treatment of hyperprolactinemia, acromegaly, and Parkinson's disease), dexetimide (for control of extrapyramidal symptoms induced by pipothiazine palmitate), and potential drugs from Bayer, Novartis, and Merck (Figure 1).[1] Consequently, selective construction of substituted

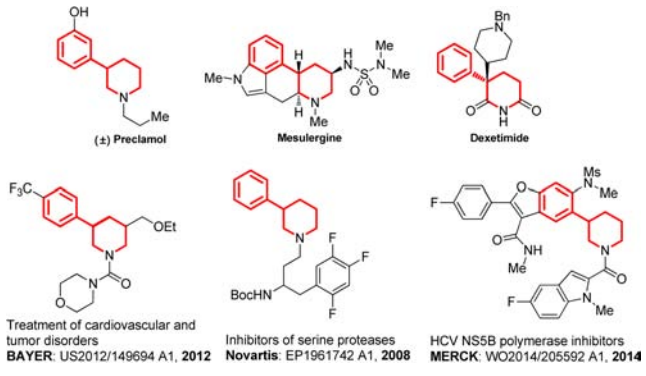


Figure 1. Bioactive 3-phenylpiperidine derivatives.

3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivatives under mild reaction conditions becomes particularly attractive. There are two main difficulties: (1) construction of piperidines and (2) installation of the aryl group at the 5-position. In the past decades, transition-metal-catalyzed cyclization has gained increasing importance as a readily available approach to valuable aza-heterocycles, particularly palladium catalysis.[2] However, few examples of the construction of this scaffold have been reported,[3] which makes the development of an efficient synthetic route highly in demand.

Allenamides, functionally derived from allenamines and bearing the amido group, inducing delocalization of the lone-pair electrons on nitrogen and therefore exhibiting improved stability, have become a powerful and versatile building block in synthetic chemistry.[4] Transition-metal-catalyzed cyclization of allenamides is a versatile strategy in the construction of aza-heterocycles because acyclic substrates are readily available.[4e−g,5] Recently, the transformations of allenamide compounds bearing olefinic side chains caught our attention. In 2010, Bäckvall and co-workers reported a palladium-catalyzed oxidative carbocyclization of aza-enallenes, efficiently delivering five-membered 2,3-dihydropyrrole motifs (Scheme 1a).[6] In 2014, Tong and co-workers developed a cyclization of vinyl iodide-tethered allenesulfonamides to give tetrahydropyridine derivatives catalyzed by palladium (Scheme 1b).[7] In 2016, the Arisawa group demonstrated a ruthenium-catalyzed intramolecular [2 + 2] cycloaddition of allenamide-enes to azabicyclo[3.1.1]-heptanes (Scheme 1c).[8] Notably, all of these reactions are intramolecular cyclizations. We expected that intermolecular coupling followed by cyclization could construct the 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine skeleton via Pd−π-allyl intermediate **A** as shown in Scheme 1.

Very recently, our group reported a palladium-catalyzed 6-endo-selective alkyl-Heck reaction of unactivated alkyl iodides to

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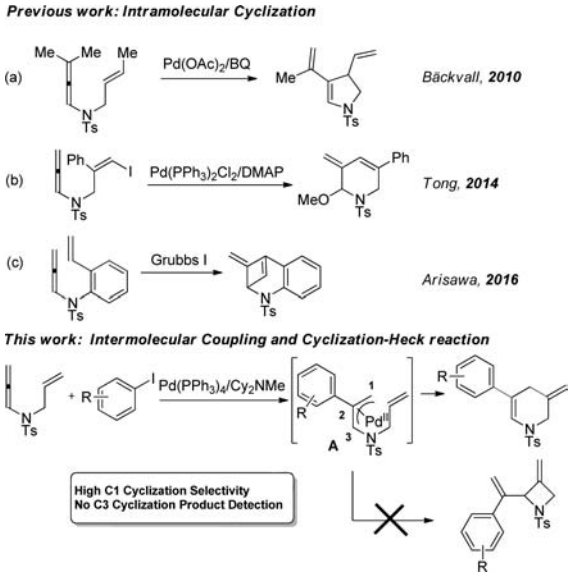
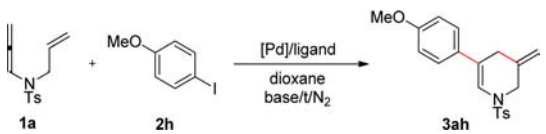
Scheme 1. Reactions of Allenamides Bearing Olefinic Side Chains



construct 5-phenyl-1,2,3,6-tetrahydropyridine derivatives.[9] To develop versatile methodologies for the synthesis of piperidine derivatives, the intermolecular coupling and cyclization-Heck reaction was achieved. Herein we are pleased to report a palladium-catalyzed strategy for the synthesis of valuable 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivatives featuring a nonconjugated diene, including one *endo*-enamine and one exocyclic double bond. Notably, the reaction proceeds with high C1 cyclization selectivity, and no C3 cyclization product is detected.

Initially, our study commenced with the cascade reaction of allenamide **1a** with 1-iodo-4-methoxybenzene (**2h**) catalyzed by $Pd(OAc)_2/PPh_3$ using K_2CO_3 as the base (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand	base	t (°C)	yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	K_2CO_3	80	29
2	$Pd(dba)_2$	PPh_3	K_2CO_3	80	23
3	$PdCl_2(PPh_3)_2$	–	K_2CO_3	80	37
4	$PdCl_2(dppf)$	–	K_2CO_3	80	33
5	$Pd(PPh_3)_4$	–	K_2CO_3	80	52
6	$Pd(PPh_3)_4$	–	K_2PO_3	80	32
7	$Pd(PPh_3)_4$	–	Na_2CO_3	80	41
8	$Pd(PPh_3)_4$	–	CH_3COONa	80	26
9	$Pd(PPh_3)_4$	–	Cs_2CO_3	80	43
10	$Pd(PPh_3)_4$	–	TEA	80	68
11	$Pd(PPh_3)_4$	–	DIPEA	80	73
12	***$Pd(PPh_3)_4$***	–	***Cy_2NMe***	***80***	***85***
13	$Pd(PPh_3)_4$	–	Cy_2NMe	50	42
14	$Pd(PPh_3)_4$	–	Cy_2NMe	100	57
15	$Pd(PPh_3)_4$	–	–	80	NR
16	–	–	Cy_2NMe	80	NR

[a]Reaction conditions: **1a** (0.2 mmol), **2h** (0.4 mmol), [Pd] (0.02 mmol), base (0.4 mmol), solvent (2.0 mL), N_2, 5 h. [b]Isolated yields.

Gratifyingly, the desired piperidine derivative **3ah** was obtained in 29% yield, accompanied by partial decomposition of allenamide **1a**. The combination of $Pd(dba)_2/PPh_3$ as the catalyst did not improve the transformation (entry 2). Then $PdCl_2(PPh_3)_2$, $PdCl_2(dppf)$, and $Pd(PPh_3)_4$ were examined, and the results showed that $Pd(PPh_3)_4$ could increase the yield to 52% (entry 5). Subsequently, various bases were screened (entries 7–12). Inorganic bases such as K_3PO_4, Na_2CO_3, CH_3COONa, and Cs_2CO_3 did not show an obvious influence on the reaction, but organic bases exhibited a quite good effect on the yield. To our delight, Cy_2NMe was found to be a good choice, affording **3a** in 85% yield (entry 12). Furthermore, the reaction is quite sensitive to the temperature. When performed at 50 °C, the reaction slowed, and the yield decreased to 42% (entry 13). When the temperature was increased to 100 °C, the reaction turned messy with some undetermined byproducts (entry 14). Two control experiments demonstrated that both the catalyst and base are necessary for this transformation (entries 15 and 16). Finally, $Pd(PPh_3)_4$ (10 mol %) and Cy_2NMe (2.0 equiv) in dioxane at 80 °C were chosen as the optimized conditions.

With the optimized conditions in hand, we subsequently explored the substrate scope of this cascade procedure, and the results are given in Table 2. Both iodobenzene and bromobenzene could give the desired product **3aa**, although the yield for bromobenzene was relatively low (54%). Iodobenzene derivatives bearing an electron-withdrawing group at the *para* position, such as nitro, acetyl, and ethyl ester, performed very well under the standard conditions and delivered the corresponding piperidine derivatives in good yields (**3ab**–**ad**). A substrate with an ethyl ester at the *ortho* position worked smoothly, giving **3ae** in 77% yield. Furthermore, the highly electron-deficient iodobenzene bearing two ethyl esters could also give **3af** efficiently in 65% yield. It is worth noting that the highly sensitive aldehyde group could survive very well in this system (**3ag**). Subsequently, iodobenzenes with various electron-donating groups were also examined. Substrates including methoxy or methyl at the *ortho*, *meta*, or *para* position or two methyl groups gave the desired 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivatives in moderate to good yields (**3ah**–**al**). Both chloro and fluoro at different positions showed quite good tolerance of the reaction conditions (**3am**–**aq**). 2-Iodothiophene-substituted **2r** delivered the corresponding product **3ar** in 68% yield.

Furthermore, the Boc-protected allenamide **1b** was synthesized and subjected to the cascade reaction. Some iodobenzene derivatives were examined. However, only iodobenzenes with an electron-withdrawing group could produce stable products, such as **3bb** with nitro and **3bc** with acetyl. Iodobenzenes with an electron-donating group, such as methoxy and methyl, could form the corresponding products, but they decomposed fully during column chromatography, which might due to the sensitive enamine structure. Methanesulfonyl-protected allenamides reacted with various iodobenzenes to generate the corresponding products in moderate yields (**3cc**, **3cm**, and **3co**). We also tried to use different protecting groups for the allenamides, but only the electron-withdrawing groups could form stable allenamides.

The scope of this palladium-catalyzed cyclization-Heck reaction was further expanded to vinyl halides. The reaction of *E*-(2-bromovinyl)benzene derivatives **2s**–**w** with **1a** smoothly afforded tetrahydropyridine derivatives **3as**–**aw** possessing a valuable conjugated 1,3-diene, which have potential to be transformed into more complicated molecules.

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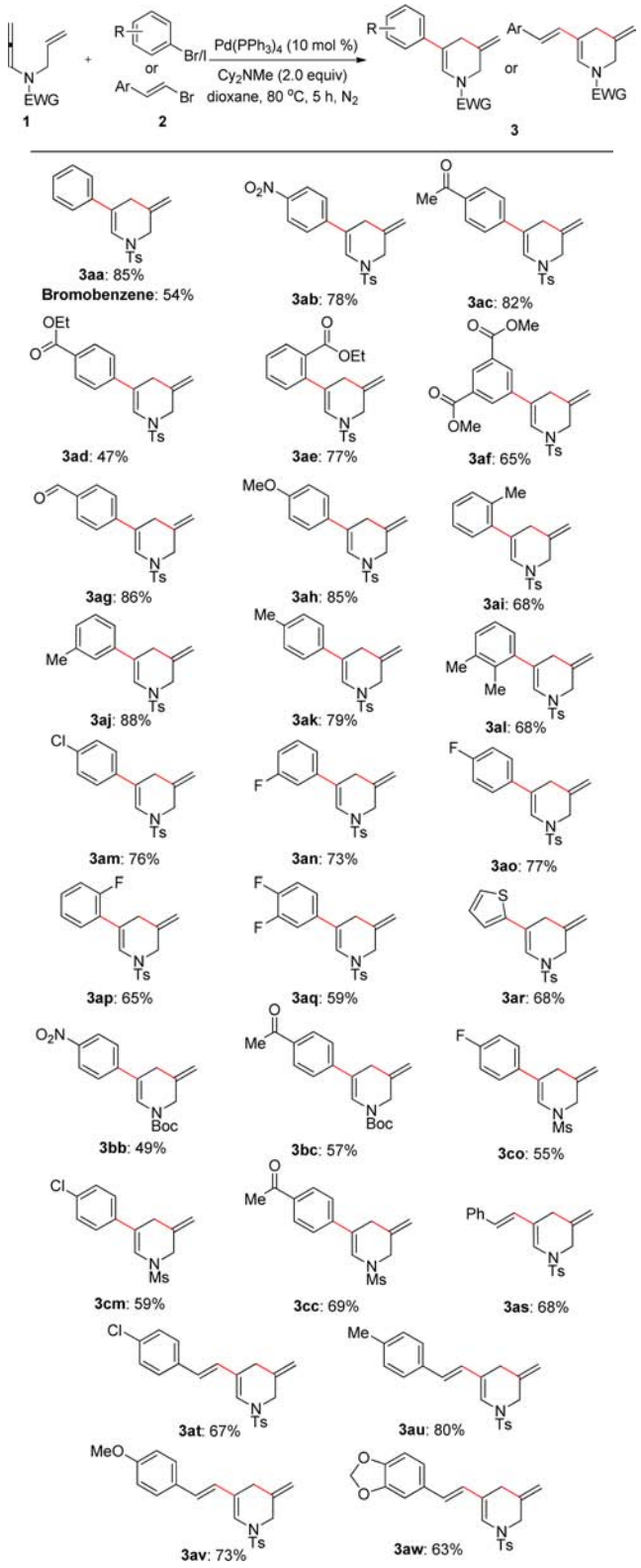
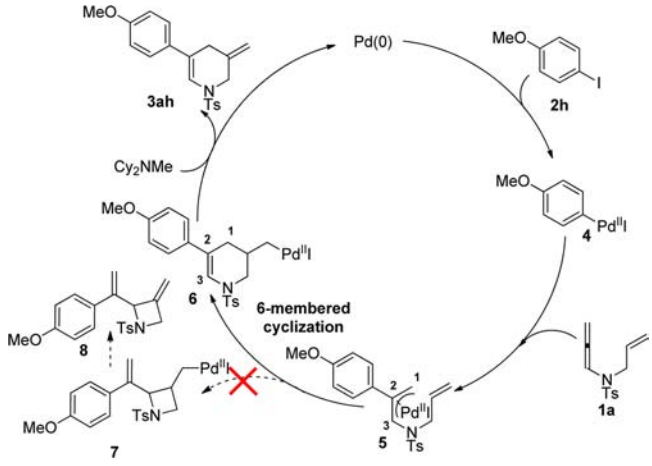
Table 2. Scope of Coupling−Cyclization-Heck Reaction of Allenamides[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(PPh_3)_4$ (0.02 mmol), Cy_2NMe (0.4 mmol), dioxane (2.0 mL), N_2, 8 h. [b]Isolated yields are shown.

A hypothesized mechanism of this transformation is shown in Scheme 2. Oxidative addition of $Pd(PPh_3)_4$ to **2h** would afford

Scheme 2. Proposed Mechanism



palladium complex **4**, and subsequent insertion of allenamide **1a** would form π-allylpalladium intermediate **5**. Subsequently, 6-*exo*-trig cyclization and β-hydrogen elimination would generate the 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivative **3ah**. Under the standard conditions, we could isolate only the six-membered cyclization product **3ah**, and no four-membered cyclization product was detected, which might be due to the high ring strain.

In conclusion, we have demonstrated a palladium-catalyzed methodology for the synthesis of valuable 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivatives featuring a nonconjugated diene, including one *endo*-enamine and one exocyclic double bond, which could be used for the further preparation of industrially and pharmaceutically important piperidine-containing compounds. Both aryl and vinyl halides performed very well under the standard conditions, delivering the corresponding products efficiently. Further synthetic applications are ongoing in our laboratory, and we are trying to realize the four-membered cyclization reaction via ligand and substrate regulation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03364.

Synthetic procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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