Highly Regioselective Palladium-Catalyzed Oxidative Coupling of Indolizines and Vinylarenes via C−H Bond Cleavage
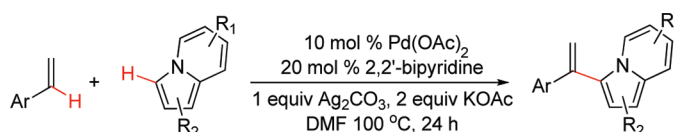
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ABSTRACT

A highly regioselective oxidative coupling reaction between indolizines and vinylarenes has been accomplished in the presence of palladium catalysts to give only the branched α-product in high efficiency. The regioselectivity is promoted significantly by bidentate nitrogen ligands.

Vinylation is one of the fundamental transformations of organic synthesis. Among the various vinylation methods,[1] the cross-coupling of aryl halides and olefins (the Heck reaction, Scheme 1) is one of the most efficient approaches with the advantage of high functional group tolerance.[2] The major drawbacks of this methodology include low regioselectivity with unsymmetrical olefins for α-products and the requirement of prehalogenation of arenes, thereby creating a significant amount of salt waste and more reaction steps.

Recently, C−H bond functionalization has attracted much attention,[3] and processes capable of achieving the oxidative vinylation of arenes using transition metal catalysts have been reported, in which aromatic sp^2 C−H bonds are coupled with olefins without the need for prior halogenation or metallization.[4] For instance, Fujiwara and co-workers have reported the palladium-assisted oxidative coupling of arenes and aromatic heterocycles with olefins.[5] Gaunt and co-workers

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described the solvent-controlled regioselective vinylation at the C2- and C3-position of indoles through the palladium-catalyzed C−H functionalization reaction.[6] Procedures have also been developed for installation of olefins through directed C−H functionalization and decarboxylation by Pd-catalyzed oxidative vinylation of indole carboxylic acids.[7] On the other hand, regioselectivity has been the most important topic for the vinylation in terms of internal olefins (linear β-product) and terminal olefins (branched α-product). Although the Stille reaction and Suzuki reaction have been used for the synthesis of branched olefins (Scheme 1),[8] there is no example for the direct oxidative vinylation to furnish the terminal olefins (α-product). In the course of our studies of the direct C−H bond functionalization,[9] we became interested in the direct vinylation of indolizines owing to the prevalence of the indolizine unit in bioactive natural products and pharmaceutical heterocycles.[10] Herein, we describe the first protocol for highly regioselective vinylation of indolizines by palladium catalysis in the presence of 20 mol % 2,2′-bipyridine and 1 equiv of Ag$_2$CO$_3$ to give only the branched α-products.

Scheme 1. Synthesis of Branched Olefins
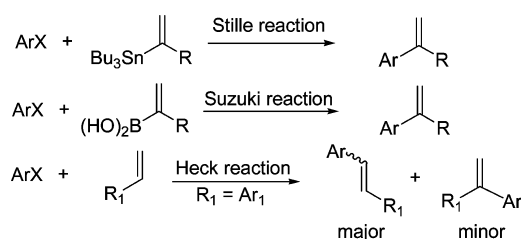
Our initial investigation in the reaction of indolizine **1a** with styrene in the presence of 10 mol % Pd(OAc)$_2$ gave poor regioselectivity and low yield; the α/β ratio was approximately 1:1.8, and the yield was 44% (Table 1, entry 1). When monodentate ligand was introduced, PPh$_3$ was less effective than pyridine. This promoted the reactivity to give a 74% isolated yield (entries 2−3). However, the competitive formation of both α-product and β-product was a major

obstacle to the development of a regioselective palladium-catalyzed vinylation. To reduce the amount of β-product formed, we employed the bidentate ligand 1,10-phenanthroline. In this case, a remarkable improvement in regioselectivity was achieved to give only α-substituted product, although the activity of the reaction was reduced (entry 4). This result highlights the key role of ligand in the regiocontrol of the reaction. We were pleased to observe that the combination of 10 mol % Pd(OAc)$_2$ and 20 mol % 2,2′-bipyridine further improved the regioselectivity to give only the α-product in 64% yield (entry 5). Further optimization indicated that the use of 5 equiv of styrene improved the yield of **3a** to 84% (entry 6). Other bidentate ligands did not favor the expected regioselective process (entries 7−9). A screen of catalyst systems showed that PdCl$_2$ and Pd(dba)$_2$ were ineffective in the reaction (Table 1, entries 10−11). In addition, the oxidant was crucial to the reaction, and no product was detected in the absence of oxidants. Among the oxidants tested, Ag$_2$CO$_3$ was more effective in oxidizing Pd(0) to Pd(II) to afford catalytic turnover, while other oxidants such as AgOAc and CuCl allowed the reaction to proceed (entries 12−14). An amount of 2 equiv of Ag(I) was required for the reaction to proceed, and a decrease in the amount of Ag(I) resulted in a reduced yield (entry 15).

Table 1. Effect of Metals, Oxidants, and Ligands on the Reaction[a]
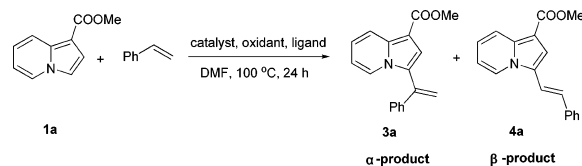
entry	catalyst	oxidant	ligand	yield %[b]
1	Pd(OAc)$_2$	Ag$_2$CO$_3$		16 (28)
2	Pd(OAc)$_2$	Ag$_2$CO$_3$	PPh$_3$	11 (15)
3	Pd(OAc)$_2$	Ag$_2$CO$_3$	pyridine	37 (37)
4	Pd(OAc)$_2$	Ag$_2$CO$_3$	L1	46
5	Pd(OAc)$_2$	Ag$_2$CO$_3$	L2	64
6	Pd(OAc)$_2$	Ag$_2$CO$_3$	L2	84[c]
7	Pd(OAc)$_2$	Ag$_2$CO$_3$	L3	32 (28)[c]
8	Pd(OAc)$_2$	Ag$_2$CO$_3$	L4	34 (25)[c]
9	Pd(OAc)$_2$	Ag$_2$CO$_3$	L5	26 (<5)[c]
10	PdCl$_2$	Ag$_2$CO$_3$	L2	25
11	Pd(dba)$_2$	Ag$_2$CO$_3$	L2	<5
12	Pd(OAc)$_2$	AgOAc	L2	62
13	Pd(OAc)$_2$	AgOTf	L2	41
14	Pd(OAc)$_2$	CuCl	L2	75[c]
15	Pd(OAc)$_2$	Ag$_2$CO$_3$	L2	36[d]

[a] Reaction conditions: styrene (0.6 mmol), indolizine **1a** (0.3 mmol), catalyst (0.03 mmol, 10 mol %), oxidant (2 equiv), KOAc (2 equiv), ligand (0.06 mmol, 20 mol %), DMF (2 mL), 100 °C, 24 h. [b] Isolated yields of α-product. The yield of β-product was presented in parentheses. [c] 5 equiv of styrene is used. [d] 0.5 equiv of Ag$_2$CO$_3$ was used. **L1** = 1,10-phenanthroline, **L2** = 2,2′-bipyridine, **L3** = 1,2-bis(diphenylphosphino)ethane, **L4** = 6,6′-bi-2-picoline, **L5** = 2,9-dimethyl-1,10-phenanthroline, dba = dibenzylideneacetone.

We next studied the generality of this regioselective oxidative coupling reaction by varying the electronic and

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steric properties of vinylarenes. As can be seen from Figure 1, the reaction of vinylarenes with electron-donating groups in the aryl ring worked well to give the corresponding oxidative coupling products in good to high yields (**3b**−**3g**). However, vinylarenes with strongly electron-withdrawing groups such as −CN and −NO$_2$ were incompatible with the reaction, and no desired products were detected. The presence of moderate electron-withdrawing groups (bromo, chloro, fluoro) was tolerated in the reaction and afforded the desired products smoothly (**3h**−**3l**). Steric hindrance decreased the reactivity of the reaction. For instance, ortho-substituted vinylarenes delivered relatively lower yields compared with their para- or meta-analogues (**3d**, **3g**, and **3l**). It is worth noting that carbon−halogen bonds tolerated the reaction conditions to give the halogen-containing products. Byproducts from cross-coupling of indolizine and the C−X bond in halo-substituted vinylarenes were not detected,[11] showing the excellent chemoselectivity. Pure products from ethyl acrylate and acylonitrile were not obtained because separation of the products from the byproduct was very difficult.
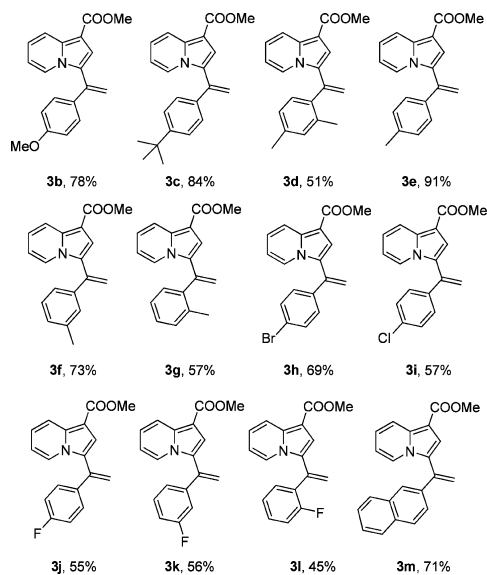

Figure 1. Reaction of indolizine **1a** with vinylarenes.

The oxidative coupling reaction was further extended to various indolizines as shown in Table 2. Methyl indolizine-1-carboxylate, ethyl indolizine-1-carboxylate, and *n*-butyl indolizine-1-carboxylate afforded the desired products **3a**, **3n**, and **3o** in good yield (entries 1−3). When 1-(indolizin-1-yl)ethanone reacted with styrene, a 70% yield was obtained (entry 4). Indolizine-1-carbonitrile and 2-methylindolizine-1-carbonitrile showed good reactivity to give the desired direct coupling products in high yield (entries 5 and 6). Methyl 7-methylindolizine-1-carboxylate was a good substrate for the reaction (entry 7). However, diethyl indolizine-

1,2-dicarboxylate was inactive (entry 8). The presence of another electron-withdrawing group (−CO$_2$Et) in the indolizine might render the heterocycles highly electron deficient and retard electrophilic palladation. Poor reactivity was also observed for other heteroarenes such as indoles and pyridines.

Table 2. Reaction of Styrene with Various Indolizines[a]

| entry	indolizine	product	yield %[b]
1	**1a**	**3a**	84
2	**1b**	**3n**	80
3	**1c**	**3o**	77
4	**1d**	**3p**	70
5	**1e**	**3q**	79
6	**1f**	**3r**	83
7	**1g**	**3s**	78
8			0

[a] Reaction conditions: styrene (1.5 mmol), indolizines (0.3 mmol), Pd(OAc)$_2$ (0.03 mmol, 10 mol %), Ag$_2$CO$_3$ (1 equiv), KOAc (2 equiv), 2,2′-bipyridine (0.06 mmol, 20 mol %), DMF (2 mL), 100 °C, 24 h. [b] Isolated yield.

According to the proposal of Cabri and others for the Heck reaction,[12] monodentate ligands lead to a neutral pathway dominating formation of the linear olefins due to the easy

(11) Reaction between C−X bond and indolizines has been reported, see: Park, C. H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159–1162.

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Scheme 2. Plausible Reaction Mechanism
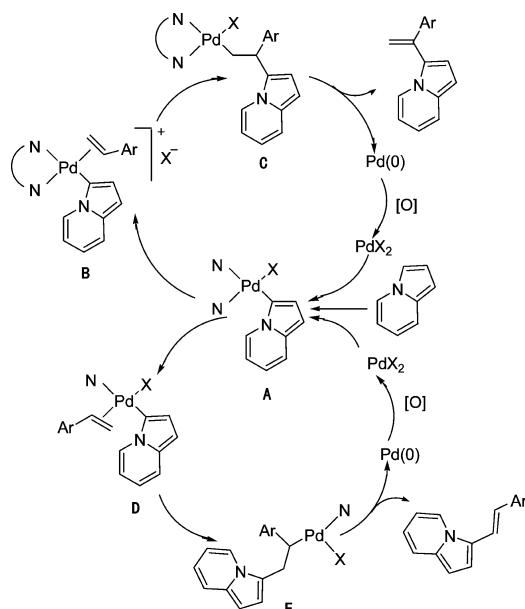
dissociation of the ligand. In contrast, the ionic pathway results in the branched olefins being favored in the presence of bidentate ligands. Indeed, we have found excellent regioselectivity with a wide range of vinylarenes and indolizines by exploiting the bidentate nitrogen ligands to give only the branched olefins. Indolizines are classified as electron-rich aromatic heterocycles, and their transformations catalyzed by palladium show strong electrophilic character with reactions occurring at the most electron-rich C3-position.[13] On the basis of the previous chemistry and our results, we propose a plausible mechanism for this new oxidative coupling reaction, as shown in Scheme 2. The electrophilic palladation first occurs preferentially at the C3-position of indolizine, and the subsequent deprotonation leads to the formation of intermediate **A**. The following coordination of vinylarenes to intermediate **A** may take place in two different ways: (1) An ionic intermediate **B** is preferentially formed in the presence of bidentate nitrogen ligands, which leads to the primary formation of intermediate **C** to afford the branched α-product. (2) Alternatively, a neutral inter-

mediate **D** may be formed due to the relatively easy dissociation of the monodentate nitrogen ligand, and such a complex should easily form intermediate **E** to finally give the linear β-product. Ag_2CO_3 would serve as an oxidant to regenerate the Pd(II).

Of particular note is the performance of a 3-substituted indolizine like *N,N*-diphenylindolizin-3-amine in this reaction in the presence of bidentate ligand 2,2′-bipyridine which gives rise to a mixture of α- and β-substituted vinylation products; the effect of the bidentate ligand on regiocontrol was still obvious, the α-product being mainly obtained (Scheme 3). This result illustrates that the nitrogen atom in indolizines could be playing a potential role in the formation of branched α-isomer products.[14] Further research is required for the elucidation of the detailed mechanism.

Scheme 3. Regioselectivity of 3-Substituted Indolizine

Ligand	3 t	4 t
20 mol % 2,2′-bipyridine	36%	23%
40 mol % pyridine	16%	40%
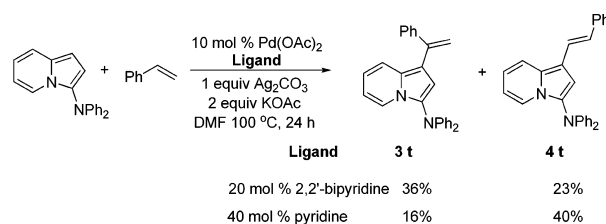
In summary, we have observed the first example of a palladium-catalyzed oxidative vinylation process that exhibits excellent regioselectivity to furnish essentially only branched olefins in the presence of bidentate nitrogen ligands. The approach has extended the scope of regioselective C−H functionalization of indolizines.

Supporting Information Available: Experimental procedure and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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