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Cyclopentadiene-Phosphine/Palladium-Catalyzed Synthesis of Indolizines from Pyrrole and 1,4-Dibromo-1,3-butadienes

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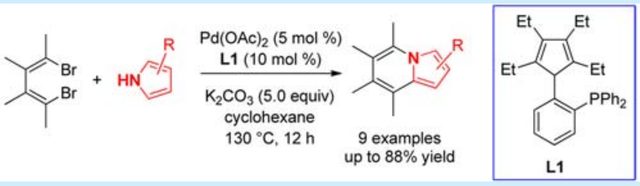
S *Supporting Information*

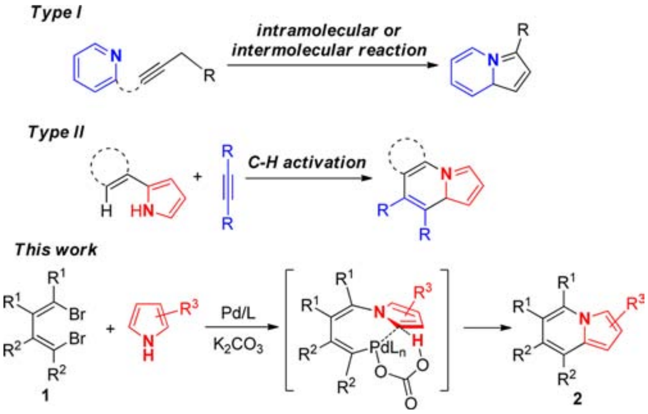
ABSTRACT: The cyclopentadiene−phosphine ligand (**L1**) and palladium were found to be an efficient catalyst system to activate the α-C(sp^2)−H bond of pyrrole and indole derivatives. Various alkenyl or aryl dibromides could be used to react with pyrrole and indole derivatives to afford multisubstituted indolizines in high yields.



Indolizine (Figure 1) is an important type of nitrogen-containing aromatic compound and found in various natural products, pharmacologically active compounds, and functional materials.[1,2] The wide application of indolizines accelerates the development of synthetic methods. Indolizines can be synthesized from pyridine and alkyne via a nucleophilic attack reaction.[3] Recently, a C−H activation strategy has been applied for the synthesis of indolizines (Scheme 1).[4] Substituents on the indolizine ring have a remarkable influence on its property. However, introduction of different substituents, especially multiple substituents, is a difficult task toward construction of diversified indolizine derivatives.

Figure 1. Structure of indolizine core.

Scheme 1. Synthesis of Indolizines



Multisubstituted 1,3-diene derivatives, such as 1,4-dibromo-1,3-butadienes **1**, are now readily available and synthetically useful for the synthesis of organic and organometallic compounds.[5,6] In this work, the multisubstituted substrates **1** are applied as a building block for the synthesis of multisubstituted indolizine derivatives **2** (Scheme 1). The Pd-catalyzed annulation process involves alkenyl or aryl C(sp^2)−N bond formation followed by forming C(sp^2)−C(sp^2) bond via alkenylation of the α-C(sp^2)−H bond of pyrrole and indole. The cyclopentadiene−phosphine ligand (**L1**) was found to be the best of the ligands examined.

As shown in Table 1, when 1,4-dibromide-1,3-butadiene **1a** was treated with pyrrole, the indolizine **2a** was obtained. In this reaction process, amination and C(sp^2)−H bond activation were involved. The optimized reaction conditions show that the cyclopentadiene−phosphine ligand **L1** which was developed by our laboratory showed high efficiency.[7] The biaryl phosphine ligands, which were widely applied in the C−N bond formation,[8] showed very low efficiency for this reaction. When PPh$_3$ was used in the reaction, 32% yield of **2a** could be obtained. These results demonstrated that the cooperation between the P moiety and the cyclopentadiene moiety of **L1** is very important in this Pd-catalyzed tandem process. In addition, this transformation is very sensitive to the base, and K$_2$CO$_3$ was found to be most effective.[9] Other bases, such as Cs$_2$CO$_3$, NaOEt, K$_3$PO$_4$, and Et$_3$N, gave moderate or low yields of **2a**. The optimal reaction conditions were found to be Pd(OAc)$_2$ (5 mol %), **L1** (10 mol %), and K$_2$CO$_3$ (5.0 equiv) in 2.0 mL of cyclohexane at 130 °C for 12 h (entry 1). Under these optimized conditions, indolizine **2a** was obtained in 85% isolated yield.

The scope of the above Pd-catalyzed tandem reaction was investigated under the optimized reaction conditions. Results are summarized in Table 2. A variety of symmetric and asymmetric dibromides **1** were applied. For the symmetric

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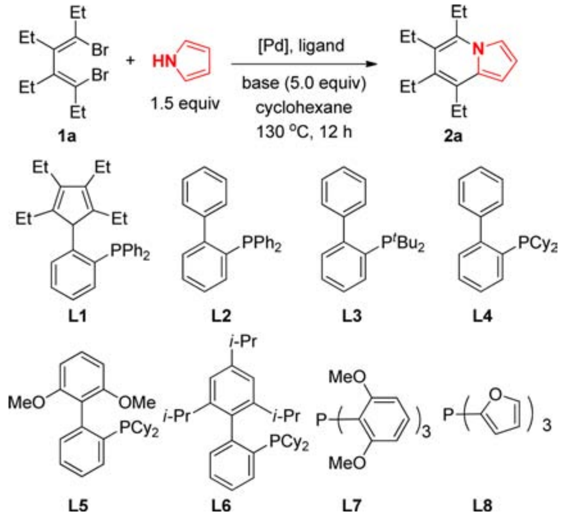
Table 1. Optimization of Reaction Conditions[a]



entry	[Pd]	ligand	base	yield of 2a[b] (%)
1	$Pd(OAc)_2$	L1	K_2CO_3	90 (85)
2	$Pd_2(dba)_3$	L1	K_2CO_3	16
3	$[Pd(allyl)Cl]_2$	L1	K_2CO_3	<5
4	$Pd(OAc)_2$	L2	K_2CO_3	12
5	$Pd(OAc)_2$	L3	K_2CO_3	<5
6	$Pd(OAc)_2$	L4	K_2CO_3	15
7	$Pd(OAc)_2$	L5	K_2CO_3	<5
8	$Pd(OAc)_2$	L6	K_2CO_3	<5
9	$Pd(OAc)_2$	L7	K_2CO_3	<5
10	$Pd(OAc)_2$	L8	K_2CO_3	18
11	$Pd(OAc)_2$	PPh_3	K_2CO_3	32
12	$Pd(OAc)_2$	L1	Cs_2CO_3	68
13	$Pd(OAc)_2$	L1	NaOEt	56
14	$Pd(OAc)_2$	L1	K_3PO_4	14
15	$Pd(OAc)_2$	L1	Et_3N	<5

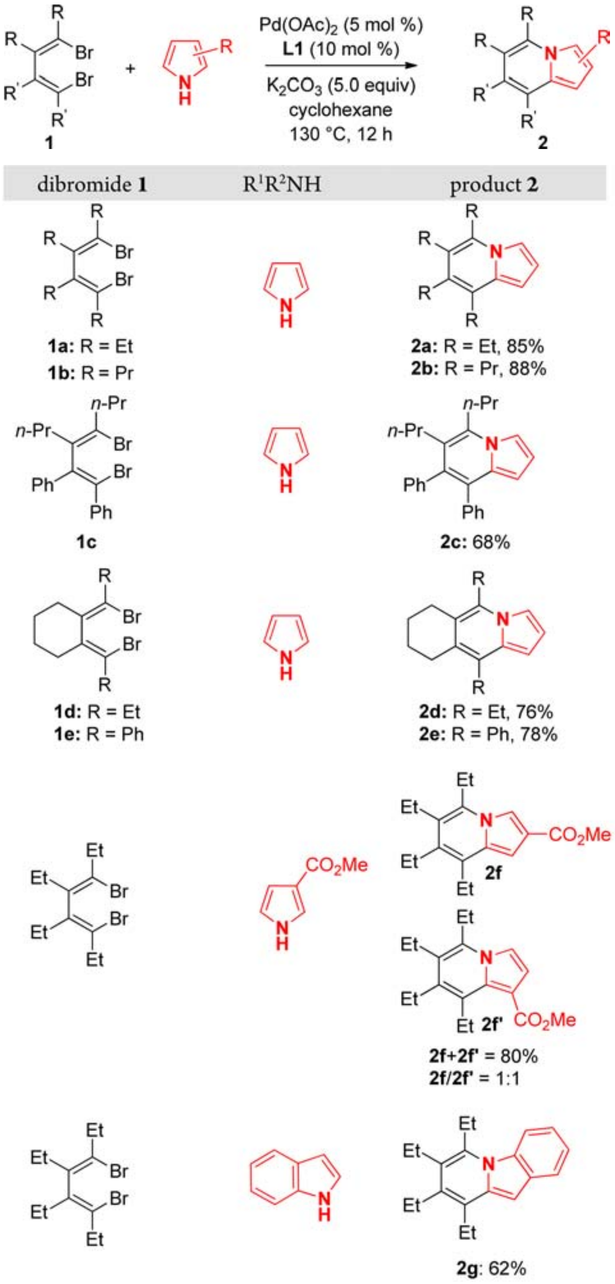
[a]Reaction conditions: **1a** (0.3 mmol), pyrrole (0.45 mmol), [Pd] (5 mol %, 0.015 mmol), ligand (10 mol %, 0.03 mmol), base (5.0 euqiv, 1.5 mmol), 2 mL of cyclohexane, 12 h. [b]Yields were determined by GC analysis of the crude reaction mixture using dodecane as an internal standard. Isolated yields are given in parentheses.

dibromides, both alkyl- and aryl-substituted dibromides could tolerate this reaction with high or moderate yield of products obtained (**2a**,**b**,**d**,**e**). When the asymmetric diphenyldipropyl-substituted dibromide **1c** was used, the COSY and NOE experiments of the product **2c** showed that the amination step selectively took place at the alkyl-substituted alkenyl bromide (see the Supporting Information), and finally, the product **2c** was obtained in 68% yield. For substituted pyrroles, such as methyl pyrrole-3-carboxylate, a mixture of **2f** and **2f′** was obtained. Furthermore, indole instead of pyrrole could also be applied in this reaction to afford product **2g** in 62% isolated yield.

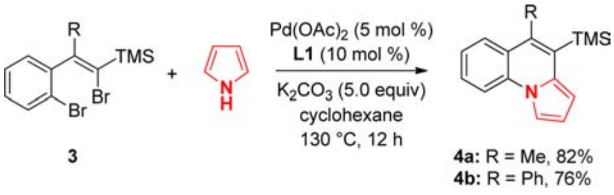
The styrene-type dibromide substrates **3** were also tested. Generally, the vinyl C−Br bond is considerably more reactive with Pd(0) than the aryl C−Br bond according to the kinetic research and DFT study in the literature.[10] However, in this case, amination of the aryl C−Br bond took place first, affording the products **4** in high yields with sole selectivity (Scheme 2). Figure 2 shows the crystal structure of **4b**.

On the basis of the above observations and previous works,[11] a possible mechanism is proposed and given in Figure 3.

Table 2. Palladium-Catalyzed Reaction of Dibromides 1 with Pyrrole and Indole



Scheme 2. Palladium-Catalyzed Reaction of Styrene-Type Dibromides 3 with Pyrrole



Intermediate **III** would be formed from dibromide **1** and pyrrole via oxidative addition/amination/oxidation addition processes. Then an electrophilic palladation with base-assisted C−H bond activation[12] via intermediate **IV** occurred to

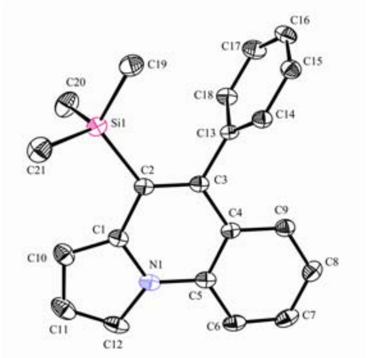


Figure 2. ORTEP drawing of **4b** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity.

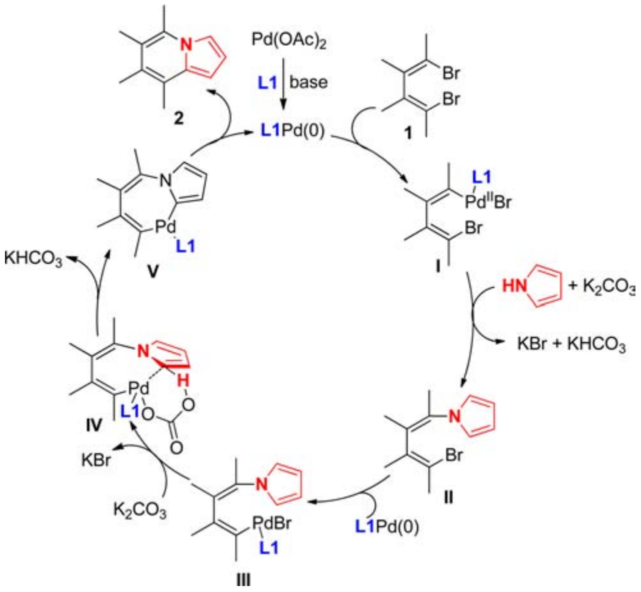


Figure 3. Proposed reaction mechanism.

generate the intermediate **V**, which undergoes reductive elimination to form the product **2**.

In summary, we have developed an efficient method to synthesize the multisubstituted indolizines from pyrrole and alkenyl bromides or aryl bromides via Pd-catalyzed tandem reaction. In this reaction, the cyclopentadiene phosphine ligand **L1** plays a very important role.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02959.

Experimental details and NMR spectra of all new products (PDF)
X-ray data for **2g** (CIF)

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Notes

The authors declare no competing financial interest.

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