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Synthesis of Indolizine Derivatives by Pd-Catalyzed Oxidative Carbonylation

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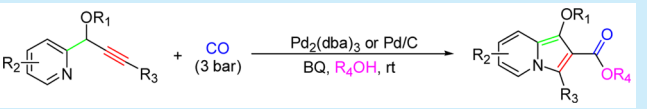
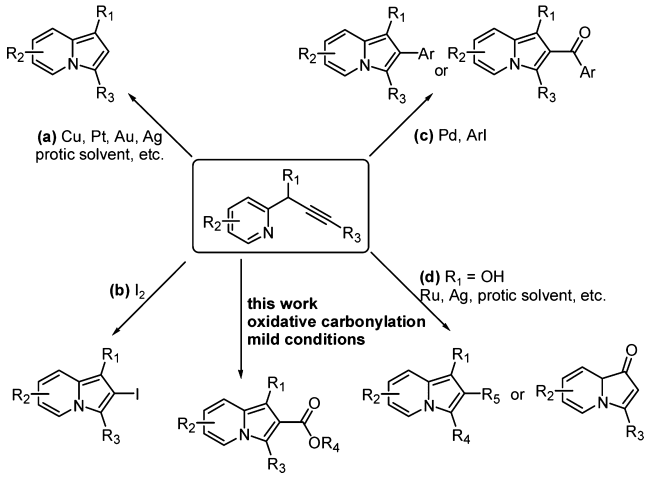
Supporting Information

ABSTRACT: An efficient synthesis of indolizine derivatives by palladium-catalyzed oxidative carbonylation of propargylic pyridines has been developed. The reaction can be conducted at room temperature and under 3 bar of CO in the presence of $Pd_2(dba)_3$ or Pd/C. The catalyst Pd/C could be easily removed from the reaction and recycled.



The construction of diverse functionalized *N*-heterocycles is an important goal in synthetic organic chemistry.[1] For example, indolizines are found in a number of natural products and biologically active compounds.[2] Among the strategies to prepare *N*-heterocycles, the synthesis of functionalized compounds with the same core structure from the same or similar starting materials has potential benefit, easily building a library to screen and optimize the lead compound.[3] For example, the synthesis of indolizines from propargylic pyridines is an attractive approach.[4−8] Indolizines could be formed by the cycloisomerization or cyclization of propargylic pyridines in the presence of metal catalysts such as Pt, Cu, Ag, Au, and In and by heating in a polar protic solvent such as water and alcohol (Scheme 1a).[4] Iodine could promote the cyclization of propargylic pyridines to form iodoindolizines (Scheme 1b).[5] Palladium-catalyzed (carbonylative)cyclization/arylation has also been used to synthesize indolizines from propargylic pyridines and aryl halides (Scheme 1c).[6] Indolizine derivatives are also prepared from 2-pyridyl alkynyl carbinols, catalyzed by Ru and Ag, or cyclized by heating in a polar protic solvent (Scheme 1d).[4b,7]

Scheme 1. Synthesis of Indolizines from Propargylic Pyridines



Transition-metal-catalyzed carbonylation has been widely used to synthesize many valuable compounds, including esters, amides, aldehydes, ketones, alcohols, etc.[9] In recent years, oxidative carbonylation has attracted considerable attention.[10,11] Pd-catalyzed oxidative carbonylation could proceed under mild conditions, which avoids the difficult oxidative addition of metal with aryl halide at high temperature and could provide diverse reaction pathways to form potentially useful compounds. To the best of our knowledge, there is only one example using the nitrogen in a pyridyl ring as the intramolecular nucleophile in oxidative carbonylation reactions, affording 11*H*-pyrido[2,1-*b*]quinazolin-11-ones from *N*-aryl-2-aminopyridines using $K_2S_2O_8$ as the oxidant in TFA.[12] Herein we report an efficient palladium-catalyzed oxidative alkoxycarbonylation of propargylic pyridines to synthesize indolizine derivatives under mild conditions.

Initially, substrate **1a** was used to study the conditions for the reaction (Table 1). In the presence of 5 mol % $Pd(PPh_3)_2Cl_2$, methoxycarbonylation product 1-pivaloxy-2-methoxylcarbonyl-3-phenyl-indolizine (**2a**) was obtained in 66% yield using 1,4-benzoquinone (BQ) as the oxidant at 60 °C (entry 1). The yield did not change when the reaction was effected at room temperature (entry 2). Then different catalyst precursors were studied. When Pd(0) type catalysts $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ were used, **2a** was obtained in 60% and 85% yields, respectively (entries 3 and 4). When the heterogeneous catalyst Pd/C was used, **2a** was obtained in 80% yield (entry 5). The commonly used palladium catalyst precursor $Pd(OAc)_2$ gave **2a** in only 49% yield (entry 6). The results indicate that phosphine ligand is not necessary. The yield of **2a** decreased when the amount of catalyst was reduced (entries 7−9). Then we examined the effect of CO on the reaction. When the pressure was reduced to

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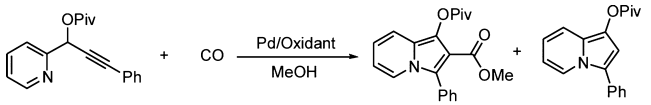
Table 1. Screening of the Reaction Conditions[a]



1a 2a 2aa

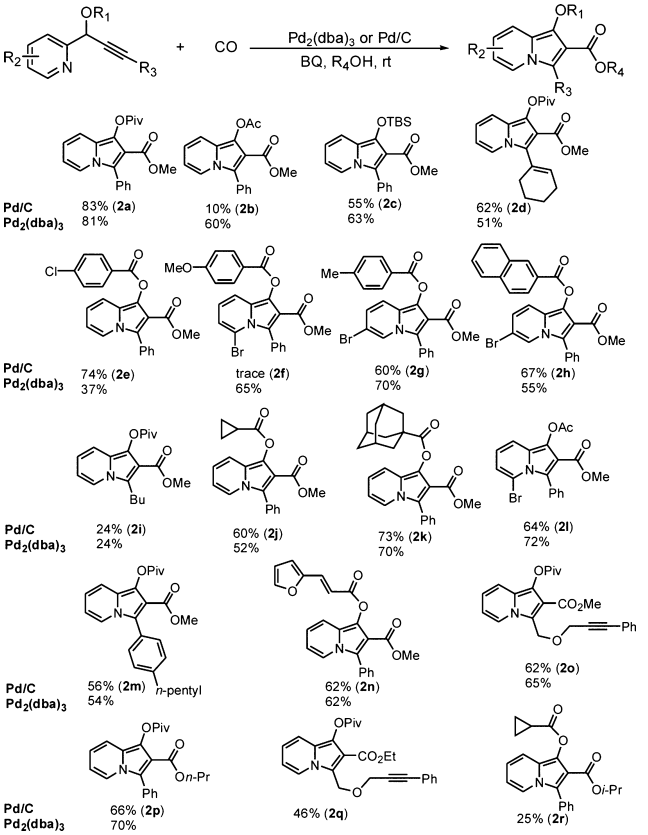
entry	cat. (mol %)	oxidant (equiv)	P_{CO} (bar)	yield of **2a** (%)[b]
1	$Pd(PPh_3)_2Cl_2$/5	BQ/2	20	66[c]
2	$Pd(PPh_3)_2Cl_2$/5	BQ/2	20	65
3	$Pd(PPh_3)_4$/5	BQ/2	20	60
4	$Pd_2(dba)_3$/2.5	BQ/2	20	85
5	Pd/C/5	BQ/2	20	80[d]
6	$Pd(OAc)_2$/5	BQ/2	20	49
7	$Pd_2(dba)_3$/0.5	BQ/2	20	69
8	$Pd_2(dba)_3$/1	BQ/2	20	73
9	Pd/C/1	BQ/2	20	64
10	$Pd_2(dba)_3$/2.5	BQ/2	2	75
11	**$Pd_2(dba)_3$/2.5**	**BQ/2**	**3**	**81**
12	$Pd_2(dba)_3$/2.5	BQ/2	5	81
13	**Pd/C/5**	**BQ/2**	**3**	**83**[d]
14	$Pd_2(dba)_3$/2.5	$Cu(OAc)_2$/2	3	<5 (**2aa**: 85)
15	$Pd_2(dba)_3$/2.5	AgOAc/2	3	43
16	$Pd_2(dba)_3$/2.5	BzOOBz/2	3	<5
17	$Pd_2(dba)_3$/2.5	BQ/0.2[e]	3	11

[a]Conditions: 0.2 mmol of **1a**, 2 mL of MeOH, room temperature, 12−15 h. [b]Isolated yield. [c]60 °C. [d]6 h. [e]1 bar air/3 bar CO.

3 bar and the palladium catalyst precursor was $Pd_2(dba)_3$ or Pd/C, compound **2a** was obtained in 81% and 83% yield, respectively (entries 10 and 13, respectively). There was little change in yield by increasing the pressure of CO to 5 bar. When the oxidant $Cu(OAc)_2$ was used instead of BQ, cycloisomerization product 1-pivaloxy-3-phenyl-indolizine (**2aa**) was obtained in 85% yield together with <5% **2a** (entry 14). Oxidant AgOAc gave **2a** in 43% yield (entry 15). When BzOOBz was used as the oxidant, most of **1a** remained (entry 16). Only an 11% yield of **2a** was obtained by using 0.2 equiv of BQ at 1 bar air/3 bar of CO (entry 17).

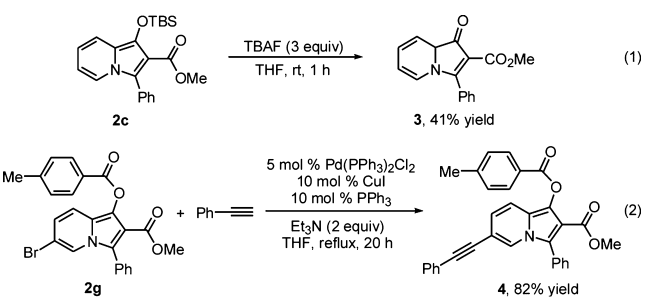
The scope of the reaction was studied in the presence of $Pd_2(dba)_3$ or Pd/C (Scheme 2). When the pivaloyl group of the substrate was replaced by the acetyl group, $Pd_2(dba)_3$ gave the corresponding product **2b** in 60% yield but Pd/C was far less effective. The substrate with a TBS group gave **2c** in 63% and 55% yields, using $Pd_2(dba)_3$ and Pd/C as the catalyst, respectively. The yields of indolizines changed when the substituent on the alkynyl moiety was replaced. Substrate **1d** with a cyclohexenyl substituent gave the corresponding product **2d** in 51% and 62% yields using $Pd_2(dba)_3$ and Pd/C as the catalyst, respectively. Product **2i** was obtained in just 24% yield using **1i** with a butyl group. Then substrates with different carboxylates were investigated. Both aromatic carboxylates and aliphatic carboxylates could be successfully converted to indolizine derivatives. Benzoxylate with the *para*-chlorine substituent, **1e**, gave **2e** in 37% yield using $Pd_2(dba)_3$ as the catalyst and 74% yield using Pd/C as the catalyst. Benzoxylate with a *para*-methoxy substituent afforded **2f** in 65% yield, using $Pd_2(dba)_3$ as the catalyst, while only traces of product resulted using Pd/C as the catalyst. Substrates **1g** with *para*-methylbenzoxylate and **1h** with 2-naphthalate afforded the corresponding products in 55−70% yield. When the carboxylate was changed to cyclopropanecarboxylate or 1-adamantanecarboxylate, the corresponding indolizines were

Scheme 2. Synthesis of Indolizines from Propargylic Pyridines[a]



[a]Conditions: 0.2 mmol of **1**, 5 mol % of Pd, 0.4 mmol of BQ, 2 mL of MeOH, room temperature, 12−15 h for $Pd_2(dba)_3$, 6 h for Pd/C.

isolated in 52−73% yields. A bromine substituent on the pyridine ring had little effect on the yields (**2f**−**2h**, **2l**). Substrate **1m** with a 4-pentyl phenyl substituent reacted to form **2m** in 54% and 56% yields using $Pd_2(dba)_3$ and Pd/C as the catalyst, respectively. The reaction works well with other alkenyl or alkynyl substituents in the substrates (62−65% yields for **2n** and **2o**), and this could enable further transformations. Other alcohols (ethanol, *i*-propanol, and *n*-propanol) were also applied for the oxidative carbonylation, affording the corresponding indolizines **2p**−**2r** in 25−70% yields. *i*-Propanol gave **2r** in 25% yield possibly because of steric hindrance. To broaden the potential application of the method, compound **2c** can be deprotected by TBAF and the C−Br bond in **2g** can be converted to C−C bond by Sonogashira coupling, affording compounds **3** and **4** in 41% and 82% yields, respectively eqs 1 and 2.



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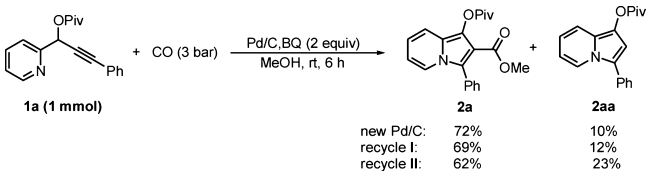
Efforts were made to recycle the reaction catalyst using Pd/C as the catalyst. The recycle reaction was carried out on a 1 mmol scale of **1a** (Scheme 3). Product **2a** was obtained in 72%

Scheme 3. Synthesis of Indolizines from Propargylic Pyridines



yield using new Pd/C, while 10% cycloisomerization product **2aa** was obtained. After simple filtration and washing with methanol, Pd/C was used for the next round of carbonylation. The yield of **1a** decreased slightly in the first recycle of Pd/C (69%). In the second recycle, the yield of **2a** decreased to 62% while the yield of **2aa** increased to 23%. The results showed that Pd/C could be separated and recycled.

In conclusion, an efficient synthesis of indolizine derivatives was developed by the palladium-catalyzed oxidative carbonylation of propargylic pyridines. The reaction could be conducted at room temperature, under 3 bar of CO, in the presence of $Pd_2(dba)_3$ or Pd/C. The recycling of the Pd/C catalyst was also realized.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02220.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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