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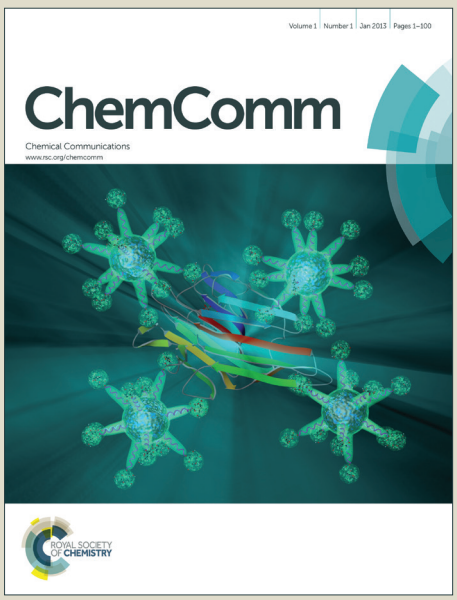

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Palladium-Catalyzed Highly Efficient Synthesis of Functionalized Indolizines via Cross-Coupling/Cycloisomerization Cascade

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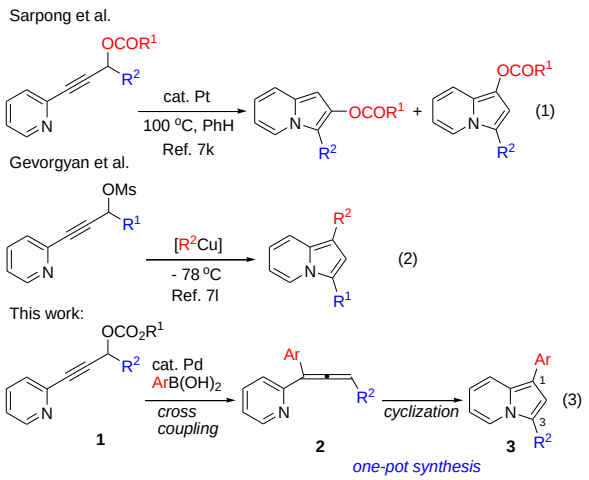
An efficient Pd-catalyzed cross-coupling/cycloisomerization of 3-(2-pyridyl) propargyl carbonates with organoboronic acids has been developed, which provides a straightforward route for the synthesis of 1,3-disubstituted indolizines with a wide variety of substituents. Mechanistic study indicates that the reaction proceeds via formation of an allenyl pyridine intermediate through palladium-catalyzed coupling reaction followed by cyclization.

Indolizine skeletons are found in a large variety of biologically active substances,[1] including naturally occurring alkaloids[2] and synthetic pharmaceuticals[3]. For example, they have been employed as antibacterial, antiviral, anti-inflammatory[4a-c] and cardiovascular agents,[4d] CNS depression agents[4e] etc. In addition, indolizine derivatives are also highly useful in the field of materials science such as in the development of dyes,[5a-b] biological markers[5c] and organic light emitting devices (OLEDs) [5d] owing to their unique photophysical properties.[5] Therefore, the development of efficient methodologies for the construction of indolizines attracted a lot of attention in recent years.[6-8] In this regard, transition metal catalysis represents one of the most important protocols for the synthesis of indolizines[7] due to its relatively mild reaction conditions, functional group compatibility and high efficiency, especially, it can promote the target molecule formation in a domino fashion. Among many approaches, metal-catalyzed cycloisomerization of pyridyl-substituted propargyl esters[7c-d, 7g, 7j-l] is one of the important route to indolizines. For example, by employing propargyl esters bearing a (2-pyridyl) group at the alkyne terminus as the substrates, Sarpong et al. have developed a Pt-catalyzed protocol to indolizines,[7k] however, a mixture of 2,3- and 1,3-disubstituted indolizines were usually generated in this reaction (Scheme 1, eq 1). Gevorgyan et al. reported that cyclization of propargyl mesylates with organocopper reagents at low temperature produced indolizines (Scheme 1, eq 2).[7l] In this reaction, the relatively unstable organocopper reagents need to be prepared in situ via reaction of organolithium or Grignard reagents with copper salts or complexes. We have developed various metal-catalyzed reactions towards indolizines,[7d-f] such as Cu-catalyzed cycloisomerization of 1-(2-pyridyl) propargyl esters,[7d] Pd/Cu-catalyzed Sonogashira coupling/cyclization,[7e] and gold-catalyzed three components coupling of pyridine-2-carboxaldehydes, alkynes, and amines[7f]. During our recent work on Pd-catalyzed cascade coupling/cyclization reactions of



Scheme 1. Construction of indolizines via metal-catalyzed cyclization of 3-(2-pyridyl) propargyl carboxylates.

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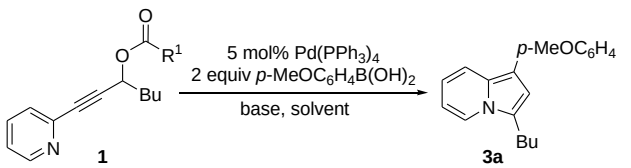
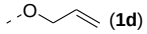
Electronic Supplementary Information (ESI) available: Experimental details, NMR spectra of all compounds. CIF files for 1047516 (**3za**), 1047517 (**3zc**), 1047518 (HCl salt of **4a**), 1047519 (HCl salt of **4b**), See DOI: 10.1039/c000000x/

1,7-diyn-3,6-bis(propargyl carbonate)s with organoborons to form polyacenes,[9] we envisioned that a Pd-catalyzed cross-coupling of 3-(2-pyridyl) propargyl carbonates **1** with readily available organoboronic acids[10] might afford allenyl pyridines **2**, which might undergo cycloisomerization under the reaction conditions to give indolizines **3** (Scheme 1, eq 3). Herein, we report our success based on this hypothesis. Notably, the synthetic methods for 1,3-aryl, alkyl or diaryl-substituted indolizines are quite rare.[7h-i,l,q]

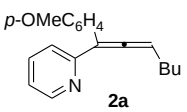
We chose the reactions of propargyl carbonate **1a** bearing an alkyl group at the propargylic position with 4-methoxyphenylboronic acid to test the hypothesis. To our delight, the desired indolizine **3a** could be obtained in moderate yields of 59-60% in THF or DMF in the presence of 5 mol% $Pd(PPh_3)_4$ and 3.0 equiv K_2CO_3 at 80 °C (Table 1, entries 2-3). The use of mixed solvents of DMF/H_2O (4:1) increased the yield of **3a** dramatically to 77% (Table 1, entry 4). Further optimizations indicated that the yield of **3a** could be improved to 82% at 100 °C for 1 h in mixed solvents of DMF/H_2O (3:1) (Table 1, entry 7). Decreasing the amount of arylboronic acid resulted in a lower yield of **3a** (70%, Table 1, entry 10). Other inorganic bases, such as Cs_2CO_3 or K_3PO_4 were also effective

Table 1. Optimization studies for the formation of 1,3-disubstituted indolizine.



entry	R^1	base (equiv)	solvent	temp (°C)	time (h)	yield(%)[a]
1	OMe (**1a**)	K_2CO_3 (3)	CH_3CN	80	2	28
2	OMe (**1a**)	K_2CO_3 (3)	THF	80	12	59
3	OMe (**1a**)	K_2CO_3 (3)	DMF[b]	80	5	60
4	OMe (**1a**)	K_2CO_3 (3)	DMF/H_2O = 4:1	80	2.5	77
5	OMe (**1a**)	K_2CO_3 (3)	DMF/H_2O = 3:1	80	3	79
6	OMe (**1a**)	K_2CO_3 (3)	DMF/H_2O = 2:1	80	2.5	72
7	OMe (**1a**)	K_2CO_3 (3)	DMF/H_2O = 3:1	100	1	82[c]
8	OMe (**1a**)	K_2CO_3 (2)	DMF/H_2O = 3:1	100	1.5	73
9	OMe (**1a**)	-	DMF/H_2O = 3:1	100	3	41
10[d]	OMe (**1a**)	K_2CO_3 (3)	DMF/H_2O = 3:1	100	1	70
11[e]	OMe (**1a**)	K_2CO_3 (3)	DMF/H_2O = 3:1	100	1	82
12	OMe (**1a**)	Cs_2CO_3 (3)	DMF/H_2O = 3:1	100	1	78
13	OMe (**1a**)	K_3PO_4 (3)	DMF/H_2O = 3:1	100	1	76
14	OMe (**1a**)	Et_3N (3)	DMF/H_2O = 3:1	100	1	48
15	OBn (**1b**)	K_2CO_3 (3)	DMF/H_2O = 3:1	100	1	78
16	O^{t}Bu (**1c**)	K_2CO_3 (3)	DMF/H_2O = 3:1	100	1.5	69
17	 (**1d**)	K_2CO_3 (3)	DMF/H_2O = 3:1	100	1	trace
18	Me (**1e**)	K_2CO_3 (3)	DMF/H_2O = 3:1	100	1	59
19	OMe (**1a**)	K_2CO_3 (3)	DMF/H_2O = 3:1	50	0.5	17[f]

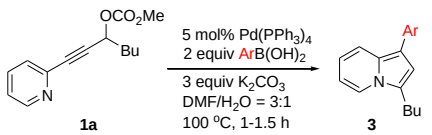
[a] ^{1}H NMR yield using CH_2Br_2 as the internal standard. [b]In this case, anhydrous DMF was used. [c]Isolated yield was 74%. [d]1.5 equiv arylboronic acid was used. [e]3.0 equiv arylboronic acid was used. [f]**2a** was also formed in 63% NMR yield (isolated yield: 56%, containing small amounts of impurity).

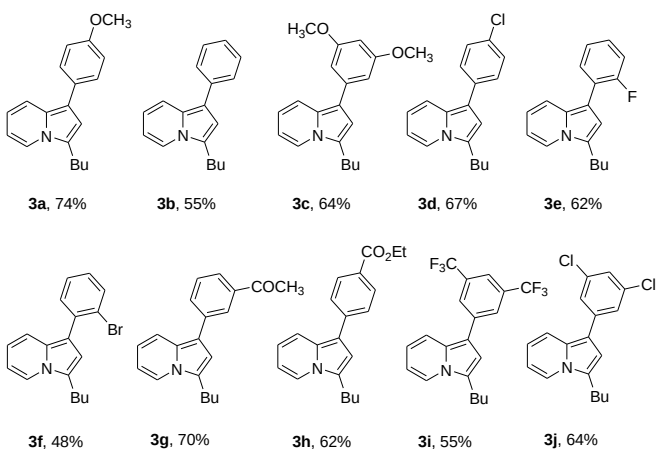


for this transformation, producing **3a** in 76-78% yields (Table 1, entries 12-13). The effect of the protection group (COR^1) was also investigated. Benzyl or *tert*-butyl carbonates, and Ac-protected substrate were accommodated in this reaction, leading to **3a** in 59-78% yields (Table 1, entries 15-16, 18). However, allyl carbonate failed to give the desired product (Table 1, entry 17). It was noted that in most cases, we could observe the formation of an allenyl pyridine intermediate **2a** generated by palladium-catalyzed coupling reaction of propargyl carbonate **1a** with arylboronic acid at the early stage of the reaction. **2a** was formed in 63% NMR yield when the reaction was carried out at 50 °C for 30 min (Table 1, entry 19). It was relatively not stable upon isolation and standing in the air. The above results strongly supported our assumption that indolizine **3** might be constructed through the tandem sequence involving the key intermediate of allenyl pyridine **2**.

With the optimized reaction conditions in hand (Table1, entry 7), the generality of this palladium-catalyzed cascade transformations was examined (Table 2). We first investigated the scope of organoboronic acids. A great variety of aryl boronic acids was compatible with the protocol, leading to indolizines **3a**-**3o** in generally moderate to good yields (35-74%). Both of the electron-rich or -poor arylboronic acids accommodated the reaction well, and the functionalities such as -MeO, -Cl, -F, -Br, -COMe, $-CO_2Et$ and $-CF_3$ on the aryl rings tolerated well during the reaction. The reactions with 4-biphenylboronic acid or 2-naphthylboronic acid were also satisfied, providing **3k** and **3l** in 61% and 63% yields, respectively. Heteroarylboronic acids such as 2-furanyl,

Table 2. Scope of arylboronic acids.[a]



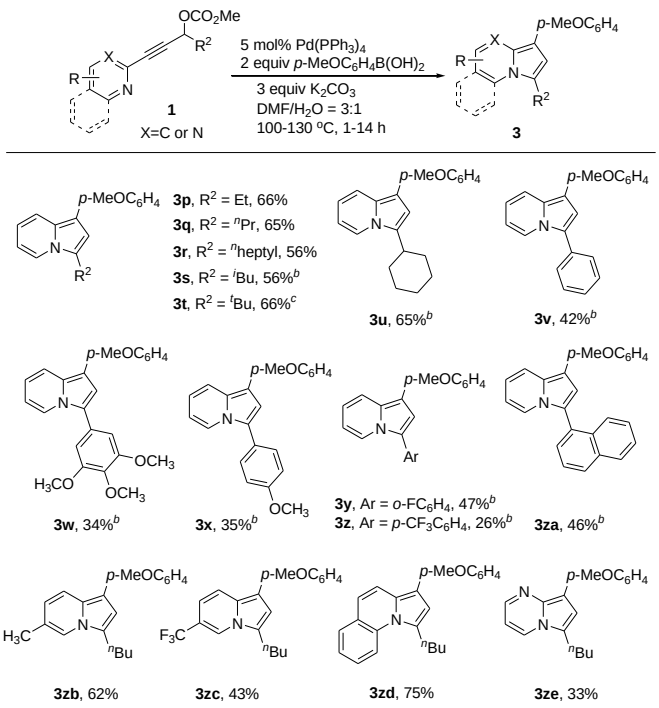


[a] Isolated yields.

3-thienyl, 5-pyrimidinyl-boronic acids were also suitable for this cyclization, furnishing **3m**-**3o** in 35-53% yields. However, employing alkylboronic acids such as *n*-butylboronic acid could not afford the desired product under the present reaction conditions.

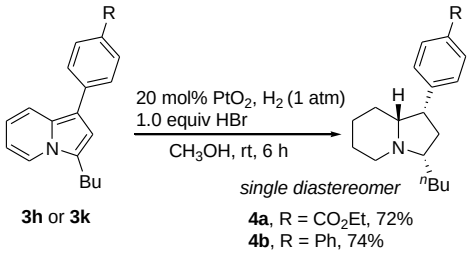
We next examined the substrate scope of various substituted propargyl carbonates using 4-methoxyphenylboronic acid as a reaction partner (Table 3). The substituent effect at the propargylic position (R^2) was examined first. A range of alkyl substituents such as ethyl, *n*-propyl, *n*-heptyl, *iso*-butyl, *tert*-butyl or cyclohexyl were well suited, and the corresponding indolizines **3p**-**3u** were obtained in 56-66% yields. It should be noted that in the case of *tert*-butyl-substituted propargyl carbonate, higher reaction temperature (130 °C) was required in order to complete the reaction. The R^2 substituent could also be aryl groups, however, the corresponding products **3v**-**3za** were formed in lower yields of 26-47% at higher reaction temperature of 110 °C, possibly due to the instability of the *in situ*-generated allene intermediates. Propargyl carbonates with a -Me, or -CF_3 group on the pyridyl ring underwent the reaction smoothly to afford **3zb** and **3zc** in 62% and 43% yields, respectively. Quinoline or pyrimidine propargyl carbonates could also be utilized in this process, producing pyrrolo[1,2-*a*]quinoline **3zd** and pyrrolo[1,2-*a*]pyrimidine **3ze** in 75% and 33% yields, respectively. It was noted that all these indolizines were fluorescent compounds, which might find the utilities in materials science. The structures of indolizines were unambiguously confirmed by X-ray crystallography of **3za** and **3zc**.[11]

Table 3. Scope of propargyl carbonates **1**.



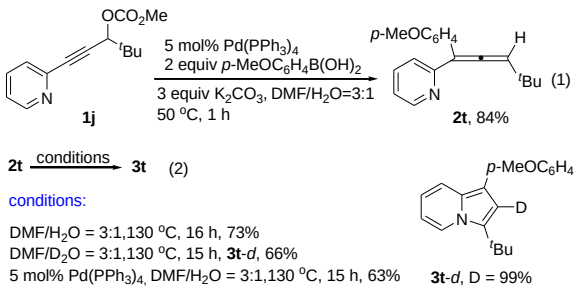
[a] Isolated yields. Unless noted, all the reactions were carried out at 100 °C. [b]110 °C. [c]130 °C, 14 h.

The obtained indolizines could be easily hydrogenated under the acidic conditions. For example, hydrogenation of **3h** or **3k** catalyzed by PtO_2 in the presence of one equiv of HBr[7a] under 1 atm of H_2 afforded **4a** or **4b** as a single diastereomer in 72% and 74% yields, respectively (Scheme 2). The structure and the stereochemistry of **4** were unambiguously confirmed by X-ray crystallographic analysis of their hydrochloride salts prepared by treatment of **4** with HCl/Et_2O solution.[11] The results indicated that hydrogenation proceeded via *syn*-addition of hydrogen atoms.



Scheme 2. Hydrogenation of indolizine **3.**

To understand the reaction mechanism, the ^{t}Bu-substituted allenyl pyridine **2t** was isolated in 84% yield upon lowering the reaction temperature to 50 °C, which was confirmed to be stable enough to undergo the further reactions (Scheme 3, eq 1). Heating a solution of **2t** in DMF/H_2O at 130 °C in the absence of Pd catalyst resulted in the formation of indolizine **3t** in 73% yield. The use of D_2O instead of H_2O afforded **3t**-*d* in 66% yield with high deuterium incorporation (99%). In addition, no deuterium incorporation was found in indolizine **3t** when heating a solution of **3t** in DMF/D_2O at 130 °C. In the presence of palladium catalyst, **3t** was formed in a lower yield of 63% (Scheme 3, eq 2). The results indicated that the cyclization of allenyl pyridine **2** to indolizine **3** might proceed without the need of the metal catalyst. It was noted that heating **2t** in neat water at 130 °C resulted in its full decomposition, likely due to the solubility issues. When DMF was used as the sole solvent, only a trace amount of **3t** was observed at 130 °C accompanied by a partial decomposition of **2t**. The results indicated that cycloisomerization of allenyl pyridines might be facilitated by water, and DMF played a role in dissolving the substrate. Recently, Sarpong et al. also discovered that cycloisomerization of propargylic ester to indolizines was promoted by water.[12] Although the detailed effect of water was not clear yet, it may stabilize the charged transition state formed during the cyclization process. It was noted that although allenyl pyridine was proposed as the key intermediate in many metal-catalyzed cycloisomerization of pyridyl-substituted propargyl esters to indolizines,[7a,7c-d,7k-l,7p] the isolation and further transformation of this intermediate was still rare.[7l]



Scheme 3. Control Experiments.

In summary, we have developed a new Pd-catalyzed cross-coupling/cycloisomerization of 3-(2-pyridyl) propargyl carbonates with organoboronic acids, which provides a straightforward route for the synthesis of 1,3-disubstituted indolizines with a wide variety of substituents. Mechanistic

study indicates that the reaction proceeds via formation of an allenyl pyridine intermediate catalyzed by palladium followed by cyclization. Cyclization of the allenyl pyridine intermediates to indolizines is promoted in H_2O/DMF upon heating without the need of the metal catalysts. Further exploration and applications of this chemistry are underway in our group.

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