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Synthesis of Pyrrolo[2,1,5-*cd*]indolizines through Dehydrogenative Heck Annelation of Indolizines with Diaryl Acetylenes Using Dioxygen as an Oxidant

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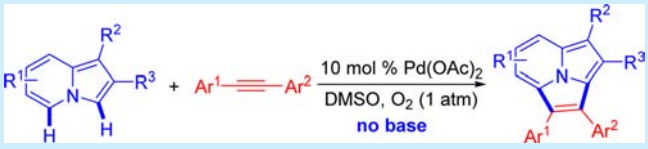
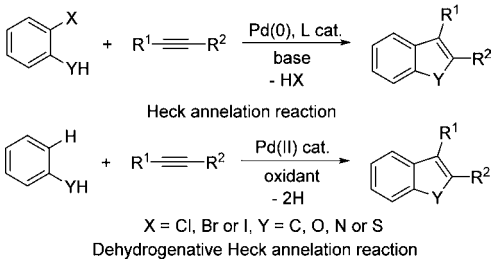
Supporting Information

ABSTRACT: A dehydrogenative Heck annelation reaction of indolizine with diaryl acetylene via dual C−H bond cleavage was developed. Oxygen gas was employed as a clean oxidant in this catalysis under base-free conditions. Diarylpyrrolo[2,1,5-*cd*]indolizines were synthesized with high atom economy. In addition, kinetic isotope experiments provided evidence for C−H bond metalation of the 5-position of the indolizine as the rate-limiting step.



Development of efficient strategies for the construction of polycyclic heterocycles with various properties is of great importance in modern organic chemistry. One of the most powerful tools is the Heck annelation reaction.[1] Over the past few years, dehydrogenative Heck annelation reactions using arenes as starting materials instead of aryl halides have been developed.[2] These methods succeed in losing only two hydrogen atoms from the substrates, which is more compatible with the atom economy principle (Scheme 1).[3]

Scheme 1. Differences between Heck Annelation and Dehydrogenative Heck Annelation



Pyrrolo[2,1,5-*cd*]indolizine, commonly known as cycl[2,2,3]-azine, is the most interesting member of the cyclazine family. Pyrrolo[2,1,5-*cd*]indolizine derivatives are of great importance in the field of pharmaceuticals and are also versatile building blocks for natural products, bioactive compounds, and drugs.[4] Moreover, pyrrolo[2,1,5-*cd*]indolizines were observed to have long wavelength absorption and fluorescence in the visible light region and were used as fluorescent probes and organic electroluminescent materials.[5] Their importance has drawn considerable attention from organic chemists and stimulated the development of new synthetic strategies to construct pyrrolo[2,1,5-*cd*]indolizines.[6]

In the past several decades, the [8 + 2]-cycloaddition of indolizine with an electron-deficient alkyne has been frequently used for the preparation of pyrrolo[2,1,5-*cd*]indolizines.[7] However, only electron-deficient alkynes could be used in this stage. Therefore, using an electron-rich alkyne to construct pyrrolo[2,1,5-*cd*]indolizine remains a challenge in this field. Recently, pyrrolo[2,1,5-*cd*]indolizines were synthesized via a palladium-catalyzed decarboxylative coupling reaction between indolizines and α,β-unsaturated carboxylic acids.[8] As a follow-up to our interest in indolizine derivatives,[9] we considered the synthesis of pyrrolo[2,1,5-*cd*]indolizine from indolizine with an electron-rich internal alkyne through the dehydrogenative Heck annelation reaction (Scheme 2).

In the preliminary study, *N*,*N*-dimethylindolizine-1-carboxamide **1a** (0.20 mmol) and 1,2-diphenylethyne **2a** (1.5 equiv) with palladium acetate (10 mol %) as catalyst and DMSO (dimethyl sulfoxide) as solvent were chosen as our model system. As the results show (Table 1), the yield of the proposed product **3aa** reached 32% under oxygen atmosphere (balloon) and base-free conditions with the dimer **9** as the main byproduct (Table 1, entry 1). The structure of **3aa** was confirmed by CCDC (Figure 1).[10] Based on the previously reported results,[9f,g,11] acetic acid or potassium acetate was added to improve the reaction selectivity between dimerization and Heck annelation. As shown in Table 1 (entries 2−4), acetic

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Scheme 2. Different Ways of Synthesizing Pyrrolo[2,1,5-*cd*]indolizines from Indolizines and Alkynes

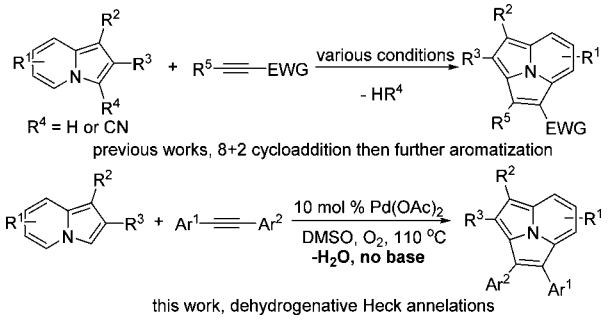
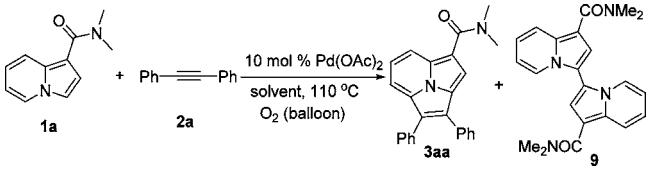


Table 1. Optimization of Reaction Conditions[a]



entry	additive	amount (%)	solvent	yield of 3aa (%)[b]
1	NA[c]	0	DMSO	32
2	acetic acid	200	DMSO	52
3	potassium acetate	200	DMSO	33
4	acetic acid	10	DMSO	57
5	trifluoroacetic acid	10	DMSO	61
6	trifluoromethanesulfonic acid	10	DMSO	55
7	pivalic acid	10	DMSO	35
8	benzoic acid	10	DMSO	59
9	2-nitrobenzoic acid	10	DMSO	67
10	2,6-difluorobenzoic acid	10	DMSO	71
11	2,6-difluorobenzoic acid	10	NMP	18
12	2,6-difluorobenzoic acid	10	DMA	15
13	2,6-difluorobenzoic acid	10	DMF	27
14[d]	2,6-difluorobenzoic acid	10	DMSO	76
15[e]	2,6-difluorobenzoic acid	10	DMSO	0

[a]Reaction conditions: 10 mol % of palladium acetate, 3.0 mL of solvent under O_2 (balloon) at 110 °C for 8 h. [b]Isolated yield. [c]No addition. [d]With 2.0 equiv of **2a**. [e]No palladium acetate.

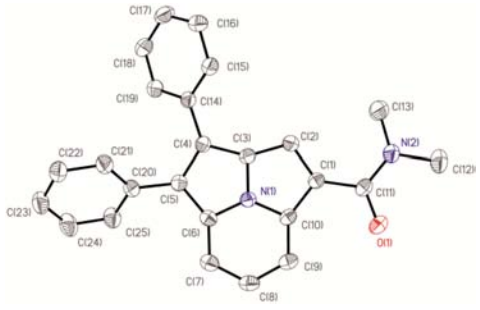
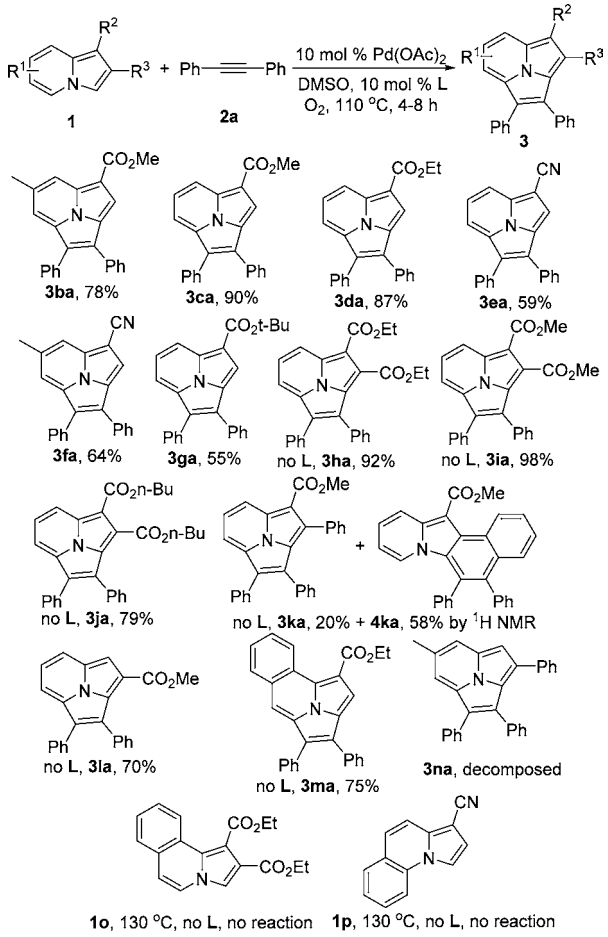


Figure 1. ORTEP of **3aa**.

acid was efficient, and 10 mol % of acetic acid as an additive was superior to 2 equiv of acetic acid. Then, a series of acids were tested for our model reaction. 2,6-Difluorobenzoic acid (**L**) was found to be the most efficient (details about the role of additive are in Supporting Information). Further investigation of reaction solvents led us to establish the optimized reaction conditions as follows: 10 mol % of palladium acetate, 10 mol % of **L**, 3.0 mL of DMSO as solvent under O_2 at 110 °C for 8 h with 2.0 equiv of **2a** (Table 1, entry 14). Importantly, no **3aa** was detected in the absence of palladium acetate (Table 1, entry 15).

Regarding the substrate scope of indolizines, a series of different indolizines coupled with **2a** were studied under standard conditions (Scheme 3). Indolizines bearing an

Scheme 3. Scope of Indolizines[a]



[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.40 mmol), 10 mol % of palladium acetate, 10 mol % of **L**, 3.0 mL of DMSO, under O_2 (balloon) at 110 °C.

electron-withdrawing group at the 1-position (**1a–g**) reacted with **2a** smoothly. Indolizines with a substituted group at the 2-position were unreactive under standard conditions. However, good yields were achieved under additive-free conditions (**1h–m**), which was in accord with our previous results.[9f,g] At the same time, indolizine without an electron-withdrawing group (**1n**) was decomposed under standard reaction conditions, while **3ka** (20%) and **4ka** (58%) were isolated by using methyl 2-phenylindolizine-1-carboxylate (**1l**) as the starting material. Moreover, fused indolizine with two electron-withdrawing groups at the 1- and 2-positions (**1o**) was unreactive even when the reaction temperature was increased to 130 °C. Notably, indolizine **1p** did not give any six-membered ring product.

To study the substrate scope and regioselectivity of diaryl acetylenes, different diaryl acetylenes were coupled with **1i** under standard conditions without any additive (Scheme 4).

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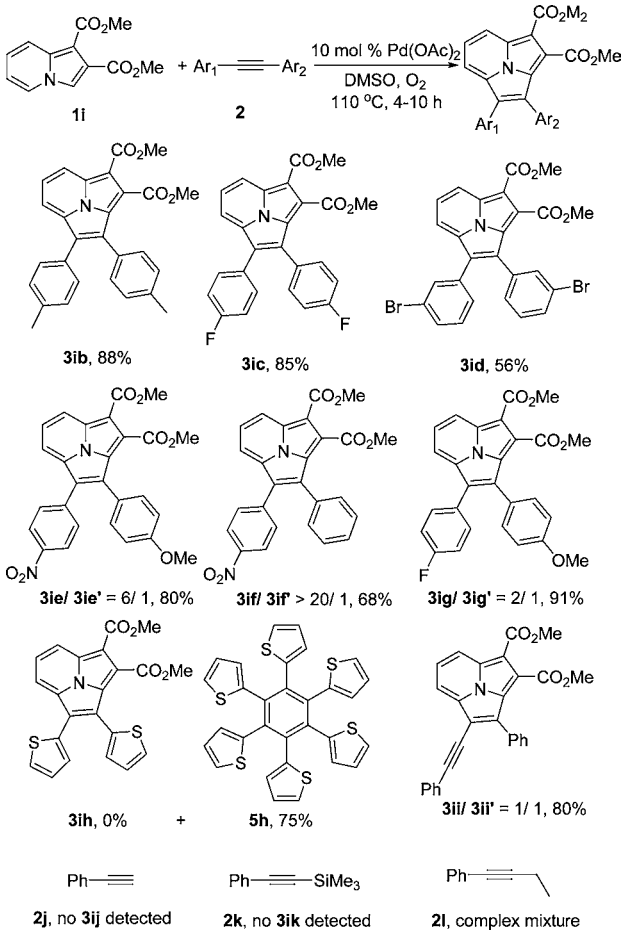
Scheme 4. Scope and Regioselectivity of Diaryl Acetylenes[a]

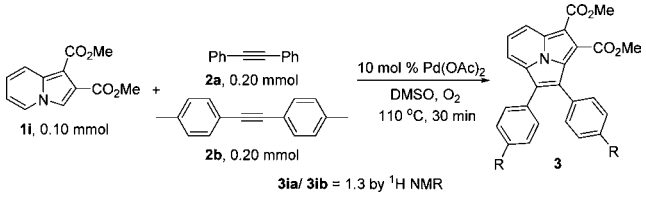


[a]Reaction conditions: **1i** (0.20 mmol), **2** (0.40 mmol), 10 mol % of palladium acetate, 3.0 mL of DMSO, under O_2 (balloon) at 110 °C.

Symmetrical acetylenes produced products in a smooth manner (Scheme 4, **2b–d**). However, 1,2-di(thiophen-2-yl)ethyne (**2h**) only gave a trimer (**5h**). Unsymmetrical acetylenes gave two isomers. The major products are always the isomers in which the phenyl-ring-bearing electron-withdrawing group is near the six-membered ring of indolizine (Scheme 4, **2e–g**). Notably, 1,4-diphenylbuta-1,3-diyne (**2i**) gave two isomers in a 1:1 ratio. These structures were confirmed by CCDC analysis.[12] Unfortunately, alkynes that only bear one aryl group (**2j–l**) were inefficient in this transformation.

To understand the regioselectivity of the unsymmetrical alkynes, a control experiment was also conducted. Indolizine **1i** reacted with an excess amount of **2a** and **2b** in one tube for 30 min (Scheme 5). The ratio of **3ia**/**3ib** was 1.3, which was measured by ^{1}H NMR. This result indicates that the alkyne

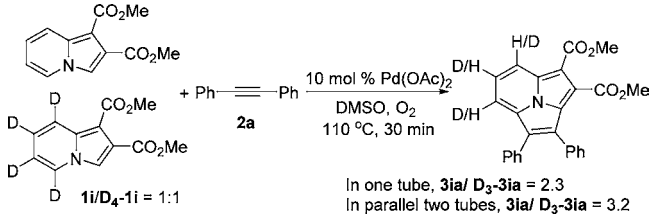
Scheme 5. Control Experiments for Understanding the Regioselectivity of Unsymmetrical Alkynes



with higher electron density would react with indolizine slower and can also explain the reason for regioselectivity of the unsymmetrical alkynes and low reactivity of **2h** with indolizine.

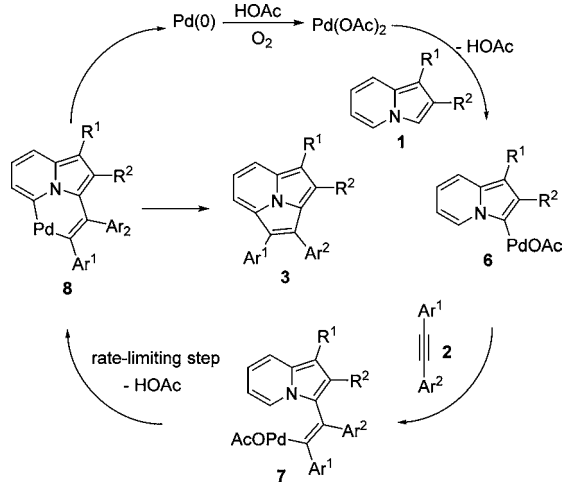
Isotope experiments were conducted to understand the reaction mechanism. As the first step, D_4-**1i** was synthesized from pyridine-d_5.[13] Then **1i** and D_4-**1i** reacted with **2a** in one tube or in two parallel tubes under standard reaction conditions for 30 min. The ratios of **3ia**/D_3-**3ia** were 2.3 and 3.2, respectively, as detected by ^{1}H NMR (Scheme 6). These results were consistent with a primary kinetic isotope effect and indicated the C–H bond metalation at the 5-position of indolizine as the rate-limiting step.

Scheme 6. Isotope Experiments



Based on our previously reported results[9f] and the present study, a plausible reaction mechanism was proposed in Scheme 7. First, palladium diacetate reacted with **1** through C–H

Scheme 7. Proposed Mechanism



activation to form intermediate **6**, and then **6** coordinated with **2** and further transformed to **7** through insertion. Then **8** was formed from **7** through a second C–H activation as the next step (the rate-limiting step of this reaction), followed by product **3** and Pd(0) generated from **8** through reductive elimination. Finally, palladium acetate was regenerated from Pd(0) under oxygen to complete the catalytic cycle.

To demonstrate the synthetic utility of this method, the reaction was conducted on 4.0 mmol scale, producing **3ia** in 98% yield (1.61 g, Scheme 8).

In summary, a palladium-catalyzed dehydrogenative Heck annelation of indolizine with diaryl acetylene was developed. Oxygen gas was used as the only oxidant under base-free conditions. For 2-unsubstituted indolizines, the catalytic amount of 2,6-difluorobenzoic acid used as an additive was crucial for the success of this transformation. A wide range of

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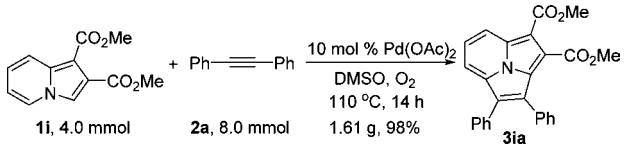
Scheme 8. Gram Scale Experiment



functional groups were tolerated both in indolizines and diaryl acetylenes. The versatility of the pyrrolo[2,1,5-*cd*]indolizine moiety should render this protocol highly attractive for both material and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data for all new compounds, and fluorescence spectra of **3aa** and **3ma**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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