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Synthesis of Indolo [1,2-*a*]Quinoxalines via a Pd-Catalyzed Regioselective C−H Olefination/Cyclization Sequence

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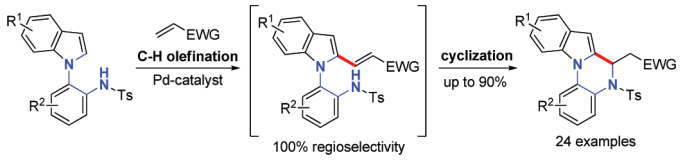
ABSTRACT



A highly efficient approach to indolo [1,2-*a*]quinoxaline derivatives through a Pd-catalyzed regioselective C−H olefination/cyclization sequence has been developed. This transformation has a wide range of substrates with various functional groups, and the corresponding heterocyclic products were obtained in good yields.

Indole/pyrrole-fused heterocycles are widely present in a large number of natural products as well as drug candidates and medicinal chemistry lead compounds.[1] Among this plethora of compounds, indole/pyrrole-fused quinoxaline derivatives have always constituted a subject of great interest due to their intriguing structures and remarkable biological activities (Figure 1). For instance, indolo [1,2-a]quinoxaline **A** exhibits promising antifungal activities *in vitro* against the phytopathogenic fungi and **B** is identified as a potential inhibitor of VEGFR-3 kinase cells.[2] In addition, 6-FQXPT, a compound bearing a pyrrolo [1,2-*a*]quinoxaline unit, has been recognized to be the second generation non-nucleoside reverse transcriptase inhibitor (NNRTI).[3] Therefore, the development of novel and highly efficient methods to construct these fused heterocyclic architectures is highly desirable for drug discovery.

Over the past decade, the transition-metal-catalyzed direct C−H activation strategy has become a powerful

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protocol for the construction of complex molecules.[4] In this context, cascade C−H oxidative olefination/cyclization

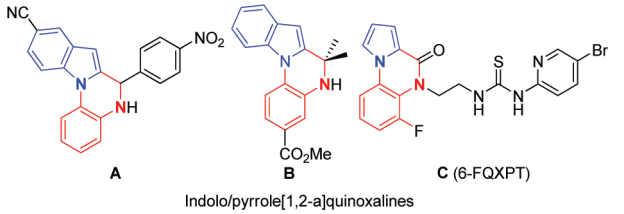
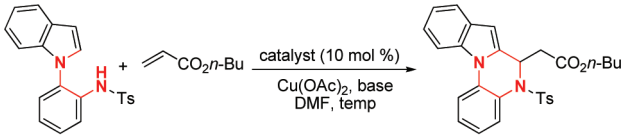


Figure 1. Representative examples of indole/pyrrole-fused quinoxaline derivatives.

processes have been widely used to efficiently generate structurally diverse heterocyclic compounds.[5,6] In the 1990s, Miura and co-workers reported their pioneering work on Pd-catalyzed cascade C−H olefination and C−X bond (X = N, O) formation utilizing phenol, benzoic acid and benzene sulphonamide.[7] More recently, related examples of Pd- and Rh-catalyzed cascade C−H olefination/cyclization reactions via the cleavage of aromatic C−H bonds of amides or benzoic acids have been successfully developed by Yu, Glorius, Li, and others.[8] Despite these advances, the application of such a cascade C−H oxidative olefination/cyclization methodology to the privileged indole and pyrrole scaffolds is still rare but highly desirable.

As part of our ongoing program on heterocycle-oriented methodology development, we describe herein a highly regioselective C−H olefination/cyclization sequence of *N*-aryl-substituted indoles/pyrroles and electron-withdrawing olefins for the synthesis of a series of novel indole/fused heterocycle derivatives.[9,10]

Table 1. Optimization of Reaction Conditions for the C−H Olefination/Cyclisation Sequence[a]



entry	catalyst	temp (°C)	base	yield (%)[b]
1	$Pd(OAc)_2$	100	NaOAc	58
2	$Pd(TFA)_2$	100	NaOAc	53
3	$PdCl_2$	100	NaOAc	54
4	$Pd(PPh_3)_2Cl_2$	100	NaOAc	39
5	$Pd(CH_3CN)_2Cl_2$	100	NaOAc	49
6	$Pd(PhCN)_2Cl_2$	100	NaOAc	51
7	Pd_2dba_3	100	NaOAc	18
8	$Pd(PPh_3)_4$	100	NaOAc	38
9	$Pd(OAc)_2$	110	NaOAc	76
10	$Pd(OAc)_2$	120	NaOAc	71
11	$Pd(OAc)_2$	110	LiOAc	71
12	$Pd(OAc)_2$	110	KOAc	70
13	$Pd(OAc)_2$	110	CsOAc	75
14	$Pd(OAc)_2$	110	CsOPiv	72
15[c]	$Pd(OAc)_2$	110	NaOAc+LiOAc	82
16[d]	$Pd(OAc)_2$	110	CsOAc+LiOAc	76

[a] Unless noted, reactions were performed with **1a** (0.20 mmol), **2a** (0.40 mmol), $Cu(OAc)_2$ (0.30 mmol), base (0.45 mmol), and Pd-catalyst (10 mol %) in DMF (2.0 mL) at the indicated temperature. [b] Isolated yield. [c] NaOAc (0.45 mmol) and LiOAc (0.45 mmol). [d] CsOAc (0.45 mmol) and LiOAc (0.45 mmol).

We commenced the cascade reaction between *N*-aryl-substituted indole derivatives **1a** and *n*-butyl acrylate **2a**.

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Gratifyingly, the use of $Pd(OAc)_2$ (10 mol %) and $Cu(OAc)_2$ as the catalytic system together with a stoichiometric amount of NaOAc as the base at 100 °C in DMF resulted in the formation of the desired indole [1,2-*a*] quinoxaline **3a** in 58% yield (Table 1, entry 1). The structure of **3a** was unambiguously established by X-ray crystallographic analysis (Figure 2). Encouraged by this result, we continued to optimize reaction conditions to further improve the chemical yield. Screening of catalysts indicated that $Pd(OAc)_2$ displayed the highest catalytic activity toward the formation of **3a** (Table 1, entries 1−8).

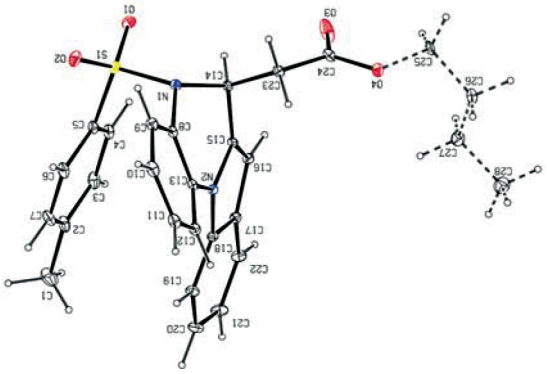


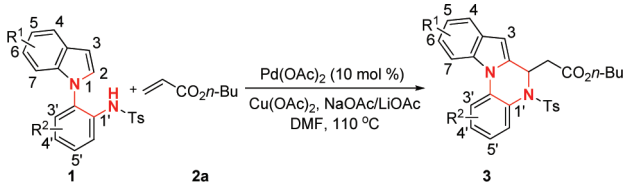
Figure 2. X-ray crystal structure of **3a**.

The reaction temperature had a significant effect on the reaction efficiency, and the yield was drastically increased to 76% when the reaction was carried out at 110 °C (entry 9). Various bases such as LiOAc, KOAc, CsOAc, and CsOPiv were found to be effective for this cascade C−H olefination/cyclization (entries 11−14). Finally, the yield of the product was further improved to 82% when a mixture of NaOAc and LiOAc was used in the reaction system (entry 15).

With the optimal conditions in hand, we then investigated the scope of this transformation using different *N*-aryl-substituted indole derivatives. As summarized in Table 2, a number of alkyl and alkyoxyl substituents can be incorporated on the indole or benzene ring at various positions without significant loss in reaction efficiency (Table 2, entries 2−6 and 9−10, $R^{1,2}$ = Me, MeO, or BnO). It is well-known that fluorine can affect the biological activity of compounds. As revealed in entries 7 and 12, we successfully utilized fluoro-substituted substrates in this cascade reaction.[11] Of note, a chloro group on the indole or phenyl ring of the substrate, which was well-tolerated in the current reaction system, could also be used for further transformation (entries 8 and 9). Notably, the catalytic system proved to be tolerant of valuable electrophilic functional groups, such as esters (entry 13). Additionally, the current catalytic system was not restricted to the use of monosubstituted substrates, but also allowed for efficient oxidative cyclization of different disubstituted *N*-arylation of indoles (entries 6 and 14). Perhaps more importantly, substrate **1o** not only demonstrated that steric interactions were well-tolerated but also showed excellent regioselectivity in our cascade catalytic system (entry 15).

Subsequently, a variety of electron-deficient terminal alkenes were examined. Scheme 1 shows that reactions of *N*-aryl-substituted indole **1a** with several acrylates **2p**−**2w** proceeded smoothly and efficiently to produce the corresponding products in generally good yields. Methyl vinyl ketone **3s** and *N*,*N*-dimethylacrylamide **3t** were also found to be competent coupling partners. Other olefins, such as vinyl Sulphone, vinyl phosphonate, and vinyl cyanide,

Table 2. Pd-Catalyzed C−H Olefination/Cyclization Sequence[a]



entry	R^1	R^2	product	yield (%)[b]
1	H	H	**3a**	82
2	4-Me	H	**3b**	80
3	5-Me	H	**3c**	81
4	6-Me	H	**3d**	88
5	5-BnO	H	**3e**	71
6	5,6-$(MeO)_2$	H	**3f**	88
7	6-F	H	**3g**	75
8	6-Cl	H	**3h**	90
9	H	4-Me	**3i**	87
10	H	4,5-$(Me)_2$	**3j**	82
11	H	4-Cl	**3k**	68
12	H	4-CF_3	**3l**	66
13	H	4-CO_2Me	**3m**	65
14	6-Cl	4-Me	**3n**	73
15	3-Me	H	**3o**	83

[a] Unless noted, reactions were performed with **1a** (0.20 mmol), **2a** (0.40 mmol), $Cu(OAc)_2$ (0.30 mmol), NaOAc (0.45 mmol), LiOAc (0.45 mmol), and $Pd(OAc)_2$ (10 mol %) in DMF (2.0 mL) at 110 °C. [b] Isolated yield.

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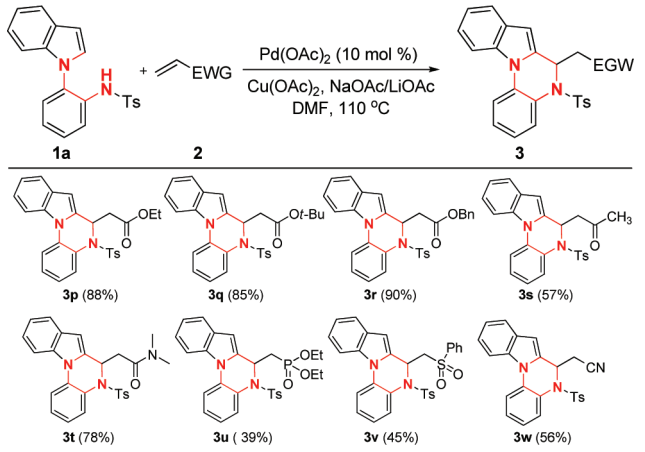
Scheme 1. Pd-Catalyzed C−H Olefination/Cyclization Sequence[a,b]

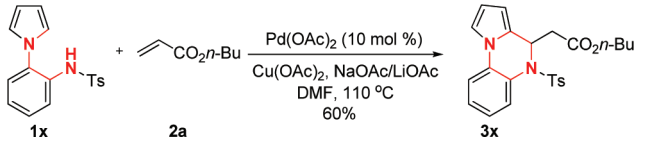


[a] Unless noted, reactions were performed with **1a** (0.20 mmol), **2a** (0.40 mmol), $Cu(OAc)_2$ (0.30 mmol), NaOAc (0.45 mmol), LiOAc (0.45 mmol), and $Pd(OAc)_2$ (10 mol %) in DMF (2.0 mL) at 110 °C. [b] Isolated yield.

could also participate in this C−H olefination/cyclization sequence, albeit with poor reactivity.

Interestingly, we were pleased to find that the indole core could be successfully extended to pyrrole-derived systems. For example, *N*-aryl-substituted pyrrole **1x** smoothly reacted with *n*-butyl acrylate **2a** affording the corresponding cyclized product in 60% yield (Scheme 2).

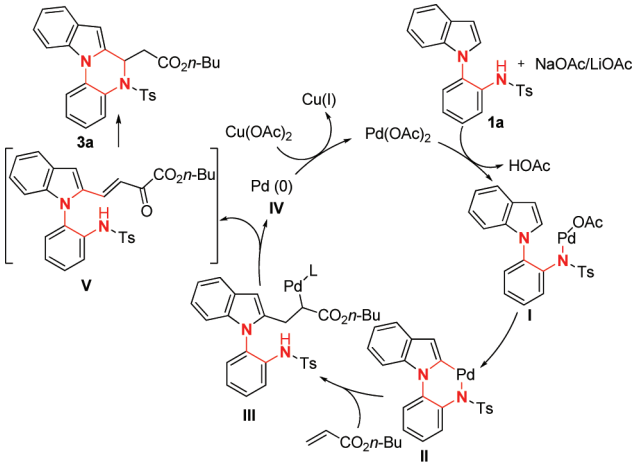
Scheme 2. Pd-Catalyzed C−H Olefination/Cyclization Sequence Reaction of a Pyrrole



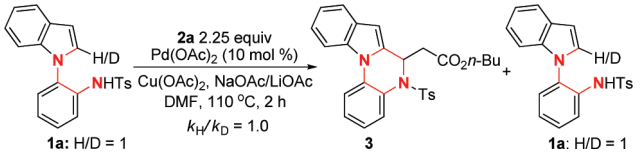
On the basis of these preliminary results, a plausible mechanism is illustrated in Scheme 3. We envisioned that an initial intermediate **I** could be generated by Pd−N bond formation with the aid of a base. Selective activation of the C−H bond at the 2-position of the indole ring formed a six-membered palladium (**II**) intermediate. Then, palladacycle **II** could smoothly undergo the Fujiwara−Moritani process with electron-deficient alkenes to provide the C−H olefination intermediate **V**.[12] Subsequently, intramolecular cyclization through C−N bond formation gave the final product.

Intermolecular kinetic isotope effects were readily obtained through a competition experiment of deuterium-

Scheme 3. Proposed Reaction Pathway



Scheme 4. Experiment for Kinetic Isotope Effects



labeled **1a** at the 2-position of the indole ring (H/D = 1) (Scheme 4).[13] It was observed that the reaction did not exhibit kinetic isotope effects (k_H/k_D = 1.0), which may imply that C−H bond cleavage at the C2 position of the indole is not involved in the rate-determining step of the overall catalytic process.

In summary, we have developed an efficient Pd-catalyzed highly regioselective C−H olefination and cyclization sequence of *N*-aryl-substituted indoles and electron-withdrawing olefins. The reaction is applicable to a wide range of substrates with various functional groups affording the corresponding indole/pyrrole-fused quinoxaline derivatives in moderate to good yields. Application of this reaction to the preparation of biologically relevant compounds is currently underway.

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Supporting Information Available. Experimental procedures and compound characterization data including X-ray crystal data (CIF) for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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