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Synthesis of Biindolizines through Highly Regioselective Palladium-Catalyzed C−H Functionalization

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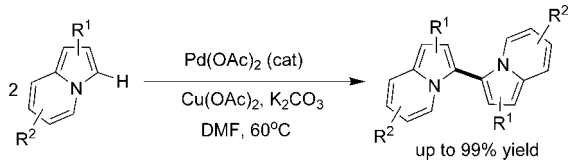

Biindolizines were synthesized under mild conditions with excellent regioselectivity in high yields through palladium-catalyzed C−H functionalization of indolizines. Synthesis of a macrocyclic compound was also achieved via intramolecular double C−H functionalization.

Indolizines are important *N*-fused heterocycles broadly found in biologically important natural products and synthetic pharmaceuticals.[1] Accordingly, synthesis and functionalization of indolizines have attracted considerable attention for several decades.[2] However, biindolizines have so far received relatively little attention despite their being rather stable, reversible two-step redox systems of theoretical and practical interests[3] and their utility in the synthesis of cyclophanes[4] or as axially chiral ligands.[5]

Historically, construction of biindolizine systems commonly involves the utilization of dehydrogenating agents, such as palladium on carbon, platinum on carbon, and potassium ferricyanide, or through an electrochemical route.[6] However, the substrate scope is rather limited under these reaction conditions, and only electron-rich substrates work well. Recently, Pd(II) salts were found to catalyze the oxidative homocoupling reaction of benzene, thiophene, and arylpyridine derivatives[7] through a C−H functionalization.[8] In addition, the cross-coupling reactions of arenes or heteroarenes were also achieved through double C−H functionalization process.[9] However, the utility of these transformations is rather limited mainly due to the low reactivity, poor yields and unsatisfactory selectivity. Recently, there are significant examples reported where a directing group has to be used for good selectivity and yields.[7b,c,9b,e−g] As part of our continuing efforts to develop efficient carbon−carbon formation processes via double C−H functionalization,[9d] herein we report a palladium-catalyzed highly regioselective oxidative coupling reaction under mild conditions for the synthesis of biindolizines through C−H functionalization. This represents a rare example in that excellent yields and regioselectivity are obtained for a transition-metal-catalyzed double C−H functionalization process without the use of a directing group.

In our initial study, the oxidative coupling of the ester group bearing indolizine **1a** was performed in mesitylene at 150 °C with 10 mol% of $Pd(TFA)_2$, 2 equiv of $Cu(OAc)_2$, and 2 equiv

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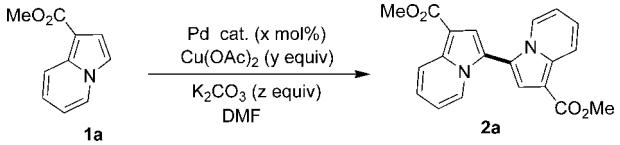
TABLE 1. Optimization of the Homo-Coupling Reaction Conditions[a]



1a 2a

entry	Pd(*x* mol %)	*y*	*z*	*T* (°C)	*t* (h)	conv. (%)[b]
1[c]	$Pd(TFA)_2$(10)	2	2	150	56	61
2	$Pd(TFA)_2$(10)	2	2	140	5	>95(93)
3	$Pd(OAc)_2$(10)	2	2	140	0.33	>95(92)
4	−	2	2	140	10	0
5	$Pd(OAc)_2$(5)	2	2	140	0.67	>95(91)
6	$Pd(OAc)_2$(2)	2	2	140	35	>95(74)
7	$Pd(OAc)_2$(5)	2	2	60	1.5	>95(95)
8	$Pd(OAc)_2$(5)	2	2	rt	120	55
9	$Pd(OAc)_2$(5)	2	1	60	0.67	>95(80)
10	$Pd(OAc)_2$(5)	2	−	60	7	94(75)
11	**$Pd(OAc)_2$(5)**	**1.5**	**2**	**60**	**2**	**>95(99)**
12	$Pd(OAc)_2$(5)	1	2	60	36	49
13[d]	$Pd(OAc)_2$(5)	0.2	2	140	55	77

[a] 0.4 mmol of **1a** in solvent (2 mL). [b] Determined by ^{1}H NMR, and the number in the parentheses indicates the yield. [c] Reaction was carried out in mesitylene. [d] O_2 balloon was used.

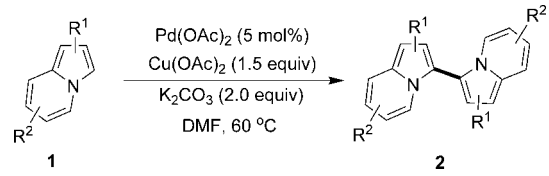
of K_2CO_3. To our delight, 61% conversion was obtained after 56 h (entry 1, Table 1). The structure of the biindolizine product **2a** was further confirmed by an X-ray analysis of a single crystal.[10] When DMF was used as the solvent, the reaction proceeded faster and full conversion was obtained in 5 h (entry 2, Table 1). Interestingly, $Pd(OAc)_2$ was found to be a better catalyst for obtaining full conversion of **1a** in a shorter reaction time (entry 3, Table 1). Notably, the reaction did not occur in the absence of the palladium catalyst (entry 4, Table 1). After the examination of the catalyst loading and the reaction temperature, we found that 5 mol% of $Pd(OAc)_2$ gave an excellent yield (95%) at 60 °C in 1.5 h (entries 5−8, Table 1). It is worthy of note that a reasonable yield (74%) can be obtained with 2 mol% of $Pd(OAc)_2$ (entry 6, Table 1). The presence of K_2CO_3 was crucial to obtain higher yield and 2 equiv of K_2CO_3 gave the best yield (entries 7, 9 and 10, Table 1). Examination of the loading of oxidant revealed that 1.5 equiv of $Cu(OAc)_2$ was sufficient to mediate the reoxidation process to give full conversion and 99% yield (entry 11, Table 1). When a catalytic amount of $Cu(OAc)_2$ (0.2 equiv) in the presence of an oxygen balloon was tested in the coupling reaction, a moderate conversion (77%) could be obtained (entry 13, Table 1).

Under the optimized conditions as described in entry 11, Table 1, the generality of the reaction was examined. We found that the oxidative coupling reaction was quite general and highly regioselective for a variety of indolizine substrates.

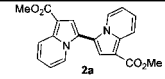
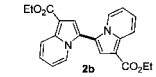
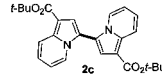
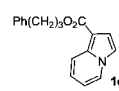
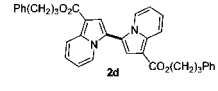
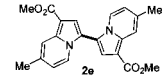
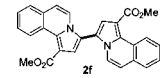
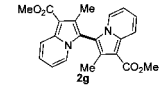
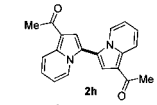
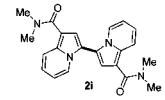
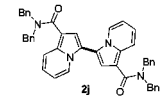
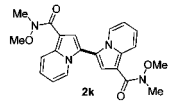
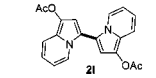
Various indolizine esters such as ethyl, *tert*-butyl, and 3-phenylpropyl esters worked well (entries 2−4, Table 2) although *tert*-butyl ester **1c** required a higher temperature (140 °C) for full conversion (entry 3, Table 2). Excellent yields were obtained when substituted indolizine esters **1e**−**f** were employed (entries 5 and 6, Table 3). A 34% yield was obtained when **1g** was employed, probably due to the steric effect of the 2-methyl substituent (entry 7, Table 2). Moreover, indolizine ketone and amides **1h**−**k** worked smoothly to give the corresponding coupling products in good to excellent yields (entries 8−11,

(10) CCDC 687313 contains the supplementary crystallographic data for product **2a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data request/cif.

TABLE 2. Scope of Oxidative Homo-Coupling of Indolizines[a]



1 2

entry	substrate	product	t (h)	yield (%)
1	 1a	 2a	2	99
2	 1b	 2b	3	93
3[b]	 1c	 2c	12	80
4	 1d	 2d	48	67
5	 1e	 2e	1	91
6	 1f	 2f	3	89
7	 1g	 2g	96	34
8	 1h	 2h	0.6	99
9	 1i	 2i	2.5	57
10	 1j	 2j	6	74
11	 1k	 2k	2	91
12	 1l	 2l	24	66

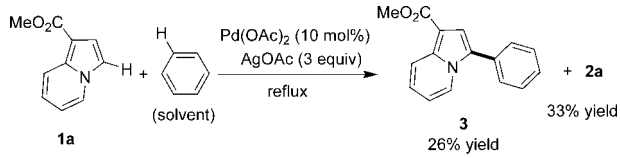
[a] **1** (0.2 M) in DMF at 60 °C with the following molar ratio: **1**/$Pd(OAc)_2$/$Cu(OAc)_2$/K_2CO_3 = 1/0.05/1.5/2. [b] Reaction was carried out at 140 °C.

Table 2). In addition to the electron-withdrawing group bearing substrates, indolizine **1l** was also tested under the optimal conditions, and the homocoupling product **2l** was obtained in 66% yield (entry 12, Table 2).

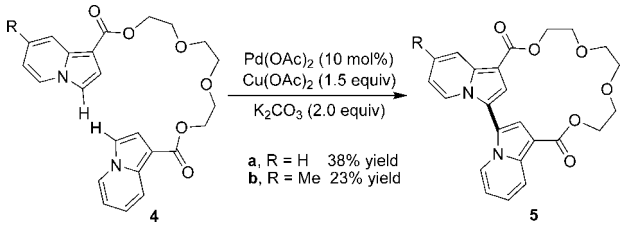
We have also explored oxidative cross-coupling reactions between indolizine **1a** and benzene (Scheme 1).[11] With 10 mol% of $Pd(OAc)_2$ and 3 equiv of AgOAc in refluxed benzene, the

(11) For Pd-catalyzed direct arylation of indolizines, see: (a) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. For mechanistic study of Pd-catalyzed direct arylation of heterocycles, see: (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

SCHEME 1. Oxidative Cross-Coupling Reaction between Indolizine 1a and Benzene



SCHEME 2. Construction of Cyclophanes by Intramolecular Oxidative Coupling Reactions



oxidative cross-coupling product **3** was isolated in 26% yield along with homocoupling product **2a** in 33% yield.

To demonstrate the utility of the current reaction, we then examined the suitability of the methodology for the synthesis of bridged macrobiindolizines, an important type of cyclophanes. Under similar conditions, intramolecular oxidative coupling products **5a** and **5b** were obtained in 38% yield and 23% yield, respectively (Scheme 2). Synthesis of macrocyclic compounds is rare through transition-metal-catalyzed C−H functionalization, and recently, White and co-workers reported a macrolactonization via Pd-catalyzed allylic C−H functionalization.[12]

In conclusion, we have developed a palladium-catalyzed highly regioselective oxidative homocoupling reaction to synthesize biindolizines through C−H functionalization of indolizines. The reaction features high efficiency of the catalyst, broad substrate scope, excellent regioselectivity and high yield in the absence of a directing group. Further investigation of the reaction mechanism and development of an efficient oxidative cross-coupling catalytic system are currently underway.

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Experimental Section

General Procedure for the Oxidative Coupling Reaction. Indolizine **1a** (70.1 mg, 0.4 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (109.0 mg, 0.6 mmol) and K_2CO_3 (110.6 mg, 0.8 mmol) were weighed under ambient conditions and added to a dry flask. Then DMF (2 mL) was added through a syringe and the mixture was stirred at 60 °C for 2 h. After the reaction was complete (disappearance of **1a** was monitored by TLC), the mixture was cooled to room temperature, filtered through a pad of celite, and the celite was washed with CH_2Cl_2 (60 mL). The filtrate was concentrated under reduced pressure. The crude product was dissolved in Et_2O (30 mL), washed with water (2 × 30 mL), brine (30 mL), and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was subjected to flash column chromatography with ethyl acetate/petroleum ether (1:10) as eluent to obtain the desired product **2a** (68.9 mg, 99% yield). IR (film) 2920, 1683, 1510, 1235, 1051, 782, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 6H), 6.74 (dd, J = 6.6, 7.2 Hz, 2H), 7.17 (dd, J = 8.7, 6.9 Hz, 2H), 7.47 (s, 2H), 7.83 (d, J = 7.2 Hz, 2H), 8.31 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.0, 104.0, 113.1, 114.6, 118.6, 120.0, 123.2, 123.8, 136.5, 165.0; MS (EI) m/z 348 (100) $[M]^+$; Anal. calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.98; H, 4.97; N, 7.91. mp: 213−215 °C.

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Supporting Information Available: Experimental procedures, characterization of the products, and the crystallographic data of compound **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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