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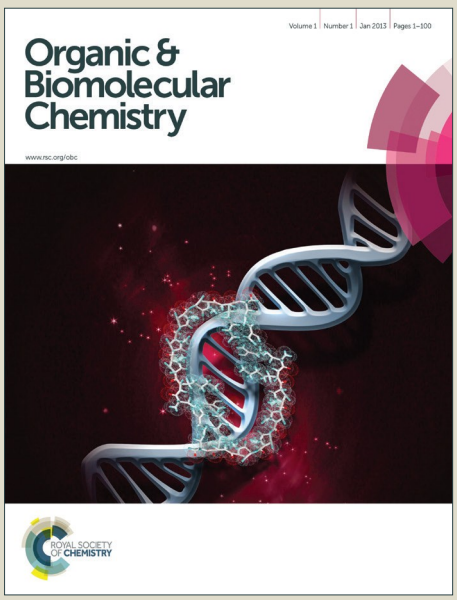

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COMMUNICATION

Pd(II)-Catalyzed Intramolecular Oxidative Heck Dearomative Reaction: Approach to Thiazloes Fused Pyrrolidinones with a C2-Azaquarternary Center

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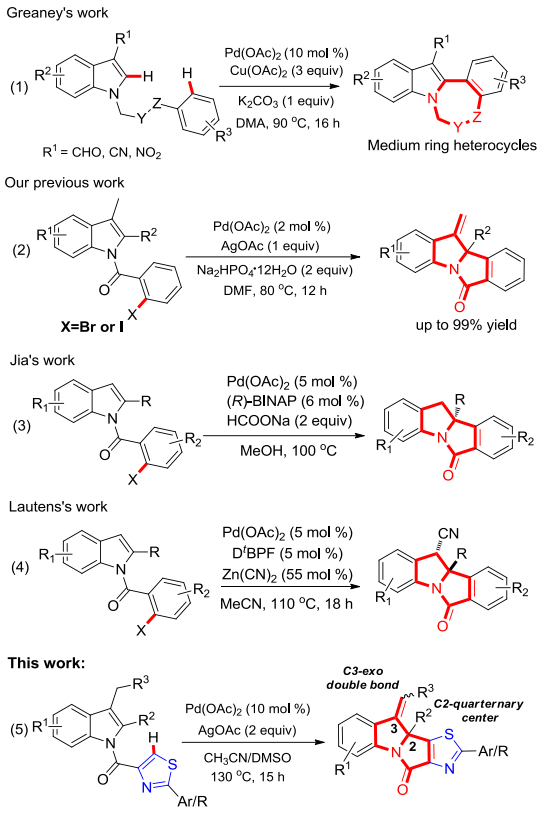
Pd(II)-catalyzed intramolecular oxidative Heck dearomative reaction to the construction of thiazloes fused pyrrolidinones with a C2-azaquarternary center and C3 *exo*-double bond has been achieved for the first time. The reaction exhibited good functional group tolerance and gram-scale capacity.

As one of the most important transitional metal catalyzed reactions, oxidative Heck reaction has drawn widely interests since 1970s.[1] Intermolecular oxidative Heck reaction[2] was applied to construct a variety of compounds containing carbon-carbon double bond,[3] while the intramolecular variant was frequently utilized to the construction of sundry cyclic structures.[4] On the other hand, as a powerful method for the construction of fused or spiro polycycles structures, transitional metal catalyzed dearomative reaction has been invested popularly.[5] Combining oxidative Heck reaction and dearomative reaction together could deliver interesting and complex ring motifs more efficiently.

In 2011, Greaney and coworkers reported an intramolecular oxidative C-H coupling reaction of C3-substituted indoles and heteroarenes for medium-ring synthesis [eqn (1)].[6] Electron-withdrawing groups in C3 position were necessary to ensure the transformations. In 2012, we reported an approach to the construction of isoindolinones fused indolines with a newly formed C2-azaquarternary center and C3-*exo* double bond *via* intramolecular Heck reaction[7] and dearomative process [eqn (2)]. Recently, Jia's group reported Pd-catalyzed intramolecular asymmetric reductive Heck reaction to construct isoindolinones fused indolines with a chiral C2-azaquarternary center [eqn (3)].[8] Lautens's group developed the first Pd-catalyzed indole bisfunctionalization *via* a diastereoselective arylcyanation [eqn (4)].[9] As is well-known, both thiazole



moieties,[10] indoline moieties and pyrrolidinones are prevalent scaffolds found in numerous natural products[11] and pharmacophores,[12] many of them possess remarkable bioactivities. In continuation of our persistent focus on the oxidative Heck reaction and heterocyclic chemistry, herein, we reported our work on Pd(II)-catalyzed intramolecular oxidative Heck dearomative reaction, leading to the formation of thiazoles fused pyrrolidinones with a C2-azaquarternary center and C3-*exo* double bond [eqn (5)].

Our initial investigation focused on the intramolecular oxidative Heck reaction of *N*-(2-phenylthiazole-4-carbonyl)-2,3-dimethylindole (**1a**) as summarized in Table 1. At the outset, we probed the representative protocol for oxidative Heck

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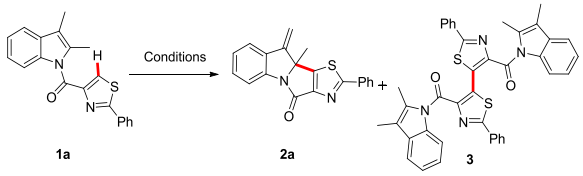
Table 1. Screening of reaction conditions[a]

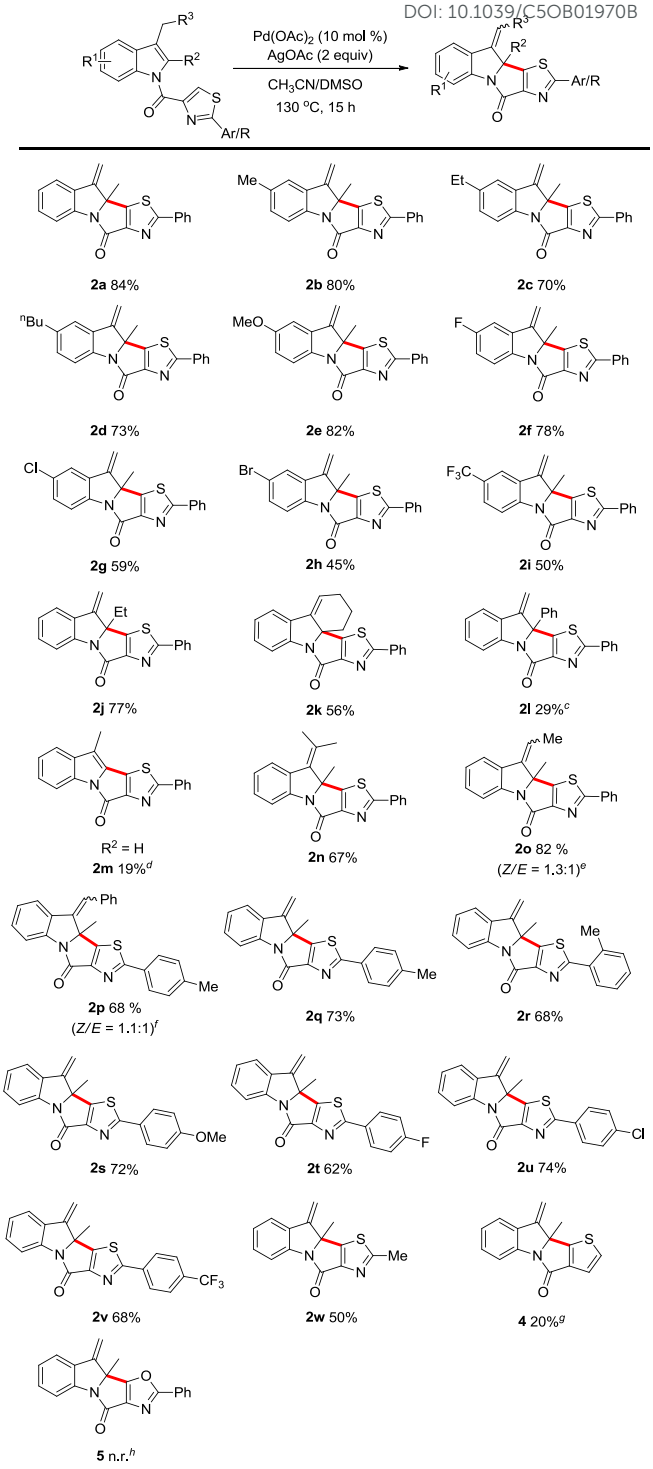


Entry	Catalyst (10 mol %)	Oxidant (2 equiv)	Solvent (2 mL)	Yield (%)[b] (**2a**/**3**)
1	$Pd(OAc)_2$	Ag_2CO_3	DMF	41/24
2	$Pd(OAc)_2$	AgOAc	DMF	55/21
3	$Pd(OAc)_2$	Ag_2O	DMF	5/60
4	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	20/0
5	$Pd(OAc)_2$	*p*-BQ	DMF	5/0
6	$Pd(OAc)_2$	$K_2S_2O_8$	DMF	0/0
7[c]	$Pd(OAc)_2$	AgOAc	DMF	53/21
8[d]	$Pd(OAc)_2$	AgOAc	DMF	55/20
9	$Pd(OAc)_2$	AgOAc	CH_3CN	70/6
10	$Pd(OAc)_2$	AgOAc	1,4-dioxane	32/10
11	$Pd(OAc)_2$	AgOAc	toluene	31/24
12	$Pd(OAc)_2$	AgOAc	^{t}BuOH	0/0
13	$Pd(OAc)_2$	AgOAc	NMP	55/0
14	$Pd(OAc)_2$	AgOAc	DMSO	14/75
15	$Pd(OAc)_2$	AgOAc	CH_3CN/DMSO[e]	77/8
16	$PdCl_2$	AgOAc	CH_3CN/DMSO[e]	40/4
17	$Pd(TFA)_2$	AgOAc	CH_3CN/DMSO[e]	60/32
18	$PdCl_2(CH_3CN)_2$	AgOAc	CH_3CN/DMSO[e]	67/30
19	$Pd(OAc)_2$	AgOAc	CH_3CN/DMSO[f]	86(84[g]) /7

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (10 mol %), oxidant in solvent (2 mL) at 130 °C for 15 h under air. [b] ^{1}H NMR yields using dibromomethane (δ = 4.80) as an internal standard. [c] 140 °C. [d] PivOH (2 equiv) was used. [e] CH_3CN/DMSO (1.98 mL / 0.02 mL). [f] CH_3CN/DMSO (3.96 mL / 0.04 mL). [g] Isolated yields.

reaction with $Pd(OAc)_2$ as catalyst and Ag_2CO_3 as oxidant in DMF at 130 °C for 15 h, offering the corresponding product **2a** in 41% yield with a homocoupling byproduct **3** in 24% yield (entry 1). The characteristic peaks at 5.20 and 5.63 ppm in the ^{1}H NMR spectrum and 72.5 ppm in the ^{13}C NMR spectrum of compound **2a** should be assigned as the two hydrogens of the terminal double bond and azaquarternary carbon respectively, which indicated the formation of C3-*exo* double bonds and the C2-azaquarternary center.[13] A screen of oxidants revealed AgOAc to be ideal, providing **2a** in 55% yield (entry 2). The use of Ag_2O or other oxidants, such as *p*-BQ, $Cu(OAc)_2$ or $K_2S_2O_8$ failed to afford the desired product **2a** in ideal yields (entries 3-6). Unexpectedly, neither higher temperature nor using the PivOH as an additive could enhance the yield of **2a** (entries 7-8). Solvents screening (entries 10-14) indicated that the yield of **2a** could be improved to 70% when CH_3CN was used as the solvent (entry 9). It was noteworthy that most of **1a** was converted to **2a**/**3** when DMSO was used as the solvent (entry 14). This result suggested that DMSO might play a vital role in stabilizing the Pd(0) intermediate by inhibiting its aggregation into Pd(0) black and promoting the reoxidation of Pd(0) to Pd(II) by oxidants to process the catalytic cycle.[14] And we were pleased to see that the yield of **2a** was further improved to 77% using CH_3CN and DMSO as the co-solvent. Screening the ratios of CH_3CN/DMSO[15] revealed that ideal yield could be obtained when the ratio was set to 99:1 (*v*/*v*) (entry 15). Replacing

Table 2. Substrate scope [a, b]



[a] Reaction conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (1 mmol) in CH_3CN/DMSO (3.96 mL / 0.04 mL) at 130 °C under air for 15 h. [b] Isolated Yields. [c] The yield was determined by ^{1}H NMR with dibromomethane as internal standard. [d] 50% starting material (**1m**) was recovered. [e] The *Z*/*E* ratio was determined by ^{1}H NMR. [f] The *Z*/*E* ratio was determined according to the isolated yields. [g] 20 mol % Cy_3P was added. [h] No reaction and 90% substrate was recovered.

$Pd(OAc)_2$ with other palladium catalysts such as $PdCl_2$, $Pd(TFA)_2$ and $PdCl_2(CH_3CN)_2$ offered **2a** in lower yields (entries

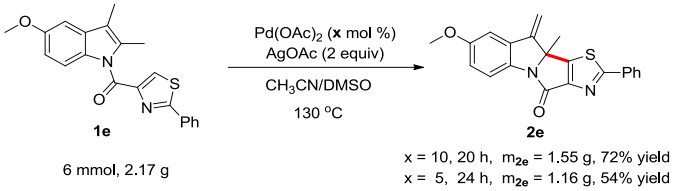
16-18). When the concentration was reduced to 0.125 M, **2a** could be obtained in 84% isolated yield (entry 19).

With the optimized catalytic system in hand, we then embarked on the investigation of the substrate scope. Firstly, we explored the effect of substituents on the benzene ring of the indole part as shown in Table 2. To our delight, for substrates containing various electron-donating groups, such as methyl, ethyl, *n*-butyl and methoxyl, the reactions proceeded well under the optimized reaction conditions and afforded the desired products **2b**-**2e** in good yields from 70% to 82%. The substrates bearing electron-withdrawing groups, such as fluoro and trifluoromethyl afforded **2f** and **2i** in 78% and 50% yields. The substrates with chloro or bromo group reacted smoothly to give **2g** in 59% yield and **2h** in 45% yield. Then, we investigated the substituent effect at the C2- and C3-position of indole derivatives. The substrates bearing ethyl group at the C2-position afforded **2j** in 77% yield and *N*-acyl tetrahydrocarbazole gave the pentacyclic compound **2k** in 56% yield. Indole with phenyl at C2 position delivered the oxidative Heck dearomative product **2l** in 29% yield with some intramolecular cross dehydronative coupling byproduct and homocoupling byproduct.[16] When *N*-acyl 2-methyl indole (**1m**, R^2 = H) was used, an oxidative Heck product **2m** was obtained in 19% yield. When C3 position was substituted with isopropyl, **2n** was obtained in 67% yield. The substrates with ethyl or benzyl on C3 position offered **2o** in 82% yield (*Z*/*E* = 1.3:1) and **2p** in 68% yield (*Z*/*E* = 1.1:1), respectively. The reaction conditions were next applied to substrates with various substituted thiazole core. The substrates with electron-donating groups on the benzene ring of the thiazole afforded **2q**-**2s** in 68%-73% yields. The ones with electron-withdrawing or halogen groups such as fluoro, chloro and trifluoromethyl gave the corresponding products **2t**, **2u** and **2v** in 62%, 74% and 68% yields with some incomplete consumption starting materials recovered. The substrate bearing a methyl group at the C2 position of the thiazole provided **2w** in 50% yield accompany with partially homocoupling product produced. Replacement of the thizaole group with the thiophene group led to the cyclization product **4** in 20% yield with large number of starting material recovered. The oxazole substrate could not offer the intramolecular oxidative Heck product **5** under the optimized conditions.

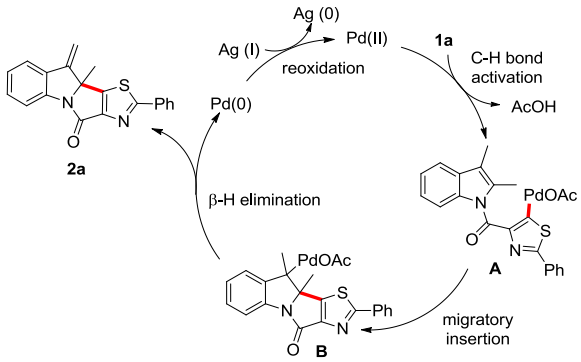
To test the practicality of our reaction, a gram-scale evaluation was carried out (Scheme 1). The intramolecular oxidative Heck dearomative reaction of **1e** in a 6.0 mmol scale gave the desired product **2e** (1.55 g) in 72% yield under standard condition. Compound **2e** could also be obtained in 1.16 g (54% yield) with 5 mol % $Pd(OAc)_2$ as the catalyst by prolonging the reaction time to 24 h.

On the basis of previous reports,[17] a plausible catalytic cycle was proposed as outlined in Scheme 2. Firstly, palladation of the thiazole at C5 position formed palladium intermediate **A**, which was followed by intramolecular coordination of the palladium center to the olefin of the indole and migratory insertion provided intermediate **B**. Since no hydrogen existed on the C2 position of intermediate **B**, the desired product **2a** was generated through β-H elimination of the C3 methyl group. Finally, Pd(0) was reoxidized by Ag(I) in the reaction system to give Pd(II) to complete the catalytic cycle. Intermediate **A** could also couple with another molecule **1a** through C-H bond activation at C5 of thiazole ring and following reductive elimination gave the homocoupling byproduct **3**.[17]

Scheme 1. The large scale experiment



Scheme 2. Proposed reaction mechanism for intramolecular oxidative Heck dearomative process



In conclusion, we have developed the first palladium catalyzed intramolecular oxidative Heck dearomative reaction for the synthesis of thiazoles fused pyrrolidinones with an C2 azaquarternary center and C3 *exo*-double bond in moderate to good yields. The reaction exhibited good functional group tolerance and gram-scale capacity. Research on the detailed reaction mechanism and extension to other heteroaromatic substrates are currently undergoing in our laboratory.

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