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Palladium Catalyzed Tandem Ring Opening−Ring Closing Reaction of Diazabicyclic Alkenes: A Facile One Pot Strategy for Cyclopentannulation of Heterocycles

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Catalytic tandem reactions constitute a powerful tool in synthetic organic chemistry due to its bond-forming economy, structure economy and eco-friendly nature.[1] Cyclopentane fused heterocycles are important intermediates in the synthesis of biologically important molecules such as thromboxane inhibitor, prostacyclin analogues, diazepinoindolines, antipsychotics, antiobesity agents, and 5-HT2 receptor ligands (Figure 1).[2] However there has been only scant attention in developing a general methodology for fusing a cyclopentene moiety to heterocycles.[3] All the attempts reported involve several steps and were tedious. Wolfe et al. have utilized various palladium catalyzed reactions of alkenes toward the assembly of O- and N-heterocycles.[3f,g] In this paper we disclose a simple, one pot strategy for cyclopentannulation of heterocycles.

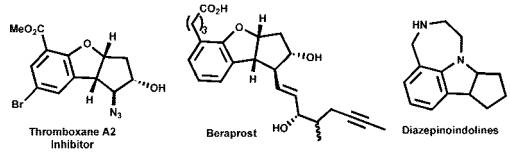
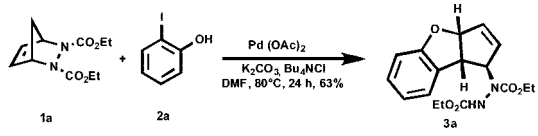


Figure 1. Biologically important cyclopentannulated heterocycles.

The reactivity of azabicyclic alkenes[4] have been extensively investigated with monocentered nucleophiles.[5,6] These investigations resulted in the formation of either 3,4- or 3,5- disubstituted cyclopentenes. Acid catalyzed rearrangements of these bicyclic alkenes were also reported.[5b,7] In continuation of our interest in the chemistry of bicyclic hydrazines,[6] we were interested in checking the reactivity of bicentered nucleophiles like *ortho* functionalized aryl iodides, the chemistry of which was explored extensively by Larock.[8] Herein we report Pd-catalyzed couplings of *o*-iodophenol and *o*-iodoaniline with azabicyclic olefin. The reaction affords cyclopentene fused benzofuran and indoles, presumably through a tandem ring opening−ring closing pathway.

Our preliminary studies involved azabicyclic alkene **1a** and *o*-iodophenol **2a** as substrates. When **1a** and **2a** were catalyzed with $Pd(OAc)_2$ in the presence of additive Bu_4NCl and K_2CO_3, in DMF solvent at 80 °C, cyclopentene fused dihydrobenzofuran **3a** was obtained in 63% yield (Scheme 1).

Scheme 1. Palladium Catalyzed Cyclopentannulation



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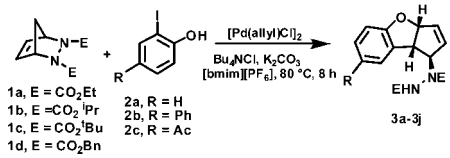
The product **3c** was crystallized from methanol, and the structure and stereochemistry was unambiguously confirmed by single crystal X-ray analysis.[9]

The scope of this reaction was then investigated under optimized conditions[9] (Table 1). In all the cases, the azabicyclic alkene **1a**−**1d** reacted with *o*-iodophenols **2a**−**2c** leading to the corresponding cyclopentannulated products in good to excellent yield, and the results are summarized in Table 1.

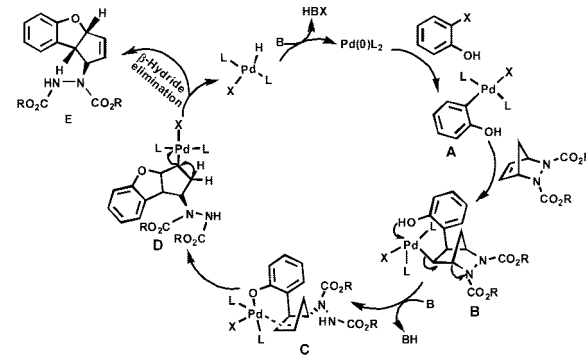
Table 1. Pd-Catalyzed Reaction of Azabicyclic Olefins with 2-Iodophenol[a]



entry	alkene	*o*-iodophenol	product	yield (%)
1	**1a**	**2a**	**3a**	94
2	**1b**	**2a**	**3b**	88
3	**1c**	**2a**	**3c**	86
4	**1d**	**2a**	**3d**	87
5	**1a**	**2b**	**3e**	78
6	**1b**	**2b**	**3f**	81
7	**1c**	**2b**	**3g**	80
8	**1d**	**2b**	**3h**	75
9	**1a**	**2c**	**3i**	60
10	**1b**	**2c**	**3j**	55

[a] Reaction conditions: alkene (1.5 equiv), 2-iodophenol (1 equiv), Bu_4NCl (1 equiv), K_2CO_3 (2 equiv), $[Pd(allyl)Cl]_2$ (5 mol%), $[bmim][PF_6]$ (2 mL), 80 °C, 8 h.

Scheme 2. Proposed Catalytic Cycle for Cyclopentannulation



Based on these results, we propose a plausible mechanism (Scheme 2). The mechanism may involve two stages, the initial one being the ring opening of bicyclic alkene.[6] The first step of the catalytic cycle involves oxidative addition of Pd(0) into aryl

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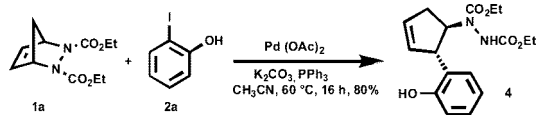
iodide to form $Ar-PdL_2X$ **A** and subsequent coordination to the alkene. The next step is carbopalladation **B** which is followed by oxypalladation and subsequent ring opening assisted by trace amounts of iodine present in aryl iodide to form the intermediate **C**. The second stage starts with addition of oxypalladated species to the double bond to form **D** followed by β-hydride elimination to yield the cyclopentene fused benzofuran.[10]

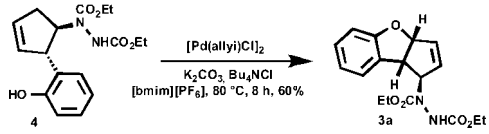
As already mentioned, the reaction was not working in the absence of additive, Bu_4NCl. This can be attributed to the ability of chloride ions to regenerate and stabilize the Pd(0) species.[11] When the reaction was repeated under the optimized conditions by adding 10 mol % of PPh_3, it resulted in the formation of 3,4-disubstituted cyclopentene **4** along with the product **3a**. When the additive was replaced by PPh_3, the reaction resulted in the exclusive formation of cyclopentene **4** (Scheme 3).

Scheme 3. Tuning the Reaction towards 3,4-Disubstituted Cyclopentene



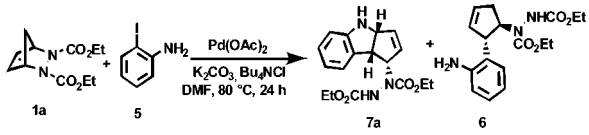
To prove the intermediacy of 3,4-disubstituted cyclopentene in the proposed mechanism, we subjected the cyclopentene **4** to cyclopentannulation conditions. As expected the reaction afforded cyclopentannulated benzofuran **3a** (Scheme 4).

Scheme 4. Intramolecular Oxypalladation−Cyclization



We were then interested in whether the developed methodology could be utilized toward the synthesis of cyclopentene fused nitrogen heterocycles. In an initial attempt, the bicyclic alkene **1a** was treated with *o*-iodoaniline **5** in the presence of catalyst $Pd(OAc)_2$, additive Bu_4NCl, and K_2CO_3, in DMF solvent at 80 °C, and the reaction afforded a mixture of 3,4-disubstituted cyclopentene **6** along with the cyclopentene fused dihydroindole **7a** (Scheme 5).

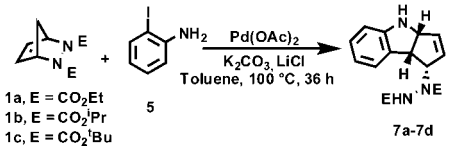
Scheme 5. Pd-Catalyzed Cyclopentannulation of Indole



Under the optimized conditions[9] the reaction was repeated with different bicyclic alkenes **1a**−**1c** and *o*-iodoaniline **5**. All the attempts resulted in the formation of cyclopentene fused dihydroindoles in good to excellent yields (Table 2). In all cases trace amounts of 3,4-disubstituted cyclopentene product were isolated.

In conclusion, we have developed a novel one pot strategy for the cyclopentannulation of heterocycles. Using this methodology, we could tune the reaction to the formation of either 3,4-disubstituted cyclopentenes or cyclopentene fused heterocycles by careful manipulation of the reaction parameters. We are currently focused on utilizing this methodology toward the total synthesis of biologically important molecules.

Table 2. Pd-Catalyzed Reaction of Azabicyclic Olefins with 2-Iodoaniline[a]



entry	alkene	product	yield (%)
1	**1a**	**7a**	93
2	**1b**	**7b**	85
3	**1c**	**7c**	75

[a] Reaction conditions: alkene (1.5 equiv), 2-iodoaniline (1 equiv), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2 equiv), LiCl (1 equiv), toluene (2 mL), 100 °C, 36 h.

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Supporting Information Available: General experimental procedure, spectroscopic characterization of new compounds, and single crystal X-ray data of compound **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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