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Palladium/Lewis Acid Mediated Domino Reaction of Pentafulvene Derived Diazabicyclic Olefins: Efficient Access to Spiropentacyclic Motif with an Indoline and Pyrazolidine Fused to Cyclopentene

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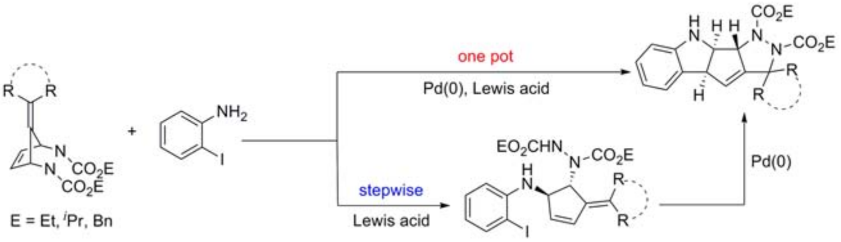
ABSTRACT



A palladium/Lewis acid mediated stepwise and one-pot transformation of pentafulvene derived diazabicyclic olefins is described. The reaction offers a facile strategy for the synthesis of novel spiropentacyclic motifs with indoline and pyrazolidine fused to the cyclopentene core.

Catalytic domino transformations allow a rapid increase in molecular complexity[1] from readily available starting materials. These reactions are of great significance in the search for green and environmentally friendly methods, as it delivers products in one-pot transformations. Among domino reactions, skeletal rearrangements of simple precursors are powerful processes for generating molecular diversity with atom economy.

Investigations from various groups[2] and our own laboratory[3] have exploited the diverse reactivity pattern of pentafulvenes in cycloaddition reactions. In contrast, there is only scant information available on the synthetic utility of pentafulvene derived diazabicyclic olefins.[4] In conjunction with our interest in the chemistry of pentafulvenes and transition metal catalyzed synthetic transformations of heterobicyclic olefins,[5] we have explored the Lewis acid/palladium mediated transformation of pentafulvene derived bicyclic hydrazines which led to the formation of a new spiropentacyclic framework having cyclopentene fused to indoline and pyrazolidine skeletons. Indole and its

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derivatives constitute the structural unit of a number of biologically active molecules in medicinal chemistry and natural products.[6] Among them, the rigid cyclopentane fused indolines are an integral component of a plethora of bioactive molecules.[7] Some of the important molecules with indoline and indole core are shown in Figure 1.

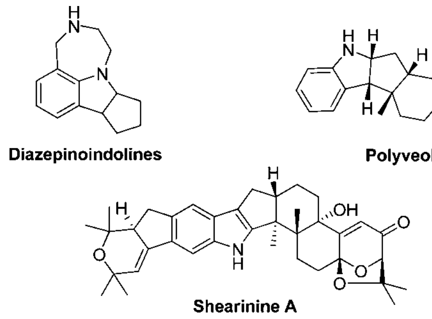
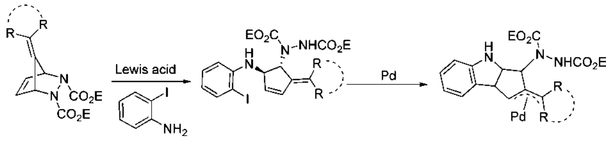


Figure 1. Important molecules with indoline and indole core.

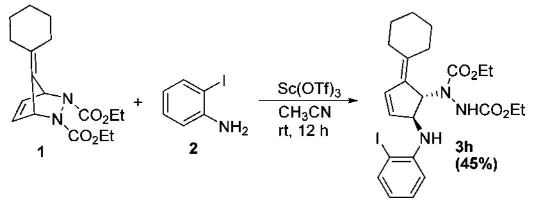
Desymmetrization of heterobicyclic olefins under palladium and Lewis acid catalyzed conditions affords 3,4- or 3,5-disubstituted cyclopentanoids (Micouin et al.,[8] Lautens et al.,[9] Pineschi et al.,[10] and Miller et al.[11]). Lewis acid and palladium catalyzed rearrangement of bicyclic hydrazines was effectively utilized by Micouin and co-workers toward the synthesis of molecules with potential biological activity.[8d,e]

Scheme 1. Present Strategy to Generate Functionalized Polycycle through π-Allylpalladium Complex



It is to be noted that the Lewis acid catalyzed reactions of bicyclic hydrazines proceed through the formation of transient species,[8a,9,10] which further reacts with a nucleophile leading to various products. We envisaged that proper selection of the Lewis acid, nucleophile, and reaction parameters may lead to the development of efficient catalytic domino strategies toward various functionalized polycycles (Scheme 1). Herein we report the palladium/Lewis acid catalyzed stepwise and one-pot transformation of pentafulvene derived diazabicyclic olefins affording novel spiropentacyclic motifs with indoline and pyrazolidine fused to a cyclopentene core.

Scheme 2. Lewis Acid Catalyzed Desymmetrization of Fulvene Derived Diazabicyclic Olefin



With this perspective, we chose triflates of Sc and Yb for our studies. Sc(III) and Yb(III) triflates are known to catalyze unique transformations in organic synthesis.[12] In order to exploit the exocyclic double bond of pentafulvenes, we chose the pentafulvene derived bicyclic hydrazines for our preliminary investigations. Our experiments started with the reaction of **1** and 2-iodoaniline **2** using Sc(OTf)$_3$ as the Lewis acid in acetonitrile at room temperature (Scheme 2). *trans*-3,4-Disubstituted alkylidenecyclopentene **3h** was formed exclusively in 45% yield. The structure and stereochemistry of the compound was unambiguously confirmed by single crystal X-ray analysis (Figure 2 and Supporting Information). The stereoselective formation of the product **3h** can be attributed to the steric nature of the substituents on the exocyclic double bond.

Detailed optimization studies were carried out to find the best conditions for this transformation (Table 1).

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Table 1. Screening of the Reactivity of Various Lewis Acids towards Bicyclic Olefin in Different Solvents[a]

entry	Lewis acid	solvent	yield (%)
1	$Sc(OTf)_3$	CH_3CN	45
2	$Sc(OTf)_3$	DMF	29
3	$Sc(OTf)_3$	THF	48
4	$Sc(OTf)_3$	toluene	93
5	$Yb(OTf)_3$	toluene	85
6	$Zn(OTf)_2$	toluene	80
7	$La(OTf)_3$	toluene	83
8	$Cu(OTf)_2$	toluene	27
9	$AlCl_3$	toluene	49

[a] Reaction conditions: alkene (3 equiv), 2-iodoaniline (1 equiv), catalyst (2 mol %), solvent (2 mL), at rt.

Screening of various Lewis acids revealed that $Sc(OTf)_3$ is the best catalyst for this transformation. From an extensive screening of reaction parameters, the best yield was obtained with 3 equiv of bicyclic olefin and 1 equiv of 2-iodoaniline in the presence of 2 mol % $Sc(OTf)_3$ in toluene at room temperature. Under the optimized conditions, **3h** was obtained in 93% yield.

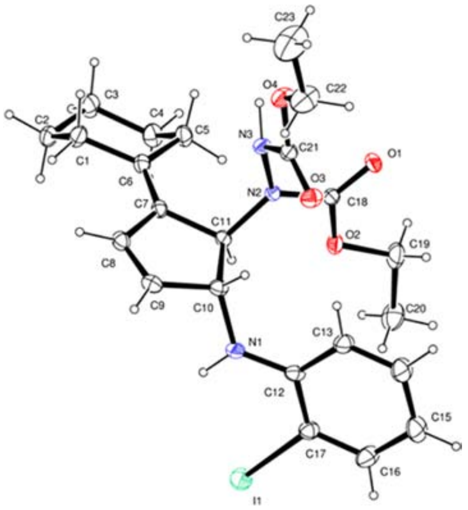


Figure 2. Single crystal X-ray of **3h**.

The diazabicyclic olefins derived from different pentafulvenes gave substituted alkylidene cyclopentenes in good to excellent yields (Figure 3). To investigate the reactivity of substituted 2-iodoanilines, we carried out the reaction of 2-iodoanilines bearing $-NO_2$ and $-CF_3$ substituents. Both $-NO_2$ and $-CF_3$ substituted 2-iodoanilines afforded alkylidene cyclopentenes in moderate to good yields (Figure 3).

To explore the synthetic utility of the alkylidenecyclopentenes, the intramolecular Heck cyclization was conducted in the presence of $Pd(OAc)_2$ (5 mol %), PPh_3, and Cs_2CO_3 in acetonitrile at 80 °C. Gratifyingly, the indoline-pyrazolidine fused cyclopentene was obtained in 72% yield (Scheme 3).

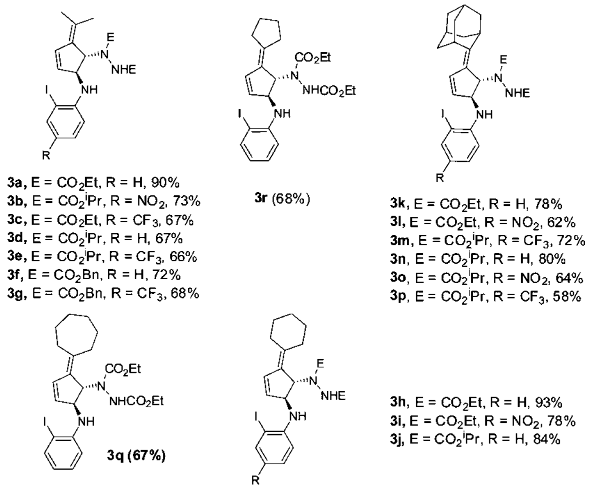
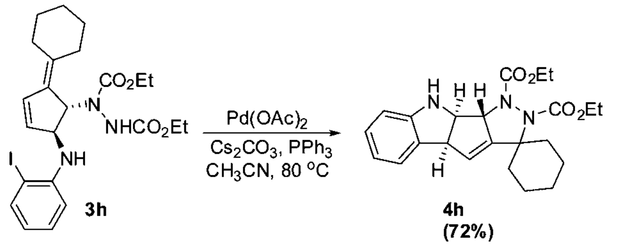


Figure 3. Substrate scope for Lewis acid catalyzed desymmetrization.

The intramolecular Heck cyclization of various alkylidenecyclopentenes was next examined, and the tandem palladium catalyzed cyclization smoothly afforded the corresponding indoline-pyrazolidine fused cyclopentenes in moderate to good yields (Figure 4).

Scheme 3. Synthesis of Derivatized Indoline by Intramolecular Heck Cyclization



The structure and stereochemistry of the spiropentacyclic molecules were supported by spectral analysis and unambiguously confirmed through single crystal X-ray analysis of **4d**.

A plausible mechanism for the formation of indoline-pyrazolidine fused cyclopentene is illustrated in Scheme 4. The first step of the catalytic cycle is the oxidative addition of Pd(0) to the aryl iodide, which leads to the formation of **A**. Coordination of species **A** to the double bond followed by the generation of a π-allylpalladium complex affords the key intermediate **C**. The base assisted intramolecular nucleophilic attack furnished the product.

Finally, in order to evaluate the one-pot efficiency of this method, a tandem reaction was performed in the presence of a Lewis acid and palladium catalyst (Scheme 5). Interestingly, indoline-pyrazolidine fused cyclopentene was

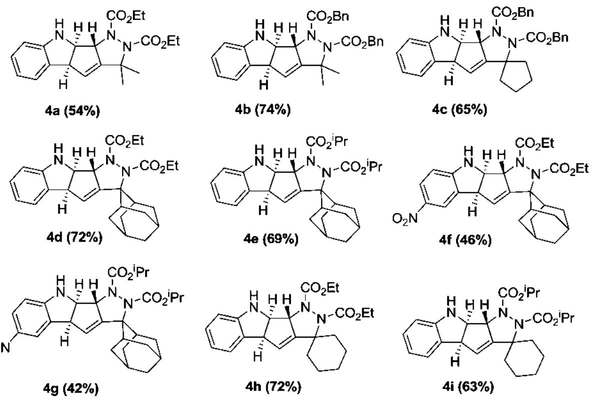
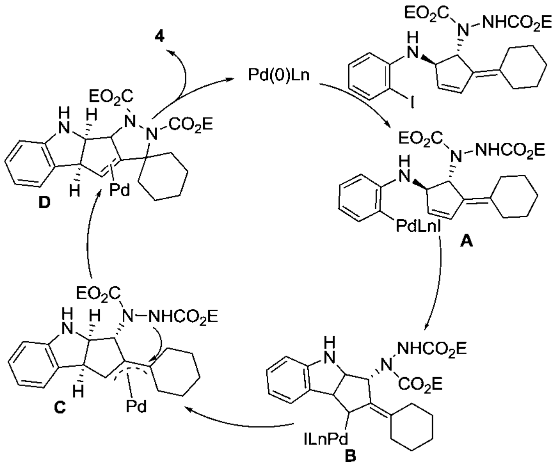


Figure 4. Substrate scope for intramolecular Heck cyclization.

Scheme 4. Proposed Catalytic Cycle Underlying the Mechanism of Tandem Cyclization

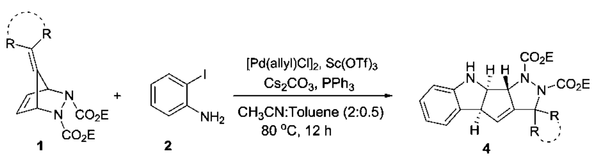


obtained in moderate yield. Detailed optimization studies were carried out to find the best conditions for the one-pot reaction (see Supporting Information). The use of 5 mol % [Pd(allyl)Cl]$_2$, 2 mol % Sc(OTf)$_3$, 10 mol % PPh$_3$, and 1.5 equiv of Cs$_2$CO$_3$ in a 2:0.5 mixture of acetonitrile−toluene resulted in the exclusive formation of a spiropentacyclic molecule.

The reaction was found to be general with various pentafulvene derived bicyclic hydrazines (Figure 5).

In summary, we have developed a Lewis acid/palladium mediated strategy for the synthesis of a new spiropentacyclic motif having indoline and pyrazolidine fused to the cyclopentene core. The reaction involves multiple bond formations. It also shows that the proper positioning of "palladium active" functional groups in the diazabicyclic olefins helps in passing the palladium baton from initial organopalladium addition to the strained olefin, ultimately delivering complex polycycles in a one-pot transformation.

Scheme 5. One-Pot Synthesis of Indoline Derivative



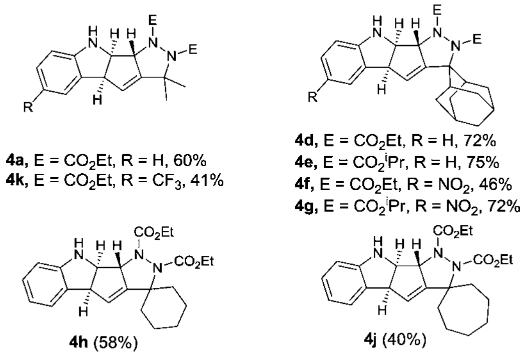


Figure 5. Substrate scope for one-pot strategy.

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Supporting Information Available. Experimental details and characterization data are available. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.