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Pd(0)-Catalyzed Alkenylation and Allylic Dearomatization Reactions between Nucleophile-Bearing Indoles and Propargyl Carbonate

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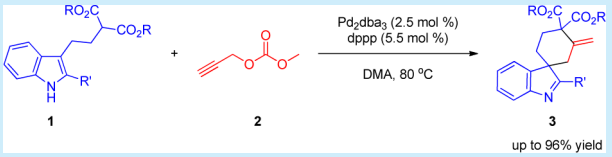
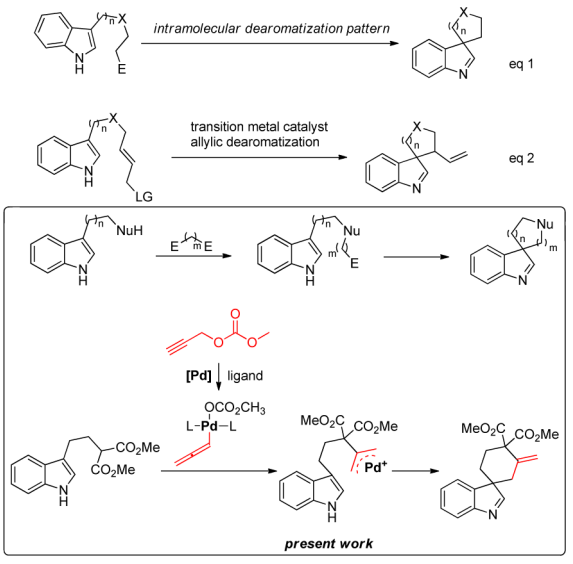
Supporting Information

ABSTRACT: Spiroindolenine derivatives were synthesized by intermolecular Pd-catalyzed dearomatization of indoles. The reaction between nucleophile bearing indoles and propargyl carbonate proceeds in a cascade fashion providing spiroindolenines or spiroindolines in good to excellent yields.



Polycyclic skeletons embedded within indoline moieties represent important structure motifs in numerous natural products and pharmaceuticals.[1] For the construction of these valuable scaffolds, the strategy of dearomatization of indole derivatives involving a cascade sequence has recently attracted much attention due to its synthetic efficiency.[2] Among them, the synthesis of C-3 spirocyclic indolines are particularly challenging. In this area, successful approaches have taken advantage of the nucleophilicity of indoles and a preinstalled intramolecular electrophile (Scheme 1, eq 1).[3] In these cases, relatively long synthetic routes are required for preparing such designed substrates. We and other groups have reported transition-metal catalyzed allylic dearomatizatation reactions of indole derivatives to provide sprioindolenines (Scheme 1, eq 2).[4] In contrast, an intermolecular cascade sequence of a simple indole which contains a tethered nucleophile with a bifunctional dual electrophile has great potential to build spirocyclic indolenine derivatives in a very convergent and direct manner (Scheme 1). To the best of our knowledge, only sparse examples utilizing such a reaction pattern have been reported.[5] η^3-π-allenylpalladium intermediates, generated from propargyl carbonates in the presence of Pd (0) catalyst, are known to react with carbonucleophiles to form π-allylic intermediates.[6] We envisaged that the cascade reaction between nucleophile bearing indoles and propargyl carbonate could be enabled by Pd (0) catalyst providing a straightforward synthesis of spiroindolenine. Herein we report a cascade reaction sequence whereby an intermolecular alkenylation of a malonate with a propargyl carbonate is followed by cyclization of the indole moiety onto the resulting π-allyl species (Scheme 1).

Scheme 1. Pd(0)-Catalyzed Reactions between Nucleophile-Bearing Indoles and Propargyl Carbonate



At the outset, substituted indole **1a** and propargyl carbonate **2** were chosen as the model substrates to test our hypothesis. Initially, various ligands were tested in the presence of 2.5 mol % of Pd_2dba_3 with THF as the solvent. As shown in Table 1, monodentate ligand $(4\text{-}MeOC_6H_3)_3P$ or X-Phos did not afford any desired product (entries 1 and 2, Table 1). To our delight, the reaction with dppf could provide the desired product **3a** in 17% yield (entry 3, Table 1). Other bidentate ligands such as dppe, dppb, and dppp were also tested, and dppp could provide the best result (21% yield, entries 4−6, Table 1). Thus, in the presence of 2.5 mol % of Pd_2dba_3 and 5.5 mol % of dppp, we then tested various solvents including dioxane, *o*-xylene, DMF, and DMA (entries 7−10, Table 1). The reaction with DMA provided the highest isolated yield of **3a** (49% yield, entry 10, Table 1).

Further screening of the ratio of **2** to **1a** revealed that 1.3 equiv of **2** was optimal for this reaction (entries 10−12, Table 1). When the reaction was operated at 80 °C, an increased yield was achieved (75%, entry 13, Table 1). Further examination of substrate concentration led to the highest yield (96% yield, entry 18, Table 1) at a low substrate concentration.

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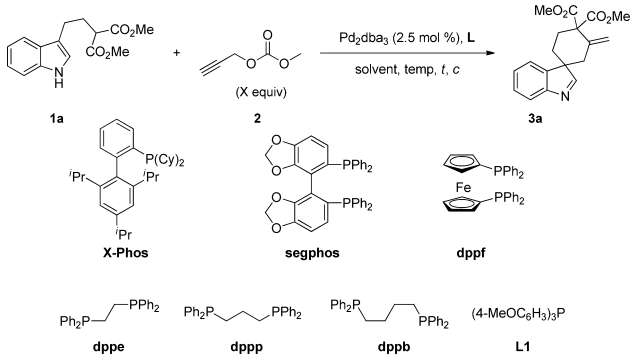
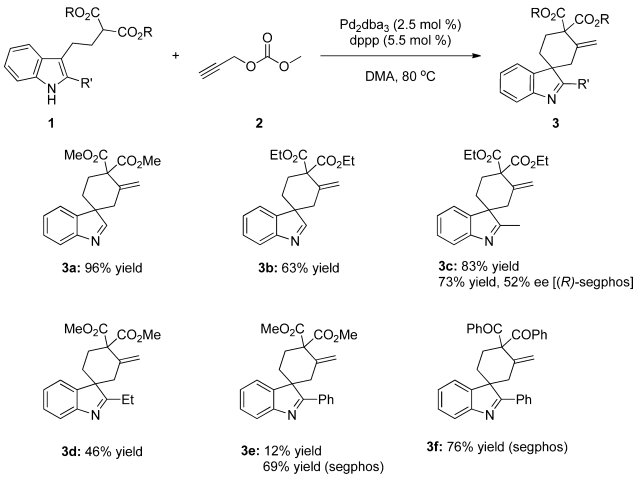
Table 1. Optimization of the Reaction Conditions



entry[a]	ligand	solvent	temp (°C)	time (h)	X	c (mol/L)	yield[c] (%)
1[b]	**L1**	THF	50	24	1.3	0.067	NR
2[b]	X-Phos	THF	50	24	1.3	0.067	NR
3	dppf	THF	50	24	1.3	0.067	17
4	dppe	THF	50	24	1.3	0.067	NR
5	dppb	THF	50	24	1.3	0.067	17
6	dppp	THF	50	24	1.3	0.067	21
7	dppp	dioxane	50	24	1.3	0.067	NR
8	dppp	*o*-xylene	50	24	1.3	0.067	NR
9	dppp	DMF	50	24	1.3	0.067	38
10	dppp	DMA	50	24	1.3	0.067	49
11	dppp	DMA	50	24	2.0	0.067	45
12	dppp	DMA	50	24	4.0	0.067	41
13	dppp	DMA	80	12	1.3	0.067	75
14	dppp	DMA	80	12	1.3	0.2	42
15	dppp	DMA	80	12	1.3	0.1	71
16	dppp	DMA	80	12	1.3	0.05	80
17	dppp	DMA	80	12	1.3	0.04	89
18	dppp	DMA	80	12	1.3	0.033	96

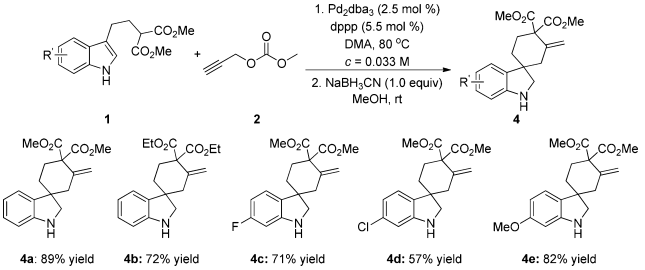
[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.26 mmol), Pd_2dba_3 (2.5 mol %), and **L** (5.5 mol %) in solvent. [b]Reaction conditions: **1a** (0.2 mmol), **2** (0.26 mmol), Pd_2dba_3 (2.5 mol %), and **L** (11 mol %) in THF. [c]Isolated yield.

Scheme 2. Substrate Scope

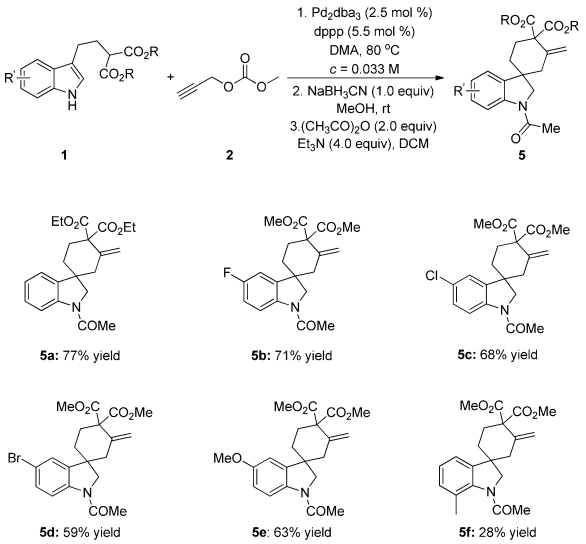


Under the optimized reaction conditions [0.2 mmol **1**, 0.26 mmol **2**, 2.5 mol % Pd_2dba_3, 5.5 mol % dppp, DMA (6 mL), 80 °C], the scope of the reaction was then explored. As summarized in Scheme 2, the substrate **1b** bearing ethyl ester also worked well to afford product **3b** in 63% yield.

Scheme 3. Substrate Scope for One-Pot Dearomatization and Reduction



Scheme 4. Substrate Scope for One-Pot Dearomatization, Reduction, and *N*-Acetylation



Interestingly, when a methyl was introduced to the 2-position of the indole moiety, a satisfactory yield (**3c**, 83% yield) was obtained. A preliminary enantioselective study disclosed that product **3c** could be obtained in 73% yield and 52% ee by using (*R*)-SEGPHOS as the ligand. However, when more bulky substituents were tested, significant decreasing of yields was found (**3d**, 46% yield and **3e**, 12% yield). Finally, improvement of the yield could be realized by using SEGPHOS as the ligand (**3e**, 69% yield and **3f**, 76% yield).

In general, the spiroindolenine product bearing no substituent at the C2 position of the corresponding indole is not stable under acidic conditions. To address this problem, one-pot reaction by including an in situ reduction was carried out to convert the imine moiety to the corresponding amine. As shown in Scheme 3, for substrate **1a**, the reduction product **4a** was obtained in an excellent yield (89%). Under this operation, several substrates by varying the ester group or the substituent on the indole ring were investigated. In all cases, the substrates bearing a substituent (6-F, 6-Cl, 6-OMe) regardless of the electronic property could be smoothly converted to dearomatized products in reasonable yields.

As shown in Scheme 3, since the in situ reduction operation could only provide the substrates with a 6-substituent in good yields, further manipulation of the product was necessary. Thus, a further protection of amine by reacting with acetic anhydride was added to the one-pot procedure. The results are shown in Scheme 3. Subjecting substrate **1b** into this three-step, one-pot procedure led to the isolation of amide **5a** in 77% yield. For

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substrates with various substituents on the 5-position of the indole moiety, moderate to good yields were achieved (**5b**−**e**, Scheme 4). The substrate with a methyl group at the C7 position could also be tolerated (**5f**, 28% yield, Scheme 4). The moderate yield was mainly caused by the steric hindrance of the methyl group during the acetylation of amine step. Finally, the structure of the products was determined by an X-ray crystallographic analysis of a single crystal of **5d**.[7]

In summary, we have developed an intermolecular Pd-catalyzed dearomatization of nucleophile bearing indoles, which provides an efficient synthesis of spiroindolenine and spiroindoline derivatives. Further extension of the reaction scope and development of a highly enantioselective variant are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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