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Convenient synthesis of spiroindole derivatives via palladium-catalyzed cyclization of propargyl chlorides

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ABSTRACT

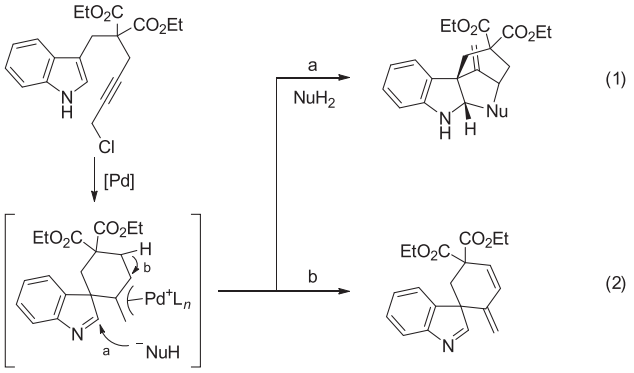
Herein, we report the palladium-catalyzed cyclization reactions of indoles bearing a propargyl chloride side chain at their 3-position. In the presence of an external nucleophile, such as a sulfonamide or malonate, indoles bearing a propargyl group at their 3-position gave fused tetracyclic spiroindolines preferentially. However, in the absence of an external nucleophile, the same substrates afforded spiroindoles. Our attempts to develop a catalytic asymmetric spirocyclization onto a propargylpalladium species are also presented in this paper.

1. Introduction

The palladium-catalyzed reactions of propargyl compounds provide efficient approaches for the formation of carbon–carbon and carbon–heteroatom bonds.[1] The pioneering work of Tsuji and co-workers revealed that double nucleophilic additions proceeded at the central and terminal carbons of the propargylic moiety when soft carbon- or oxo-nucleophiles were employed.[2] This chemistry is particularly useful for the construction of carbo- and heterocyclic frameworks, including furans,[3] cyclobutanes,[4] indenes,[5] cyclopentanones,[6] cyclic carbonates,[7] benzofurans,[8] and indoles,[9] especially when it is used in combination with an inter- or intramolecular nucleophilic addition reaction as the terminating step.

Spirocyclic compounds are currently attracting considerable interest in organic chemistry because of their unique molecular structure and diverse biological activities.[10] In particular, enantioenriched spiroindoles and spiroindolines represent important structural motifs that can be found in a wide range of biologically active natural products and synthetic compounds.[11] As part of our ongoing efforts towards the construction of heterocyclic frameworks based on the palladium-catalyzed reactions of propargyl/allenic compounds, we recently became interested in the intramolecular nucleophilic addition reactions of indoles as a strategy for the synthesis of spiroindoles. It was envisaged that this strategy would provide facile access to tetracyclic spiroindolines when it was used in combination with the intermolecular nucleophilic cyclization of an external nucleophile (Scheme 1, Eq. 1, path a). We also expected that running the same reaction without using an external nucleophile would promote β-hydride elimination (path b) to produce spiroindoles bearing a conjugated diene moiety (Eq. 2).

In 2013, Hamada and co-workers reported the development of a palladium-catalyzed intramolecular spirocyclization of phenol-based propargylic carbonates (Scheme 2, Eq. 3).[12] When



Scheme 1. Our concept: palladium-catalyzed spirocyclization of indole-based propargyl compounds.

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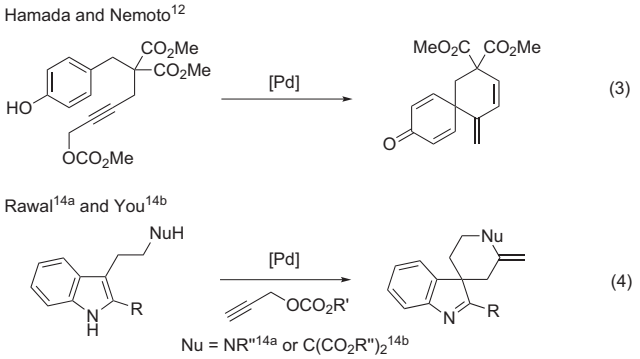
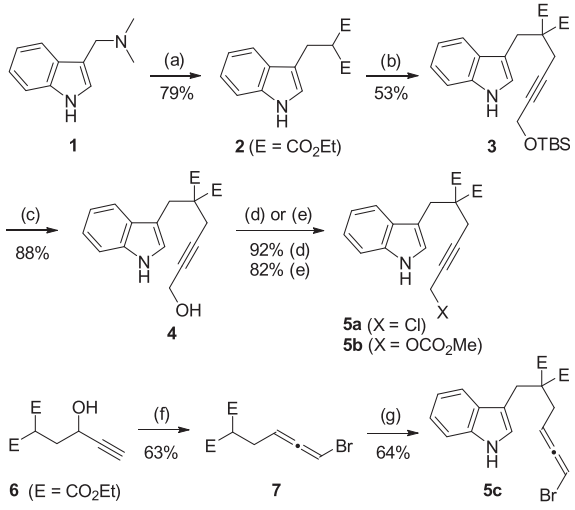


Scheme 2. Related palladium-catalyzed spirocyclization reaction using propargyl compounds.

tryptamine-derived carbonates were used, this reaction produced spiroindoles bearing an azepine moiety. Immediately after our communication in 2014,[13] the groups of Rawal[14a] and You[14b] independently reported the intermolecular reactions of indole-based dual nucleophiles and propargyl carbonates as general strategies for the synthesis of spiroindoles (Eq. 4). In this paper, we report the full details of our recent investigations into construction of tetracyclic spiroindolines (Eq. 1) and conjugated diene-type spiroindoles (Eq. 2) via the palladium-catalyzed cyclization of propargyl chlorides. Our attempts to achieve a catalytic asymmetric spirocyclization onto a propargylpalladium species have also been presented.

2. Results and discussion

The route used for the preparation of substrates **5a**–**c** is shown in Scheme 3. In accordance with a literature procedure,[15] gramine (**1**) was converted to the corresponding malonate **2**. The subsequent alkylation of **2** followed by a desilylation reaction afforded propargyl alcohol **4**. Substrates **5a** and **5b** were obtained by the reaction of **4** with NCS/PPh_3 or $ClCO_2Me$/pyridine, respectively. Bromoallene **5c** was prepared from propargyl alcohol **6** using an established procedure for the formation of bromoallenes.[16] The treatment of **6** with TrisCl (Tris=2,4,6-triisopropylbenzenesulfonyl) and DMAP gave the corresponding sulfonate, which was converted to bromoallene **7** by treatment with $CuBr\cdot SMe_2$ in the presence of LiBr. Finally, the introduction of the indole unit to **7** was achieved by



Scheme 3. Preparation of substrates **5a**–**c**. (a) diethyl malonate, ethyl propiolate, Et_2O, rt; (b) $BrCH_2C{\equiv}CCH_2OTBS$, NaH, THF, 0 °C to rt; (c) TBAF, THF, 0 °C; (d) NCS, PPh_3, CH_2Cl_2, rt; (e) $ClCO_2Me$, pyridine, CH_2Cl_2, 0 °C; (f) TrisCl, DMAP, CH_2Cl_2, then $CuBr\cdot SMe_2$, LiBr, THF, 50 °C; (g) **1**, ethyl propiolate, Et_2O, rt.

its reaction with gramine (**1**) in the presence of ethyl propiolate to give bromoallene **5c**. The other substrates were also prepared in the same manner (see Supplementary data).

Our studies began with a series of screening experiments to identify the optimal reaction conditions using propargyl chloride **5a** as a model substrate (Table 1). The reaction of **5a** with 5 mol % $Pd(PPh_3)_4$, $TsNH_2$ and Cs_2CO_3 in THF gave spiroindole **9a**, the β-hydride elimination product, in only 20% yield (entry 1). When the reaction was conducted in the presence of 5 mol % $Pd(dba)_2$ and the bidentate ligand 1,1′-bis(diphenylphosphino)ferrocene (dppf), the desired reaction proceeded smoothly to afford the tetracyclic spiroindoline **8a** in 47% yield (entry 2). A variety of different inorganic bases (entries 3–5), ligands (entries 6–10) and solvents (entries 11–13) were also screened against the reaction, and the results revealed that the use of 1,4-bis(diphenylphosphino)butane (dppb) as the ligand with Cs_2CO_3 as the base in THF gave the best results, with compound **8a** being isolated in ca. 72% yield (entry 9). However, the main problem with these conditions was found to be poor reproducibility. Operating under the assumption that the poor reproducibility of these conditions was related to the purity of $Pd(dba)_2$, we investigated the use of $Pd_2(dba)_3\cdot CHCl_3$ following its recrystallization from $CHCl_3$.[17] This change afforded the desired product **8a** in 72% yield reproducibly (entry 14).

With the optimized conditions in hand, we proceeded to examine the performance of the reaction in the presence of a variety of different nucleophiles. The results are summarized in Table 1 (entries 15–19) and Scheme 4. The reaction with sulfonamides (e.g., $PhSO_2NH_2$, $MtsNH_2$, $NsNH_2$, and $MsNH_2$) gave the corresponding tetracyclic spiroindolines **8b**–**e** in moderate yields (entries 15–18). In contrast, benzylamine was found to be inert as the external nucleophile, with the β-hydride elimination product **9a** being isolated as the major product (entry 19). Interestingly, the use of dimethyl malonate as the nucleophile resulted in the formation of the regioisomeric spiroindoline **10a** (17%) and spiroindole **9a** (15%) as shown in Scheme 4. The use of acetyl acetone, which is a more acidic carbon nucleophile than dimethyl malonate, led to an increase in the yield of spiroindoline **10b** (50%), along with spiroindole **9a** (20%).

It is well known that bromoallenes are the synthetic equivalents of propargyl compounds including chlorides and carbonates in palladium-catalyzed transformations.[18] With this in mind, we examined the reactions of propargyl carbonate **5b** and bromoallene **5c** (Scheme 5). Unfortunately, these reactions gave the desired spiroindoline **8a** in only 8–14% yield. These results therefore demonstrated that substrates of this type are less effective for this reaction than propargyl chloride **5a**.

We next examined the scope and limitations of the reaction using a series of different indole substrates (Table 2). *N*-Substituted indoles **5d** and **5e** did not produce the spirocyclic products (entries 1 and 2). In contrast, indoles bearing an electron-withdrawing fluorine group (**5f**) or electron-donating methoxy group (**5h**) at their 5-position reacted smoothly under the optimized conditions to give the desired products **8i** and **8k** in good yields (entries 3 and 5). However, when compound **5g** bearing a bromine group at the 5-position of the indole was used as a substrate, a slightly lower yield (43%) of spiroindoline **8j** was observed. The lower yield observed in this case was attributed to side reaction(s) involving the aryl bromide moiety of the substrate, as well as the aryl bromide of the product **8j**.

We then turned our attention to the selective synthesis of the β-elimination product **9** (Table 3). It was envisaged that **9** could be efficiently produced under the same reaction conditions in the absence of an external nucleophile. This assumption was based on the results of our previous reaction, where the use of 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand afforded spiroindole **9a** as the major product in 62% yield (Table 1, entry 7).