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Concise Synthesis of Annulated Pyrido[3,4-*b*]indoles via Rh(I)-Catalyzed Cyclization

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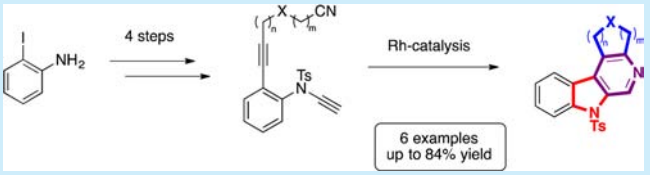
Supporting Information

ABSTRACT: The synthesis of pyridines bearing multiple ring fusions poses a considerable challenge for organic chemists. To address this problem, we describe the synthesis of a small library of pyrido[3,4-*b*]indoles via an efficient, five-step sequence. The key transformation is a Rh(I)-catalyzed [2 + 2 + 2] cyclization that forms three rings in one reaction flask. Our method is high yielding, accommodates a variety of functional groups, and suffers no entropic costs as ring size increases.



Nitrogen-containing heterocycles are widely used in drug discovery for the appropriate balance they offer with respect to polarity, aqueous solubility, and membrane permeability. In addition, the diversity in size and shape of these substructures plays a pivotal role in molecular recognition. In a recent review,[1] the aromatic heterocycle pyridine was found in nearly 6% of all FDA-approved small molecule pharmaceuticals. Given this prevalence, organic chemists have developed numerous methods toward their synthesis. One goal that still remains underexplored is the regioselective polyfunctionalization of pyridines. This is particularly important since nearly 50% of all pyridine-containing drugs are substituted more than once.

Commonly known as *β*-carbolines, pyrido[3,4-*b*]indoles contain an indole ring fused to the pyridine scaffold. These structures have been found to disrupt DNA replication and transcription,[2] elicit strong neuropharmacological effects,[3] and exhibit excellent cytotoxicities against cancer cells, fungi, and bacteria.[4] Natural *β*-carbolines such as harman and norharman have received significant attention from the synthetic community due to their ability to bind to DNA via intercalation.[5] Less common are annulated *β*-carbolines that contain an extra carbo- or heterocycle fused to the pyridine ring. The more notable examples, shown in Figure 1, include Ambocarb (inhibitor of voltage-gated sodium channels),[6] a lactam-fused *β*-carboline (anticancer agent, IC_{50} = 2.6 *μ*M),[7] and a lactone-fused *β*-carboline (benzodiazepine receptor antagonist, IC_{50} = 0.2 nM).[8]

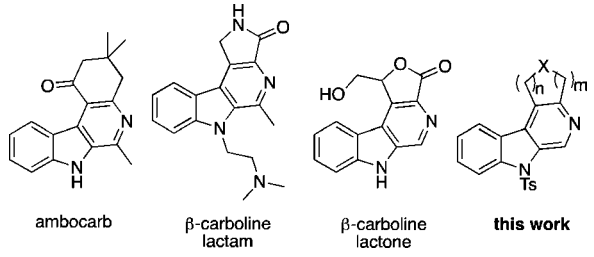


Figure 1. Annulated pyrido[3,4-*b*]indoles.

The fusion of additional rings onto the *β*-carboline core is difficult to achieve efficiently from a naked scaffold. We hypothesized that more complex pyridines could be prepared if the aromatic ring itself was formed very late in the sequence. Since metal-catalyzed [2 + 2 + 2] cyclization reactions are widely used to create pyridines in one step,[9,10] we envisioned that additional fused rings could be generated concurrently.[11] Using this strategy, we recently reported a three-step synthesis of an annulated pyrido[3,4-*b*]indole via palladium-mediated tandem catalysis.[12] While the synthesis of this pyridine was novel mechanistically, the scope of the methodology is so far limited to only a single substrate. In this letter, we report a general method for the synthesis of annulated pyridines via a late-stage, Rh(I)-catalyzed [2 + 2 + 2] cyclization.

The synthesis of polycyclic systems such as these is difficult to achieve in one step. In 2002, Witulski reported the synthesis of annulated *β*-carbazoles via an intramolecular Cp*Ru(COD)-Cl-catalyzed [2 + 2 + 2] cyclization.[13] Using this work as inspiration, we sought to replace the terminal alkyne with a nitrile, thereby providing access to annulated pyrido[3,4-*b*]indoles from acyclic precursors in one step.

The synthesis of the required intramolecular substrate toward these molecules is shown in Scheme 1. We began by preparing substituted aryl iodide **4** according to a two-step literature procedure.[13] Treatment of iodoaniline **1** with *p*-toluenesulfonyl chloride gave the sulfonamide **2**, which was converted to the *N*-alkynyl sulfonamide **4** under basic conditions. Upon reacting **4** with alkynyl nitrile **5a** under palladium-catalyzed Sonogashira cross-coupling[14] conditions for 1 h, we obtained diynyl nitrile **6a** in 68% yield. This reaction

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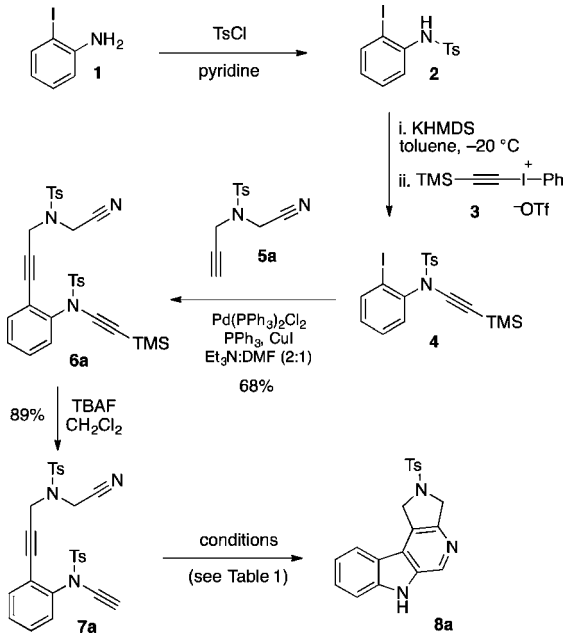
Scheme 1. Synthesis of Ring-Fused Pyridoindole



was closely monitored by TLC and worked up immediately after the starting material had been consumed in order to prevent cyclotrimerization of **6a**. Removal of the trimethylsilyl group proceeded smoothly to give **7a** in 89% yield.

With the desired intramolecular substrate **7a** in hand, and given the large precedent for metal-catalyzed [2 + 2+2] cyclization reactions, we optimized the reaction conditions with respect to metal catalyst, solvent, concentration, and exogenous ligand (Table 1). A cobalt complex under microwave irradiation

Table 1. Reaction Optimization of Cyclization

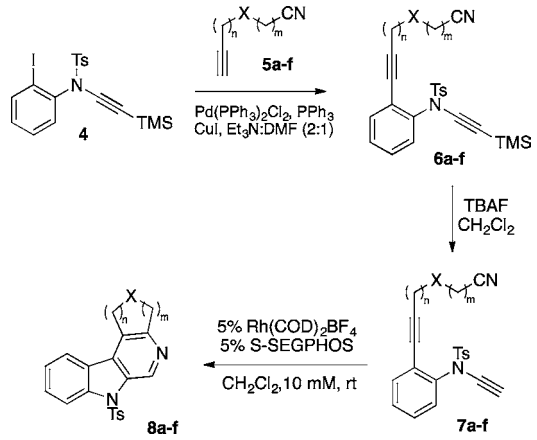
entry	conditions[a]	yield (%)
1	20% $CpCo(CO)_2$, μ-wave, $ClCH_2CH_2Cl$, 120 °C, 10 min	39
2[b]	5% $Ir(COD)Cl_2$, 10% *rac*-BINAP, toluene	17
3	5% $Ir(COD)Cl_2$, 10% *rac*-BINAP, toluene	25
4	10% Cp*Ru(COD)Cl, CH_2Cl_2	13
5	10% $Rh(PPh_3)_3Cl$, CH_2Cl_2	19
6	10% $Rh(COD)_2BF_4$, 10% *rac*-BINAP, CH_2Cl_2	55
7	5% $Rh(COD)_2BF_4$, 10% *rac*-BINAP, CH_2Cl_2	72
8[c]	5% $Rh(COD)_2BF_4$, 10% *rac*-BINAP, CH_2Cl_2	71
9	5% $Rh(COD)_2BF_4$, 5% *S*-SEGPHOS, CH_2Cl_2	84
10	5% $Rh(COD)_2BF_4$, 5% *S*-H_8-BINAP, CH_2Cl_2	30

[a]All reactions performed at 10 mM substrate concentration and at room temperature unless otherwise noted. [b]100 mM substrate concentration. [c]5 mM substrate concentration.

gave only a modest yield of pyrido[3,4-*b*]indole **8a**, despite a high catalyst loading (entry 1). An iridium(I) complex also gave a poor yield of **8a** and was accompanied by an unidentified byproduct that formed despite a 10-fold reduction in concentration (entries 2–3). Both Cp*Ru(COD)Cl and $Rh(PPh_3)_3Cl$, which were the catalysts of choice in Witulski's work, also gave a poor yield of **8a** (entries 4–5). The cationic rhodium(I) complex $Rh(COD)_2BF_4$, pioneered by Tanaka et al.,[15] gave excellent yields of **8a**. Lowering the catalyst loading and decreasing the substrate concentration resulted in higher yields and greater turnover numbers, respectively (entries 7–8). We observed an additional increase in yield of **8a** by replacing *rac*-BINAP with *S*-SEGPHOS (entry 9). Addition of *S*-H_8-BINAP resulted in a decrease in yield, indicating that the bite angle of the exogenous ligand is important.

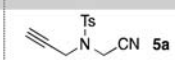
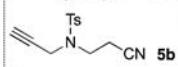
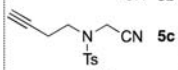
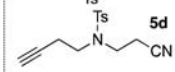
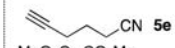
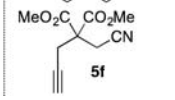
We next applied this methodology to the synthesis of a variety of pyrido[3,4-*b*]indoles bearing annulations of different size, geometry/conformation, and backbone atom composition according to Scheme 2. First, we used a collection of six

Scheme 2. Synthesis of Diverse Ring Annulations



different alkynyl nitriles as substrates during the Sonogashira coupling (**5a–f**, Table 2). With the exception of **5d**, the yields

Table 2. Substrate Scope of Methodology

entry	alkynyl nitrile **5a-f**	yield of **6a-f** (%)	yield of **7a-f** (%)	yield of **8a-f** (%)
1	 **5a**	68	89	84
2	 **5b**	91	76	71
3	 **5c**	55	65	77
4	 **5d**	46	83	75
5	 **5e**	62	75	38
6	 **5f**	62	88	41

of this step are consistently good (Table 2). However, the bulk of the mass balance comes from *in situ* formation of **8a–f**, as we have observed previously.[5] Next, tetrabutylammonium fluoride mediated desilylation proceeded in excellent yields to afford the requisite diynyl nitrile cyclization substrates **7a–f**. The instability of these molecules to long-term exposure to air and moisture prompted us to quickly cyclotrimerize them after isolation. Applying our optimized Rh(I)-catalyzed [2 + 2 + 2] cyclization conditions to these substrates led in all cases to the desired pyrido[3,4-*b*]indoles **8a–f**.

The highest yields for this reaction occurred for rings containing toluenesulfonyl-protected amines. There appears to be no limitation in the size of the desired annulation since 5-, 6-, and 7-membered rings can be prepared in excellent yields (compare entries 1–4). A fused carbocycle and an ester-functionalized carbocycle both gave slightly poorer yields for

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the final step (entries 5 and 6). This was at least in part due to the incomplete consumption of starting material, despite heating (40 °C) and longer reaction times (up to 36 h). A summary of the pyrido[3,4-*b*]indoles prepared via this method is shown in Figure 2.

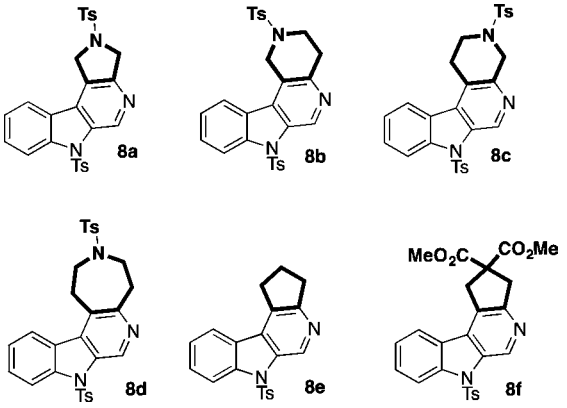

Figure 2. Summary of annulated pyrido[3,4-*b*]indoles.

In conclusion, we have described a concise method for the synthesis of six annulated pyrido[3,4-*b*]indoles. Each of these molecules can be prepared in as few as five steps from commercially available material with good overall yields. While there appears to be no entropic limitation on annulation size, efforts to introduce an ether or basic amine functional group into the backbone were not successful and will require optimization. Further investigations into the electronic requirements of this reaction scheme and the evaluation of these molecules as biological probes are currently being pursued.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02807.

Experimental procedures and full characterization (NMR, IR, and MS) of all newly synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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