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Parallel strategies for the synthesis of annulated pyrido[3,4-*b*]indoles via Rh(I)- and Pd(0)-catalyzed cyclotrimerization

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ABSTRACT

Two different pathways for the synthesis of annulated pyrido[3,4-*b*]indoles are reported using metal-catalyzed cyclotrimerization reactions. A stepwise process using Rh(I)-catalysis in the final step of the synthesis and a multicomponent, tandem catalytic approach using Pd(0)-catalysis both lead to complex nitrogen-containing heterocycles in good yields. Substituent effects are investigated for both pathways, demonstrating that the Pd(0)-catalyzed approach is more sensitive to electron-withdrawing groups.

Transition metal catalysis is a fundamental tool in organic synthesis that enables chemists to construct molecules with ever increasing complexity. Nearly every organic functional group has some affinity for one or more of the transition metals, and the resulting complexes often change the reactivity of the functional group. This can be exploited for synthetic purposes, whereby transformations that are expensive, wasteful, or difficult using traditional methods can be performed under mild conditions in the presence of a transition metal [1]. The use of transition metals for the synthesis of complex nitrogen-containing heterocycles is especially important given their prevalence in small molecule drug discovery efforts [2]. We recently reported the synthesis of pyrido[3,4-*b*]indoles, also known as β-carbolines, using a strategy that employs transition metal catalysis to fuse additional rings to the core pyridine scaffold [3]. While annulations to pyridoindole heterocycles do not appear frequently in the chemical literature, some notable examples have potent biological effects, including the inhibition of ion channels [4], binding to neurochemical receptors and DNA [5,6], and cytotoxic and cytostatic activity [7–9]. New methods to rapidly synthesize these molecules would enable an even wider study of their biological activity. Furthermore, understanding the mechanism and generality of these transition metal-catalyzed reactions would facilitate the construction of new heterocycles with increasingly complex architectures. In this Letter, we report two parallel strategies for the synthesis of annulated pyrido[3,4-*b*]indoles: 1) a stepwise Rh(I)-catalyzed sequence, and 2) a one-pot tandem catalytic sequence using Pd(0).

Our synthesis of annulated pyrido[3,4-*b*]indoles used the retrosynthetic strategy outlined in Fig. 1, which made use of a late-stage cyclotrimerization [10–18] to build the core heterocyclic framework and a Sonogashira reaction [19] to create a diynylnitrile substrate from simpler starting materials. Our initial investigations using this strategy focused on the annulation of different sized rings to the pyrido[3,4-*b*]indole by exchanging the alkynylnitrile tether [3]. In this study, we investigated the effects of substitution

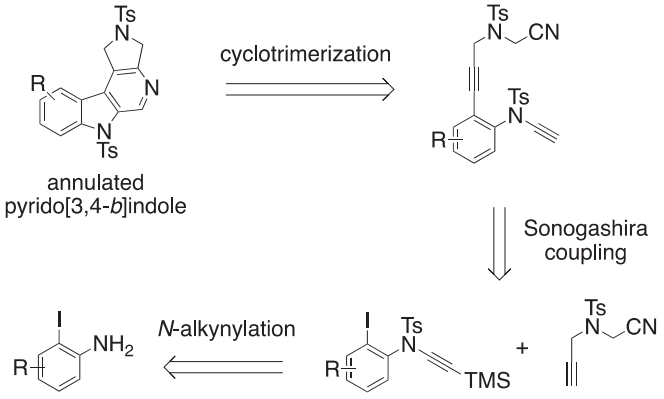

Fig. 1. Retrosynthetic analysis for annulated pyrido[3,4-*b*]indoles.

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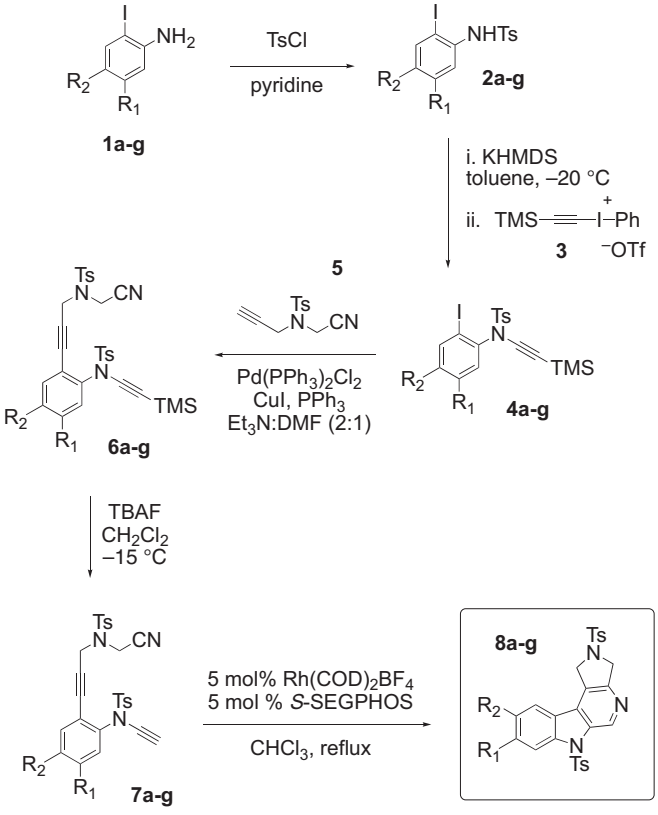
pattern on the starting substrates to determine the electronic requirements for this sequence.

The synthesis of differentially substituted pyrido[3,4-*b*]indoles is outlined in Scheme 1. We began by following a two-step literature procedure [20] to prepare the requisite *N*-(trimethylsilyl)ethynyl-2-iodoanilines **4a–g** in good yield from substituted 2-iodoanilines. A palladium-catalyzed Sonogashira reaction using a nitrile-tethered alkyne **5** resulted in the preparation of substrates **6a–g**. After removal of the trimethylsilyl group with TBAF, a rhodium(I)-catalyzed intramolecular cyclotrimerization [14] reaction afforded the desired annulated pyrido[3,4-*b*]indoles **8a–g**.

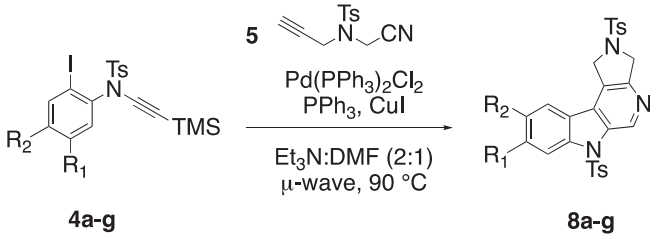
Table 1 shows the yields for each step of this sequence for six different substrates containing a diversity of functional groups. Both electron-withdrawing and electron-donating groups resulted in moderate to good isolated yields for each step in the synthesis using optimized conditions. The *N*-alkynylation reaction using the hypervalent iodine intermediate **3** [21] nearly always resulted in some recovered starting material despite extensive optimization of the reaction conditions. In some cases, loss of the *p*-toluenesulfonyl protecting group was even observed. Thus, the moderate yields (ie. **4e**, **4f**) for this step can be attributed to a combination of incomplete deprotonation, instability of the products to strongly basic conditions, and some insolubility of **3** in toluene. It should also be noted that the Sonogashira reaction had to be closely monitored by TLC and worked up immediately after the starting material was completely consumed to avoid lower yields. Removal of the trimethylsilyl protecting group proceeded smoothly to give terminal alkynamides **7a–g** in good yields. These substrates were sensitive to hydrolysis, resulting in the formation of acetamide side products, so the reaction needed to be performed at lower temperatures. Finally, the intramolecular cyclotrimerization reaction proceeded smoothly in all cases to give the desired targets **8a–g**, with the best yields occurring for electron-rich systems. More moderate yields were observed for substrates with an electron-withdrawing group. With the exception of the **8a** (rt, CH_2Cl_2), all diynylnitrile substrates required refluxing conditions in $CHCl_3$ as solvent and close monitoring by TLC.

A frustrating problem in the synthesis of annulated pyrido[3,4-*b*]indoles via this stepwise approach was the consistently moderate yields for the Sonogashira reaction for some substrates. Upon closer inspection, much of mass balance came not from decomposition but rather from the formation of **8a–g** (Scheme 2). This led us to believe that palladium itself could catalyze the intramolecular cyclotrimerization step [22–27], obviating the need for isolation of two additional intermediates. This result was quite surprising, since it implied that a *single* palladium precursor could multitask within the same reaction flask by participating in *more than one* mechanistically unique catalytic cycle [28–34]. We previously reported a mechanistic study of this transformation for a single substrate (**8a**) [35]. Since the reaction was run overnight, had high catalyst loading, and suffered from some loss of catalytic activity over time, we searched for an improved experimental procedure that would have broader utility.

We elected to use microwave acceleration to solve the limitations in our initial synthesis of **8a**. Using substrate **4a** as our model system again, we investigated the effect of temperature, time, and the source of palladium, as shown in Table 2. The results of this optimization indicate that moderate yields for this reaction could be achieved. In each case, the most significant byproduct in this



Scheme 1. Synthesis of annulated pyrido[3,4-*b*]indoles via Rh(I)-catalysis.



Scheme 2. One-pot synthesis of annulated pyrido[3,4-*b*]indoles via Pd(0)-catalysis.

Table 1
Stepwise synthesis of annulated pyrido[3,4-*b*]indoles.

Entry	R_1 =	R_2 =	Yield of 2 (%)	Yield of 4	Yield of 6	Yield of 7	Yield of 8
a	H	H	78	83	68	89	84[b,c]
b	Cl	H	83	60	72	74	96
c	H	Cl	71	74	81	64	65
d	H	OMe	81	87	63	88	93
e	H	Me	80	48	82	83	91
f	H	CO_2Me	99[a]	38	67	90	78
g	H	F	61	88	53	79	64

[a] TsCl, DMAP, $CHCl_3$.
[b] rt, CH_2Cl_2.
[c] Ref. [3].

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Table 2
Optimization of the one-pot synthesis of annulated pyrido[3,4-*b*]indole **8a**.

Entry	Catalyst (5 mol%)	Temperature (°C)	Time (h)	Isolated yield (%)
1	$Pd(PPh_3)_4$	80	1	31
2	$Pd(PPh_3)_4$	90	1	36
3	$Pd(PPh_3)_4$	100	1	43
4	$Pd(PPh_3)_4$	80	2	44
5	$Pd(PPh_3)_4$	80	3	36
6[a]	$2 \times Pd(PPh_3)_4$	80	2	35
7	$Pd(OAc)_2$	90	1	39
8	$Pd(PPh_3)_2Cl_2$	90	1	53

[a] An additional 5% of $Pd(PPh_3)_4$ was added after 1 h, then irradiated again.

reaction was intermediate **6a**. Higher temperatures resulted in a higher yield of the derived product **8a**, presumably by accelerating the cyclotrimerization (entries 1–3). Extending the reaction time did not result in better yields (entries 4–5), nor did adding fresh catalyst (entry 6) or using $Pd(OAc)_2$ (entry 7). Optimized conditions were found that employed $Pd(PPh_3)_2Cl_2$ as catalyst precursor while being irradiated at 90 °C for 1 h (entry 8).

We can now report that the tandem catalytic sequence shown in Scheme 2 is compatible with a selection of substrates (Table 3). Treating *N*-(trimethylsilyl)ethynyl-2-iodoanilines **4b–g** with the alkynylnitrile **5** in the presence of $Pd(PPh_3)_2Cl_2$ and CuI under microwave irradiation at 90 °C for 1 h resulted in formation of **8b–e** in acceptable yields. Unfortunately, very little product was formed for substrates with a strong electron withdrawing group (**8f–g**). Significant decomposition products were observed in the synthesis of **8f**, which is consistent with the lower yield observed in the Rh(I)-catalyzed protocol. Homodimerization occurred during the synthesis of **8g**, which suggests that Glaser coupling is faster than intramolecular cyclization. Attempts to avoid homodimerization by using only two equivalents of Et_3N did not result in any product formation.

While these yields are indeed modest, our method could be attractive for certain substrates as a multicomponent coupling. First, the reaction conditions are an improvement upon our initial disclosure [35], since half as much catalyst is used and the reaction time is significantly shorter due to microwave acceleration. Second, this reaction is unique since a single palladium complex can form multiple bonds and multiple rings in a single reaction flask, thereby enabling the synthesis of annulated pyrido[3,4-*b*]indoles in as few as three steps from easily accessible starting materials. Finally, the yields for the one-pot synthesis of **8a–e** using Pd(II)-catalysis (Scheme 2 and Table 3) are on par with the stepwise method using Rh(I)-catalysis (Scheme 1 and Table 1), indicating that both pathways are viable depending on the desired substitution pattern.

In conclusion, we have described parallel pathways for the synthesis of annulated pyrido[3,4-*b*]indoles bearing a range of functional groups. A stepwise sequence that employs a Rh(I)-catalyzed cyclotrimerization in the last step is high yielding and modular. Likewise, a one-pot Pd(0)-catalyzed tandem Sonogashira—desilylation–cyclotrimerization strategy affords the same products in reasonable yields. Coupled with our recent report of the ability to expand the size of the annulation, these two transition metal catalyzed pathways provide additional synthetic tools to construct complex pyrido[3,4-*b*]indoles in a less time- and resource-intensive manner.

Table 3
Substrate scope of one-pot synthesis of annulated pyrido[3,4-*b*]indoles.

Entry	R_1 =	R_2 =	Yield of 8 (%)
a	H	H	53
b	Cl	H	51
c	H	Cl	57
d	H	OMe	43
e	H	Me	47
f	H	CO_2Me	9
g	H	F	0 (98)[a]

[a] Yield of homodimer.

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Appendix A. Supplementary data

Supplementary data (including all experimental details and the full characterization of all new compounds) to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.10.050.

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