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Synthetic Methods |*Hot Paper*|

A Palladium- and Copper-Catalyzed Synthesis of Dihydro[1,2-*b*]indenoindole-9-ol and Benzofuro[3,2-*b*]indolines: Metal-Controlled Intramolecular C–C and C–O Bond-Forming Reactions

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Abstract: A palladium- and copper-catalyzed synthesis of dihydro[1,2-*b*]indenoindole-9-ol and benzofuro[3,2-*b*]indolines has been developed, whereby the same starting material is employed for the synthesis of both heterocyclic scaffolds and the selectivity of the product is controlled by switching the choice of metal. Salient features of these cascade reactions include wide-ranging functional group tolerance, simple reaction conditions, and moderate to high yields.

Introduction

Indole-fused polycyclic heterocycles are prevalent structural motifs present in many natural products, pharmaceuticals, and bioactive molecules.[1] In particular, the indenoindoles[2] and benzofuroindolines[3] are embedded in many naturally occurring compounds, such as paspaline, yuehchukene, paxilline, phalarine, and azonazine (Figure 1). These indole-fused scaffolds exhibit wide range of biological and pharmacological properties, such as activation of potassium channel openings,[4a,b] anticancer properties,[4c] inhibition of protein kinases,[4d] antioxidant properties,[4e,f] carbonic anhydrase inhibition,[4g] regulation of gene battery enzymes,[4h] and membrane stabilization.[4i,j] Furthermore, these π-conjugated structures have also found applications in optoelectronics and advanced materials due to the structure's unique electronic properties.[5] Although considerable efforts have been made to synthesize these heterocycles,[6] the development of operationally simple procedures with improved efficiency and substrate scope remains highly desirable.

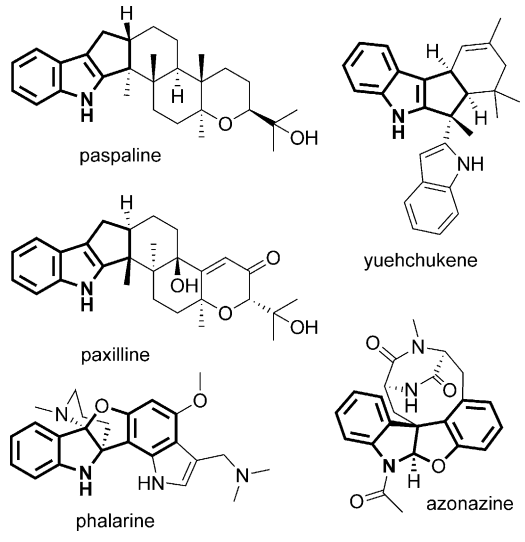

Figure 1. Representative bioactive natural products.

Palladium-catalyzed α-arylation of alkyl or aryl ketones with suitable aryl halides provides an efficient means of preparing valuable synthetic intermediates in organic synthesis.[7] After the seminal work published by Buchwald and co-workers, the palladium-catalyzed α-arylation of carbonyl moieties with aryl halides has made rapid progress and significant efforts have since been devoted to various applications.[8] Of particular importance, intramolecular α-arylation reactions are of interesting for the construction of polycyclic compounds.[9] Although such intramolecular reactions have been well explored for small size rings, larger rings have been less studied and, probably owing to difficulties in the formation of large-size palladacycle intermediates. We envisioned that if larger rings could be synthesized by α-arylation, the carbonyl group, intact in the ring, could be subsequently captured with a suitable nucleophile in a cascade manner to construct fused heterocycles.

Moreover, copper-catalyzed Ullmann-type C(aryl)–N, C(aryl)–O, and C(aryl)–C bond-forming reactions have proven an efficient method in organic synthesis for more than 100 years.[10] Recently, these reactions have become an attractive synthetic tool towards the construction of various heterocycles.[11] In comparison with palladium, copper-catalyzed cascade reactions have been less explored and there is a lot of scope to investigate in this area. We presumed that involving the Ullman reactions in a cascade sequence could lead to the generation of useful heterocycles.

During the last decade, transition metal-catalyzed cascade reactions have emerged as an important synthetic route to

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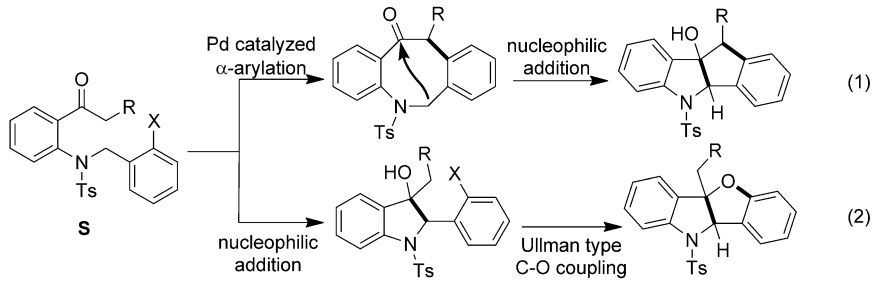
build complex heterocycles, as well as natural products.[12] Evidently, cascade reactions have distinct advantages, such as atom and time economy, effective multistep one-pot reactions, and reductions in waste and labor. In light of these facts and our ongoing research interest in the development of transition metal-catalyzed synthetic methodologies,[13] we report herein a palladium-catalyzed intramolecular α-arylation followed by nucleophilic addition with ketones to synthesize dihydro[1,2-*b*]indenoindole scaffolds [Scheme 1, Eq. (1)]. In addition, we have also discovered a copper-catalyzed intramolecular cascade approach to benzofuro[3,2-*b*]indolines by nucleophilic addition with ketones followed by Ullman-type C–O bond formation [Scheme 1, Eq. (2)]. By switching the catalyst between palladium and copper, a divergent synthesis of two different heterocycles from the same starting material has been developed.



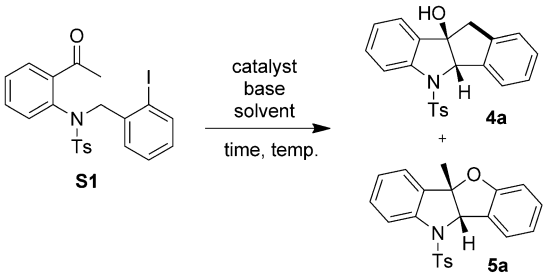
Scheme 1. Proposed reaction strategy.

Results and Discussion

To realize the hypothesis, we prepared the starting materials **S1**–S**20** from sulfonylation of 2-amino acetophenone derivatives followed by *N*-alkylation with 2-halo benzylbromides (see the Supporting Information). Compound **S1** was used as the model substrate for the optimization studies (Table 1). Initially, we used $[Pd(PPh_3)_4]$ as a catalyst, with which various bases such as K_2CO_3, Cs_2CO_3, KO*t*Bu, KOH and NaOH were screened using acetonitrile as a solvent at reflux temperature (Table 1, entries 1–5). To our delight, KOH afforded the desired product in 69% yield, whereas the other bases were inferior to this. The identity of compound **4a** was unambiguously confirmed by X-ray analysis.[14] In addition to this, we detected the other possible benzofuro[3,2-*b*]indoline (**5a**) product at trace levels. To further improve the reaction yield, various palladium(0), palladium(II), and nickel(0) catalysts (Table 1, entries 6–11) were screened, but none of them provided a better yield than $[Pd(PPh_3)_4]$ (entry 4). Solvent studies revealed that acetonitrile was crucial for this transformation and other solvents were unfavorable (Table 1, entries 11–15). When we increased the equivalents of base, the reaction yield was further improved to 77% (Table 1, entry 16). Altering the catalyst loading in either directions from the optimized quantity had little effect on the reaction yield (Table 1, entries 18 and 19). Finally, we identified the conditions outlined for entry 16 as optimum for the synthesis of dihydro[1,2-*b*]indenoindole-9-ol.

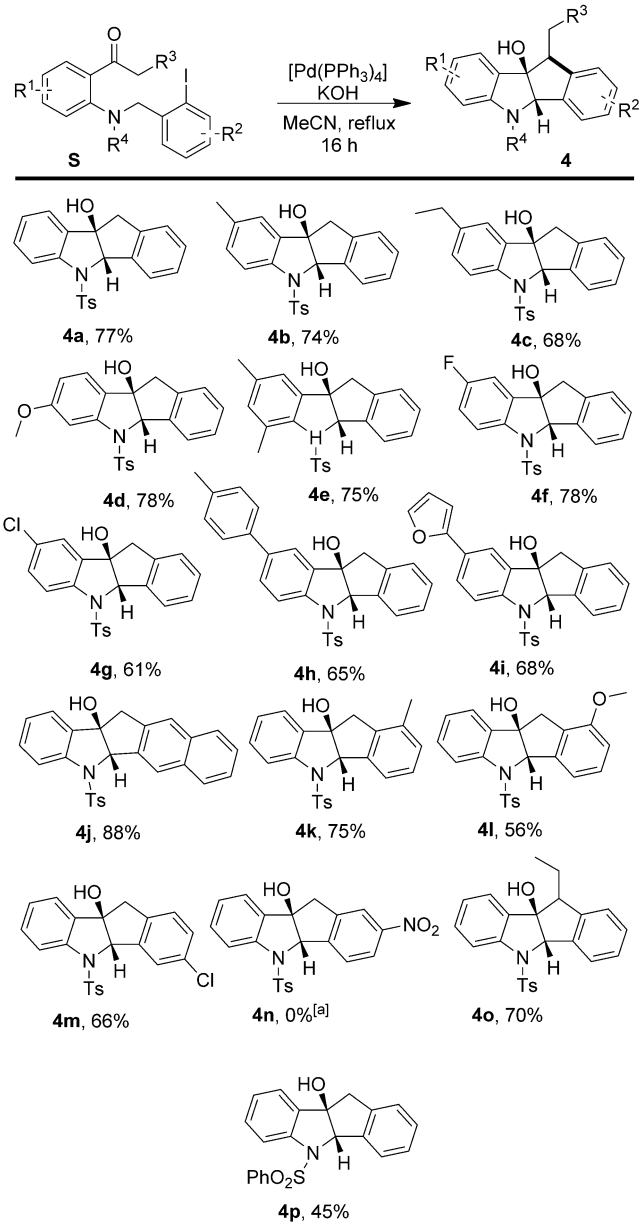
Having established the optimized reaction conditions, we moved to examine the scope and limitation of the cascade process for the synthesis of compound **4** (Scheme 2). With aryl substituent R^1 as either electron-donating (**4a–e**) or electron-withdrawing groups (**4f** and **g**), the reaction generally worked well and the desired products were isolated in high yields. Notably, substrates in which R^1 was an aryl or heteroaryl group were also suitable for this process (**4h** and **i**). The reaction also proceeded smoothly with the other aryl substituent R^2 as various groups including naphthyl, methoxy, methyl and chloro at different positions (**4j–m**), producing the expected products in moderate to good yields. However, substrate **S14** (R^2 = nitro) failed to give the expected product (**4n**). Instead, the benzofuro[3,2-*b*]indoline compound **5n** was formed in 40% yield. The probable reason may be that the highly electron-withdrawing nature of the nitro

Table 1. Optimization studies for dihydro [2,3-*b*]indenoindoles.



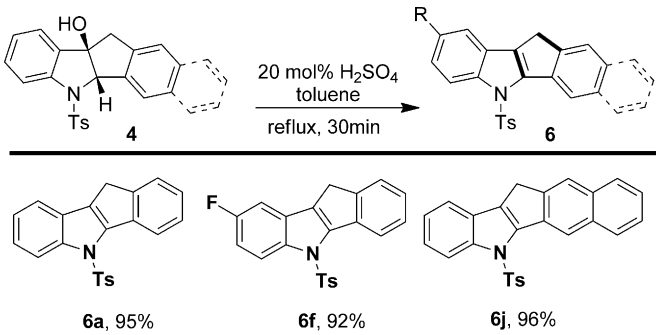
Entry	Catalyst	Base	Solvent	*t* [h]	Yield of **4a**/**5a** [%]
1	$[Pd(PPh_3)_4]$	K_2CO_3	MeCN	24	–/–
2	$[Pd(PPh_3)_4]$	Cs_2CO_3	MeCN	24	–/–
3	$[Pd(PPh_3)_4]$	KO*t*Bu	MeCN	24	–/20
4	$[Pd(PPh_3)_4]$	KOH	MeCN	24	69/trace
5	$[Pd(PPh_3)_4]$	NaOH	MeCN	24	30/trace
6[b]	$Pd(OAc)_2$	KOH	MeCN	24	–/–
7[b]	$PdCl_2$	KOH	MeCN	24	–/–
8	$[Pd(dba)_3]$	KOH	MeCN	24	62/trace
9	$[Pd_2(dba)_3]$	KOH	MeCN	24	65/trace
10	$[PdCl_2(PPh_3)_2]$	KOH	MeCN	24	–
11	$[Ni(cod)_2]$	KOH	MeCN	24	–
12	$[Pd(PPh_3)_4]$	KOH	DMF	24	–
13	$[Pd(PPh_3)_4]$	KOH	DMSO	24	–
14[c]	$[Pd(PPh_3)_4]$	KOH	toluene	24	25/trace
15[c]	$[Pd(PPh_3)_4]$	KOH	dioxane	24	trace/trace
16[d]	**$[Pd(PPh_3)_4]$**	**KOH**	**MeCN**	**16**	**77/trace**
17[e]	$[Pd(PPh_3)_4]$	KOH	MeCN	12	55/–
18[f]	$[Pd(PPh_3)_4]$	KOH	MeCN	16	78/trace
19[g]	$[Pd(PPh_3)_4]$	KOH	MeCN	20	70/trace

[a] Reaction conditions (unless otherwise stated): Compound **S1** (200 mg), catalyst (10 mol%), base (3 equiv) in solvent (3 mL) at 80 °C for given time. [b] 20 mol% of PPh_3 was added. [c] Reaction performed at 110 °C. [d] 4 equiv of base was used. [e] 6 equiv of base was used. [f] 20 mol% of catalyst was used. [g] 5 mol% of catalyst was used; dba = dibenzylideneacetone, cod = 1,5-cyclooctadiene.



Scheme 2. Substrate scope for synthesis of indeno[1,2-*b*]indole-9-ol products **4**. Reaction conditions: Substrate **S** (200 mg), $[Pd(PPh_3)_4]$ (10 mol%), and KOH (4 equiv) in MeCN (3 mL) at reflux for 16 h. [a] Instead of **4n**, **5n** was formed in 40% yield.

group disfavors the α-arylation process and the competitive nucleophilic addition reaction dominates. With regards to the ketone substituent R^3, the reaction of substrate **S15** (R^3 = ethyl) proceeded well to give the corresponding product **4o**, which suggests that this protocol is suitable for various substituted ketones. Moreover, substrate **S16**, in which the nitrogen substituent R^4 was benzenesulfonyl rather than toluenesulfonyl, was also tolerated under the optimized reaction conditions. However, when the iodo substituent of compound **S1** was replaced with bromo, the reaction was failed to proceed. The structures of **4a** and **4d** were determined by X-ray analysis (see the Supporting Information).[14]



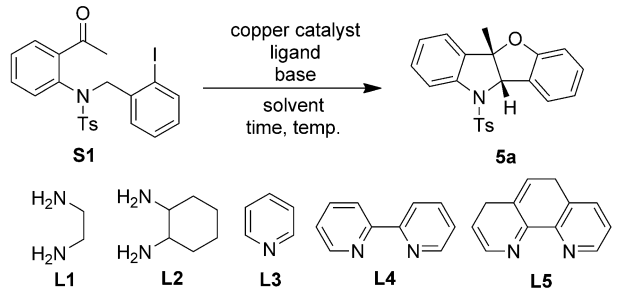
Scheme 3. Further transformation of compound **4**. Reaction conditions: Compound **4** (75 mg) and conc. H_2SO_4 (20 mol%) in toluene (3 mL) at reflux for 30 min.

The synthetic utility of **4** was demonstrated by its conversion into tetrahydroindeno[1,2-*b*]indoles under acid catalysis (Scheme 3). A few representative examples were smoothly converted into the corresponding dehydrated products, **6a**, **f**, and **j**, in excellent yields with the aid of a catalytic amount of sulfuric acid in toluene.

During the optimization studies of compound **4**, we observed traces of benzo[3,2-*b*]furoindolines (**5**) and this prompted us to think whether a copper catalyst system could be developed to achieve this product exclusively by nucleophilic addition followed by C–O bond formation [Scheme 1, Eq. (2)]. To test our hypothesis, we commenced optimization studies (Table 2). In our initial investigation, **S1** was used as a model substrate and various copper salts (Table 2, entries 1–6) were screened using 1,2-cyclohexanediamine (mixture of *cis* and *trans*) (**L2**) as the ligand and KO*t*Bu as a base in aceteonitrile and DMF at 80 °C. Among these, $Cu(OTf)_2$ provided the maximum yield of 55% and was thus chosen as the catalyst for further studies. The influence of ligands (**L1**–**L5**) was then screened and 1,10-phenanthroline (**L5**) proved most efficient (Table 2, entries 7–10). The reaction was studied with various bases, such as K_2CO_3, Cs_2CO_3, LiO*t*Bu, NaOH, but none of them led to an improved reaction yield (Table 2, entries 11–15) in comparison to KO*t*Bu. From the solvent studies, we found DMF to be superior to the other solvents (Table 2, entries 16–18). Either increasing or decreasing the reaction temperature also led to reduced yields (Table 2, entries 19 and 20). When we increased the amount of catalyst, the yield was not improved (Table 2, entry 21). Finally, the conditions outlined in entry 10 were identified as the optimized reaction conditions for benzofuro[3,2-*b*]indoline synthesis.

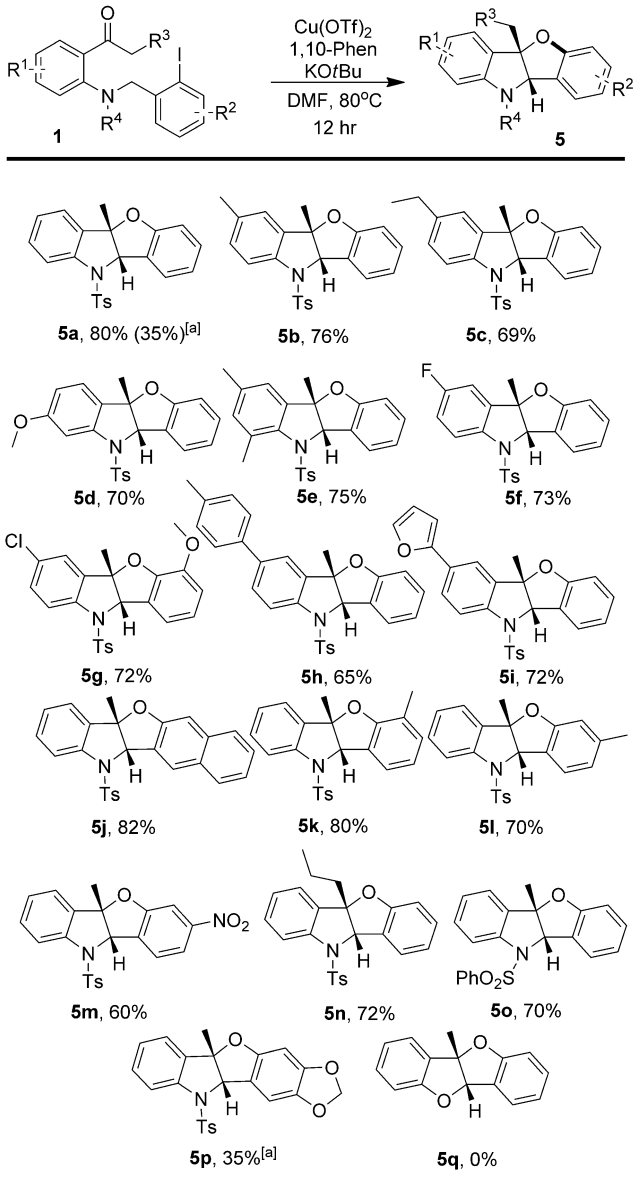
The optimized reaction conditions were then employed to investigate the substrate scope of the copper-catalyzed cascade synthesis of compound **5** (Scheme 4). Various electron-donating (**5a**–**e**), halide (**5f**, **5g**), aryl (**5h**), and heteroaryl (**5i**) substituents were tested as R^1, with the reaction proceeding smoothly to give the desired products in moderate to high yields. Similarly, substrates with R^2 as groups such as naphthyl, methyl, and nitro also afforded the corresponding products (**5j**–**m**). Interestingly, the propyl-substituted compound **5n** was smoothly prepared under the reaction conditions. As the *N*-substituent, instead of tosyl, the benzenesulfonyl group was

Table 2. Optimization studies for benzofuro[3,2-*b*]indolines.



Entry	Catalyst/ligand	Base	Solvent	*T* [°C]/	*t* [h]	Yield [%]
1	CuI/**L2**	KO*t*Bu	MeCN	80	12	22
2	CuI/**L2**	KO*t*Bu	DMF	80	12	48
3	$Cu(OAC)_2$/**L2**	KO*t*Bu	DMF	80	12	35
4	$Cu(OTf)_2$/**L2**	KO*t*Bu	DMF	80	12	55
5	$CuCl_2$/**L2**	KO*t*Bu	DMF	80	12	40
6	$CuBr_2$/**L2**	KO*t*Bu	DMF	80	12	25
7	$Cu(OTf)_2$/**L1**	KO*t*Bu	DMF	80	16	40
8	$Cu(OTf)_2$/**L3**	KO*t*Bu	DMF	80	16	30
9	$Cu(OTf)_2$/**L4**	KO*t*Bu	DMF	80	16	62
10	**$Cu(OTf)_2$/L5**	**KO*t*Bu**	**DMF**	**80**	**12**	**80**
11	$Cu(OTf)_2$/**L5**	K_2CO_3	DMF	80	24	–
12	$Cu(OTf)_2$/**L5**	KOH	DMF	80	12	30
13	$Cu(OTf)_2$/**L5**	Cs_2CO_3	DMF	80	24	–
14	$Cu(OTf)_2$/**L5**	LiO*t*Bu	DMF	80	16	–
15	$Cu(OTf)_2$/**L5**	NaOH	DMF	80	16	–
16	$Cu(OTf)_2$/**L5**	KO*t*Bu	DMSO	80	16	45
17	$Cu(OTf)_2$/**L5**	KO*t*Bu	toluene	110	16	40
18	$Cu(OTf)_2$/**L5**	KO*t*Bu	dioxane	100	16	45
19	$Cu(OTf)_2$/**L5**	KO*t*Bu	DMF	120	8	70
20	$Cu(OTf)_2$/**L5**	KO*t*Bu	DMF	60	24	25
21[b]	$Cu(OTf)_2$/**L5**	KO*t*Bu	DMF	80	16	50

[a] Reaction conditions (unless otherwise stated): Compound **S1** (200 mg), catalyst (10 mol%), ligand (20 mol%), base (3 equiv) in solvent (3 mL) at given temperature and time. [b] 2 equiv of base was used.



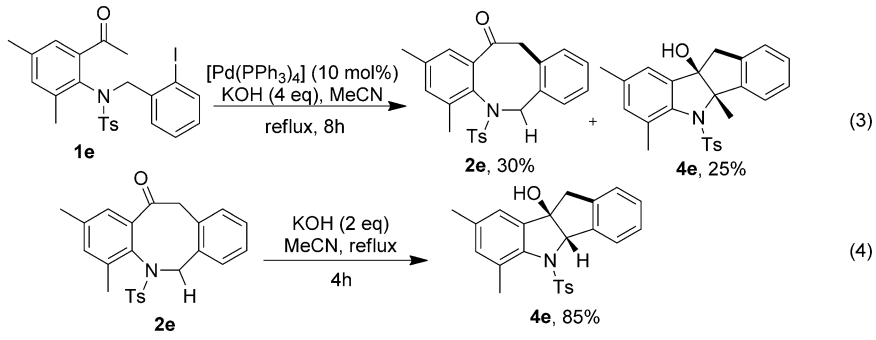
Scheme 4. Substrate scope of benzofuro[3,2-*b*]indolines. Reaction conditions: Substrate **S** (200 mg), $Cu(OTf)_2$ (10 mol%), 1, 10-phenanthroline (20 mol%), and KO*t*Bu (3 equiv) in DMF (3 mL) at 80 °C for 12 h. [a] Instead of iodo, bromo was employed in the starting material.

also tolerated in the reaction conditions and the respective compound was isolated in 70% yield. When we switched the iodo substituent in the precursors for bromo (**5a**, **5p**), the corresponding products were obtained, albeit in lower yields (note that these substrates were incompatible in Scheme 2). Unfortunately, the oxygen-substituted precursor failed to react (**5q**). The reason could be that the methylene group adjacent to oxygen was less acidic than NTs and the base may not have been able to deprotonate it. The structures of compound **5a**, **5b**, **5m**, and **5n** were confirmed by single crystal X-ray analysis (see the Supporting Information).[14]

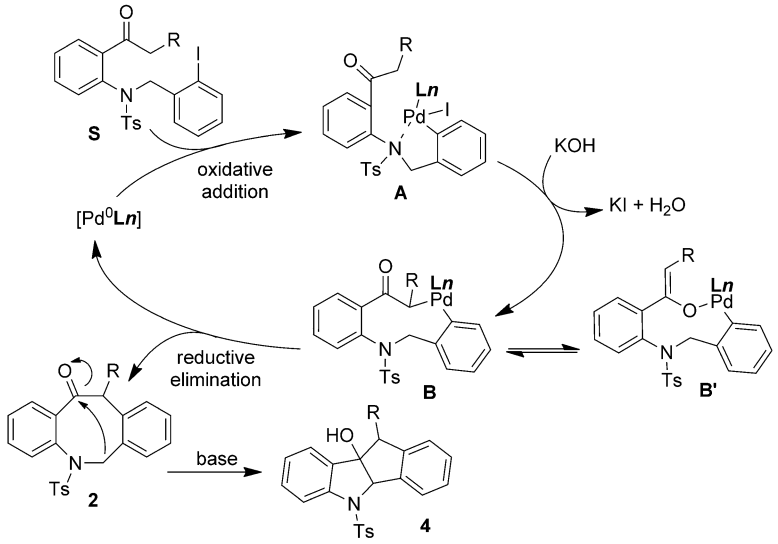
To gain more insights into the mechanism for the palladium-catalyzed cascade process, we performed some control experiments (Scheme 5). The progress of the reaction with **1e** under optimized reaction condition was stopped after 8 hand the eight-membered α-arylated intermediate **2e** was isolated [Scheme 5, Eq. (3)]. In addition, the structure was unambiguously confirmed by X-ray analysis.[14] Compound **2e** could be smoothly converted into final product under basic conditions [Scheme 5, Eq. (4)]. However, the isolation of the intermediate was only successful with compound **2e** and other such intermediates were rapidly converted into final product. These results establish that the reaction proceeds via α-arylation followed by base-mediated nucleophilic substitution.

On the basis of experimental findings and previous literature, a probable reaction mechanism was proposed for the palladium-catalyzed synthesis of dihydro[1,2-*b*]indenoindoles (Scheme 6). Initially, the Pd^0 catalyst undergoes oxidative addition with compound **S1** gives the intermediate **A**, which is apparently stabilized by internal chelation with nitrogen.[15] Next, base assisted α-arylation generates the nine-membered palladacycle intermediate **B** and subsequent reductive elimination gives intermediate **2** and regenerates Pd^0. The intramolecular nucleophilic addition reaction of intermediate **2** with base gives the final product **4**.

The tentative mechanism for the copper-catalyzed formation benzo[3,2-*b*]furoindolines is outlined in Scheme 7. The reaction



Scheme 5. Intermediate isolation and control experiment.



Scheme 6. Proposed mechanism for formation of compound **4**.

proceeds by a base-assisted intramolecular nucleophilic addition of compound **S1** to give alcohol intermediate **3**, which subsequently undergoes Ullman-type C–O coupling[16] to afford the desired compound **5**.

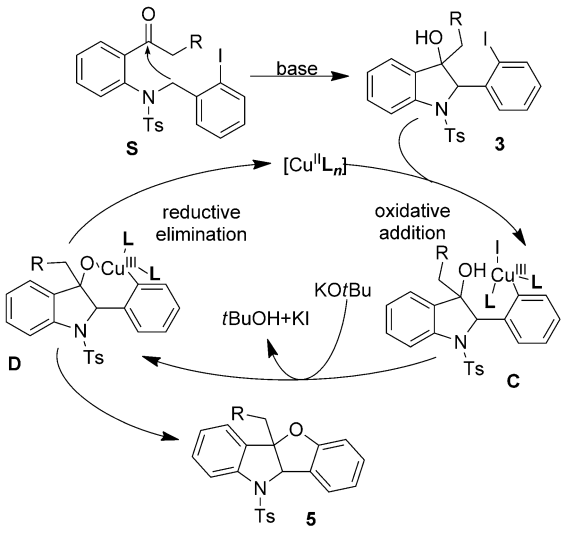
Conclusions

In summary, we have developed a simple approach to access dihydroindeno[1,2-*b*]indole-9-ol derivatives by palladium-catalyzed tandem α-arylation/nucleophilic addition. In addition, a copper-catalyzed cascade approach to benzofuro[3,2-*b*]indolines was also developed by nucleophilic addition/Ullmann-type C–O coupling. Importantly, the same precursor was utilized for the synthesis of both heterocyclic scaffolds and the product selectivity was solely determined by employing either palladium or copper as the catalyst. This protocol displays a wide substrate scope, good functional group tolerance, and provides moderate to high chemical yields. Efforts toward the biological screening of the synthesized compounds and extension of the strategy to other heterocycles are underway in our laboratory.

Experimental Section

General information and methods: All reagents and solvents were purchased from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with a Varian (400 MHz) and a JEOL (400 MHz) spectrometer. HRMS were obtained with a Micromass Q-TOF spectrometer using electrospray ionization technique. Column chromatography was performed with silica gel (100–200 mesh) as stationary phase and hexane/ethyl acetate as eluent. All reactions were monitored by thin-layer chromatography (Merck aluminum plates coated with silica gel). Melting points were measured with a MelTemp melting point apparatus. Full characterization data are included in the Supporting Information.

General procedure for the synthesis of dihydro[1,2-*b*]indenoindoles (4a–p): To an oven-dried sealed tube containing **S1** (200 mg, 0.39 mmol) in acetonitrile (3 mL) was added $[Pd(PPh_3)_4]$ (45.7 mg, 10 mol%) and KOH (88 mg, 4 equiv) and the mixture was heated at reflux with stirring for 16 h. After the reaction was completed (monitored by TLC), the mixture was poured into ice-cold water (20 mL) and extracted with EtOAc (2x25 mL). The combined organic layer was washed with brine solution (20 mL), dried, and



Scheme 7. Proposed mechanism for formation of compound **5**.

the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography to afford compound **4a** as an off-white solid (114 mg, 77% yield).

General procedure for the synthesis of benzofuro[3, 2-*b*]indolines (5a–r): To an oven-dried round-bottom flask containing **S1** (200 mg, 0.39 mmol) in DMF (2 mL) was added $Cu(OTf)_2$ (14 mg, 10 mol%), 1,10-phenanthroline (14 mg, 20 mol%), and KO*t*Bu (133 mg, 3 equiv). The resultant mixture was heated at 80 °C for 12 h or until the starting material was consumed. After reaction was completed (monitored by TLC), the mixture was poured in to ice-cold water (20 mL) and extracted with EtOAc (2x25 mL). The combined organic layer was washed with aqueous ammonium chloride solution (20 mL), dried, and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography to afford compound **5a** as a beige solid (80% yield).

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Keywords: cascade synthesis · copper · heterocycles · homogeneous catalysis · palladium

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