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Rh(III)-Catalyzed Cascade Annulation/C−H Activation of *o*-Ethynylanilines with Diazo Compounds: One-Pot Synthesis of Benzo[*a*]carbazoles via 1,4-Rhodium Migration

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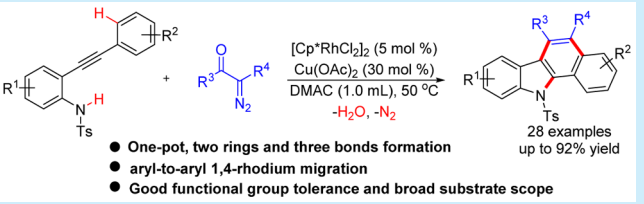
Supporting Information

ABSTRACT: A Rh(III)-catalyzed cascade annulation/C−H activation of *o*-ethynylanilines with diazo compounds has been developed. This concise method allows for the rapid formation of a number of benzo[*a*]carbazoles in high yields, exhibiting good functional group tolerance and scalability. The key to the success of this approach involves one C−N bond and two C−C bond formation, and an aryl-to-aryl 1,4-rhodium migration.



Benzo[*a*]carbazoles are privileged motifs found in natural alkaloids and pharmaceutical molecules with anticancer and antiangiogenic activities,[1] as well as in organic photovoltaic cells (OPVs), organic light-emitting diodes (OLEDs), and dye sensitized solar cells (DSSCs) due to their unique electronic and pronounced thermal stability properties (Figure 1).[2]

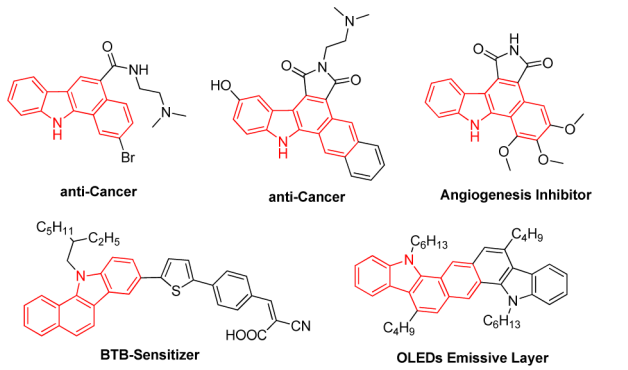
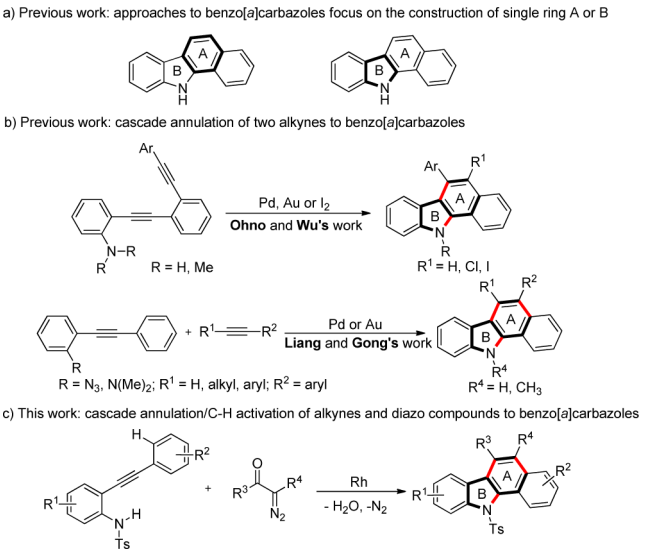


Figure 1. Alkaloids and photographic materials containing benzo[*a*]-carbazoles.

Generally, the benzo[*a*]carbazoles could be synthesized relying on the construction of ring A through photochemical cyclization,[3] palladium-, indium-, or copper-catalyzed cyclo-aromatization,[4] intramolecular Friedel−Crafts arylation,[5] Diels−Alder reaction,[6] and sequential propargylation/cyclo-isomerization[7] of preexisting indoles (Scheme 1a, left). On the other hand, the method to the synthesis of benzo[*a*]carbazoles also focused on the synthesis of ring B from amines or arylhydrazine hydrochlorides via iridium-, palladium-, or copper-catalyzed arylation/annulation,[8] copper-promoted cycloaddition,[9] and oxidative cyclo-dehydrogenation (Scheme 1a, right).[10]

Scheme 1. Synthetic Approaches to Benzo[*a*]carbazoles



Compared to previous work that mostly focused on the construction of the single A ring or B ring to achieve benzo[*a*]carbazoles, the simultaneous synthesis of A and B rings has received increasing interest, because it not only brings greatly improved synthetic efficiency but also enhances aesthetic appeal for synthetic planning. Recently, Ohno[11] and Wu[12] disclosed gold-, palladium-catalyzed or iodine-mediated intramolecular cyclization of enediynes for the synthesis of benzo[*a*]carbazoles (Scheme 1b). Liang[13] and Gong[14] developed a palladium- and gold-catalyzed intermolecular tandem cyclization of two alkynes to synthesize benzo[*a*]-

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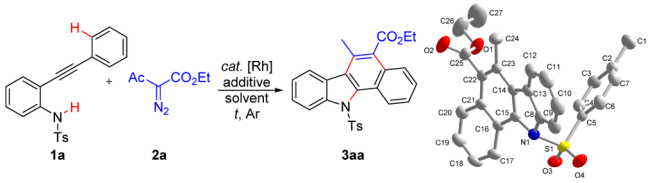
carbazoles (Scheme 1b). From the step economy as well as the functional group diversity point of view, the development of a new method to construct benzo[*a*]carbazoles utilizing easily prepared materials remains fascinating and challenging. Based on our continuous interest in the synthesis of nitrogen containing heterocycles,[15] herein, we will report a rhodium-catalyzed cascade annulation of *o*-ethynylanilines with diazo compounds to construct benzo[*a*]carbazoles. In this reaction, one C−N bond and two C−C bond formation was achieved with a one-pot procedure, and an aryl-to-aryl 1,4-rhodium migration was also involved (Scheme 1c).

Initially, we began our investigation with 4-methyl-*N*-(2-(phenylethynyl)phenyl)benzenesulfonamide **1a** and ethyl 2-diazo-3-oxobutanoate **2a** as model substrates (Table 1). A preliminary attempt with 5.0 mol % of $[Cp^*RhCl_2]_2$ in 1.0 mL DMF at room temperature led to the benzo[*a*]carbazole **3aa** in 59% yield, and the structure was unambiguously identified by single crystal X-ray analysis (entry 1). Replacing $[Cp^*RhCl_2]_2$ with $[RhCl(COD)]_2$ resulted in no product (entry 2). A brief examination of solvents revealed that dipolar aprotic solvent DMAC was an ideal choice, which afforded **3aa** in 70% yield (entry 4). The yield of **3aa** increased to 81% in the presence of $Cu(OAc)_2$ when several copper salts were tested (entries 5−8). Considering the anion may play an important role in the reaction efficiency, several acetates were then tested and lower yields were obtained compared with $Cu(OAc)_2$ (entries 9−10). By increasing the temperature to 50 °C, the yield could be further increased to 91% (entry 11). Control experiments indicated that $[Cp^*RhCl_2]_2$ was indispensable to this reaction (entries 12−13).

With the optimized conditions in hand, we then investigated the substrate scope of the *o*-ethynylanilines and diazo compounds to test the generality of this cascade cyclization, and the results are summarized in Scheme 2. The presence of methyl and methoxyl groups at C4- or C5-positions of the aniline ring afforded **3ba**, **3da**, and **3ea** in 91%, 81%, and 71% yields. The halogen and electron-withdrawing groups delivered **3ca**, **3fa**−**ia** in 46−79% yields. The phenyl ring bearing electron-donating and -withdrawing groups at the *meta*- and *para*-positions performed smoothly and afforded **3ka** and **3la**−**qa** in moderate to good yields. Notably, to increase product diversity, a heteroaryl-substituted substrate was also attempted. 4-Methyl-*N*-(2-(thiophen-2-ylethynyl)phenyl)-benzenesulfonamide **1r** gave **3ra** in 20% yield. When the ester group of **2a** was altered from ethyl to methyl, *tert*-butyl, isopropyl, and benzyl groups, **3ab**−**ae** were obtained in 82−92% yields. By changing the R^3 group to *n*-propyl, cyclopropyl, and cyclohexyl groups, **3af**, **3ag**, and **3ah** were prepared in 84%, 87%, and 50% yield, respectively. Ethyl 2-diazo-3-oxo-3-phenylpropanoate **2i** offered **3ai** in 70% yield. When 3-diazopentane-2,4-dione **2j** was tested, the desired product **3aj** was generated in 59% yield. Unfortunately, no corresponding product could be obtained when 2-diazo-1-morpholinobutane-1,3-dione **2k** was used. To improve the practicability of this reaction, a gram-scale reaction was conducted and **3aa** was isolated in 94% yield (1.29 g).

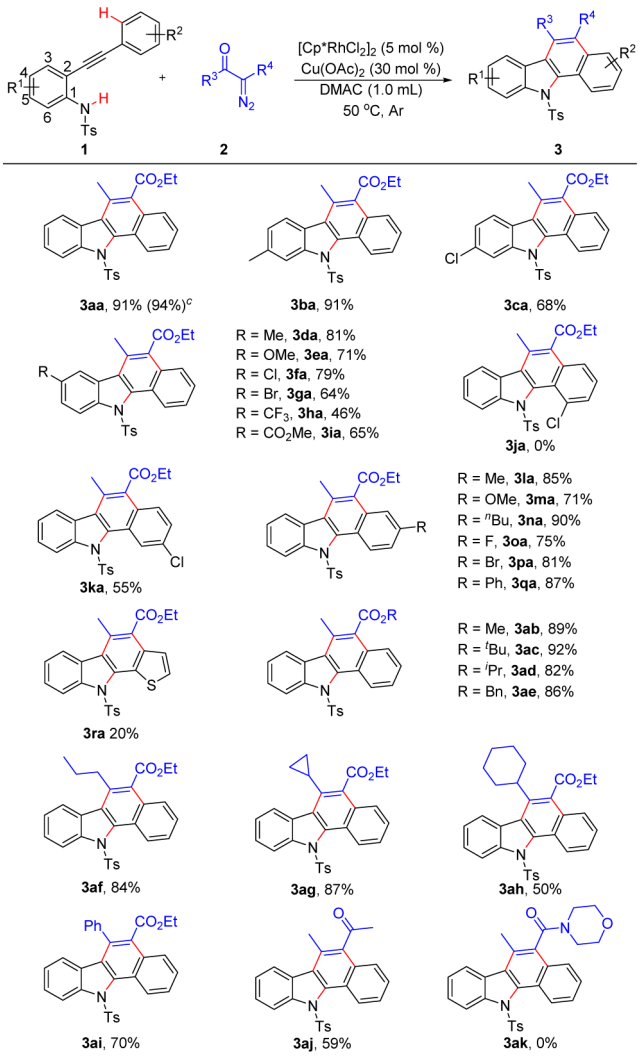
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	additive	solvent	yield (%)[b]
1	$[Cp^*RhCl_2]_2$	–	DMF	59
2	$[RhCl(COD)]_2$	–	DMF	nd[c]
3	$[Cp^*RhCl_2]_2$	–	THF	<5
4	$[Cp^*RhCl_2]_2$	–	DMAC	70
5	$[Cp^*RhCl_2]_2$	$CuCl_2$	DMAC	33
6	$[Cp^*RhCl_2]_2$	CuO	DMAC	61
7	$[Cp^*RhCl_2]_2$	CuBr	DMAC	70
8	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	DMAC	81
9	$[Cp^*RhCl_2]_2$	NaOAc	DMAC	66
10	$[Cp^*RhCl_2]_2$	KOAc	DMAC	45
11[d]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	DMAC	91
12[d]	–	$Cu(OAc)_2$	DMAC	nd[c]
13[d]	$[Cp^*RhCl_2]_2$	–	DMAC	75

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), additives (30 mol %), solvent (1.0 mL), at room temperature under Ar atmosphere for 12 h, sealed tube. [b]Isolated yields. [c]nd = not determined. [d]The reaction was conducted at 50 °C.

Scheme 2. Substrate Scope[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2$ (30 mol %), DMAC (1.0 mL), at 50 °C under Ar for 12 h, sealed tube. [b]Isolated yields. [c]3.0 mmol scale.

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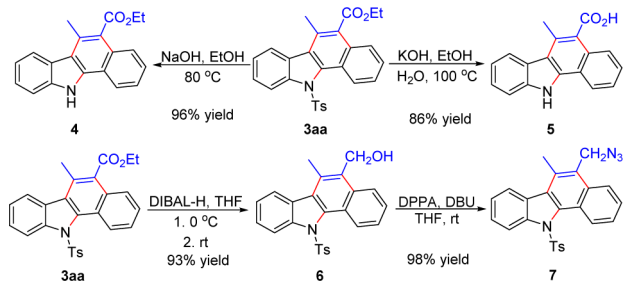
With the aim to further evaluate the practicability of this reaction, late-stage modification of **3aa** was conducted and is shown in Scheme 3. The sulfamide and ester group in **3aa**

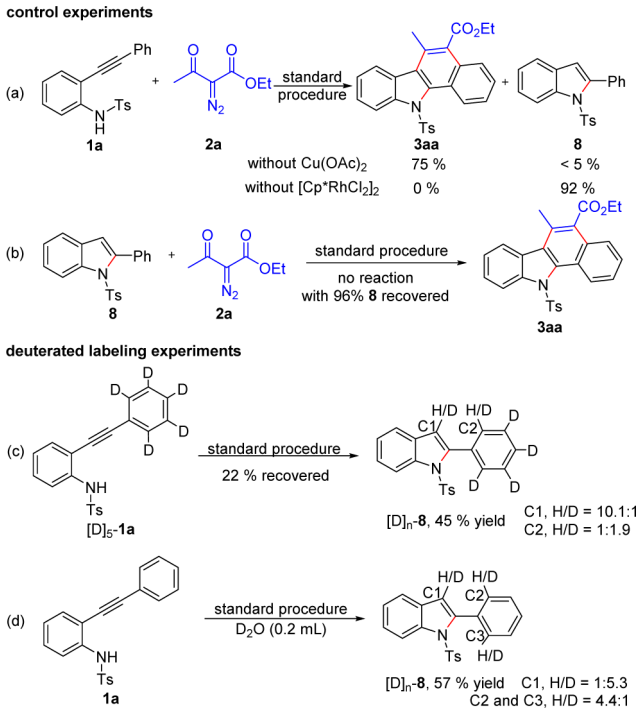
Scheme 3. Derivatization of Benzo[*a*]carbazole 3aa



could be hydrolyzed, and the corresponding products **4** and **5** were obtained in 96% and 86% yields. After the hydrogenation of **3aa**, compound **6** with a hydroxyl group was obtained in 93% yield. Besides, **6** could react with DPPA to provide the benzo[*a*]carbazole **7** in 98% yield.

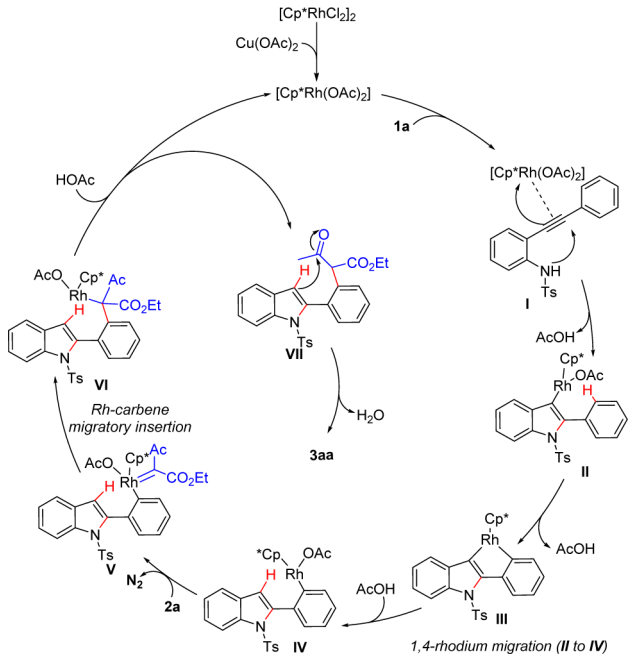
To gain some mechanistic insight into this transformation, control experiments and deuterated labeling experiments were carried out. **3aa** could be obtained in 75% yield when $[Cp^*RhCl_2]_2$ was used as the sole catalyst, while only single cyclic product 2-phenyl-1-tosyl-1*H*-indole **8** could be detected with $Cu(OAc)_2$ as the sole catalyst (Scheme 4a). Considering

Scheme 4. Mechanistic Experiments



that indole **8** was the possible intermediate for this reaction, we then examined the reaction between **8** and ethyl 2-diazo-3-oxobutanoate **2a** under the standard conditions (Scheme 4b); no desired product **3aa** was observed. These results suggested that indole **8** as an intermediate was not involved in this transformation. Moreover, the reaction was exclusively catalyzed by Rh(III) active species and $Cu(OAc)_2$ did not take part in the catalytic cycle, but just helped to generate Rh(III) active species. In order to further illustrate the 1,4-rhodium migration process, a deuterated labeling experiment with $[D]_5$-**1a** was conducted under the standard conditions (Scheme 4c). The observed incorporation of hydrogen at the C2 of indole **8** indicated the occurrence of 1,4-rhodium migration (see Supporting Information (SI) for details). Additionally, we examined the reaction of **1a** in a 5:1 mixture of DMAC/D_2O solvent (Scheme 4d). The presence of D_2O provided deuterated $[D]_n$-**8** in 57% yield (see SI for details). This result suggested that the aryl-to-aryl 1,4-Rh(III) migration occurred in a concerted metalation−deprotonation/reprotonation sequence (**II** to **IV** in Scheme 5).[16]

Scheme 5. Proposed Reaction Mechanism



Based on the above results and literature precedents,[16−20] a plausible reaction pathway of this Rh(III)-catalyzed cascade annulation/C−H activation of *o*-ethynylanilines with diazo compounds was proposed and is shown in Scheme 5. Coordination of an alkyne to active Rh(III) species affords intermediate **I**,[18] which could increase the electrophilicity of the triple bond. The nucleophilic attack of the nitrogen on the triple bond generates the benzoheterocyclic Rh(III) species **II**.[19] An acetate promoted, concerted metalation−deprotonation of **II** gives rhodacycle **III**, which could undergo acetolysis to give **IV**.[16] Subsequently, diazo compound **2a** reacts with intermediate **IV** to generate Rh-carbene intermediate **V** with the release of N_2 and Rh-carbene migratory insertion produces intermediate **VI**.[20] Upon protonation, intermediate **VII** could be achieved along with the regeneration of the active rhodium(III) species. Finally, intramolecular dehydration condensation of **VII** yields the product **3aa**.

In conclusion, we have developed a novel intermolecular cascade annulation/C−H activation of *o*-ethynylanilines with diazo compounds driven by the rhodium catalyst. The benzo[*a*]carbazoles were obtained in high yields, exhibiting good functional group tolerance and scalability. The reaction proceeds through a catalytic cycle involving intramolecular nucleophilic addition of *o*-ethynylanilines, aryl-to-aryl 1,4-

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rhodium migration. In this strategy, one C−N bond and two C−C bond formation was achieved with a one-pot procedure.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02534.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)
X-ray crystallographic data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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