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Rh^{II}-Catalyzed Synthesis of α -, β -, or δ -Carbolines from Aryl Azides**

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Carbolines and tetrahydrocarbolines are common structural motifs in pharmaceuticals and natural products.^[1] β -Carboline and its saturated analog, tryptoline, are particularly prevalent^[2,3] and continue to inspire methods to efficiently access them.^[4,5] In contrast, methods to access the δ -^[6] or α -isomer^[7] are uncommon despite the important biological properties exhibited by these carbolines. In addition to antibacterial and antiparasitic activities,^[8] δ -carbolines are potential cancer therapeutics (SYUIQ-5),^[9] and the α -carboline mescengricin was reported to be a potential neural protective agent (Figure 1).^[10] We anticipated that each structural isomer of the carboline scaffold would be readily accessible from an appropriately *ortho*-substituted aryl azide through a C–H bond amination reaction if a transition metal catalyst was found that could unlock and control the reactivity embedded in the azide.

We recently reported that ruthenium trichloride-hydrate selectively transformed aryl azides into γ -carbolinium ions.^[11] Extension of these conditions to the synthesis of the other carboline isomers, however, was not successful. Because of the paucity of methods to access δ -carbolines,^[6] we decided to find the optimal conditions for their construction. After testing a variety of metal complexes,^[12] we found that Rh^{II}-carboxylates were unique in their ability to catalyze the conversion of aryl azide **1** into **2**,^[13] and the highest yield was attained using 5 mol% of [Rh₂(esp)₂] complex in dichloroethane [Eq. (1)].^[14] Deprotonation of the δ -carbolinium ion using aqueous Na₂CO₃ produced **3**,^[15] which was easily purified using silica gel chromatography.

(1)

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The scope and limitations of δ -carbolinium ion generation was examined by exposing a series of aryl azides **1** to the optimal reaction conditions. The azides for our study were synthesized in three steps from commercial 2-bromoanilines through a Suzuki cross coupling–azidation–methylation sequence.^[16] We found that our amination reaction tolerated a range of substituents on the aryl azide portion of the substrate: azides bearing alkyl- and trifluoromethyl groups as well as halides were efficiently converted into δ -carbolinium ions (Table 1). The reaction was even tolerant of substitution adjacent to the azide (entry 8). While a range of groups was tolerated on the azide portion of the substrate, the reaction yield was severely attenuated if any additional substituents were added to the pyridinium ion moiety.

With the successful synthesis of 1-methyl- δ -carbolinium triflates **2**, the conversion of aryl azides bearing 4-substituted pyridinium ion *ortho*-substituents into β -carbolinium ions (**5**) was next attempted. To our delight, the rhodium(II)-catalyzed C–H bond amination conditions proved amenable to the synthesis of **5** from aryl azides **4** (Table 2). Subsequent reduction of the β -carbolinium ion with NaBH₄ produced tryptoline **6**, which was easily purified using silica gel column chromatography. The alkyl group on the pyridine nitrogen atom could be varied without attenuating the yield of the process as long as a stoichiometric amount of AgOTf was added (entries 2 and 3). The steric environment around azide could be increased through substitution without preventing product formation (entry 4). The electronic nature of the aryl azide could also be modulated without adversely affecting the reaction (entries 6–10): both electron donating- and electron-withdrawing groups were tolerated in the method. Importantly, *meta*-substituents could be appended to the aryl azide without compromising the yield of the reaction (entries 9 and 10). The resulting tryptolines **6i** and **6j** cannot be formed selectively from a Fischer indole synthesis.^[17]

To illustrate the synthetic utility of this Rh^{II}₂-catalyzed C–H bond amination method, ($\pm$)-horsifiline^[18,19] was synthesized (Scheme 1). The aryl azide substrate (**4k**) for our amination reaction was synthesized in three steps (Suzuki-, azidation-, and methylation reactions, 67%) from commercially available 2-bromo-4-methoxyaniline and 4-pyridinylboronic acid. Exposure of azide **4k** to our amination-reduction sequence produced tryptoline **6k** in 91%. Oxidation of **6k** using *N*-bromosuccinimide^[20] in aqueous acetic acid afforded ($\pm$)-horsifiline.^[21] Using the same oxidative conditions, tryptoline **6g** was converted into spirocyclic oxindole **7** in 71 %. Our overall yield for ($\pm$)-horsifiline and **7** for the six steps from the 2-bromo-4-substituted-anilines was 53 % and 42 %, respectively.

Finally, aryl azides with *meta*-substituted pyridinium ion *ortho*-substituents were examined as potential substrates [Eq. (2)]. In contrast to azides **1** or **4**, this class of substrates contains two C–H bonds that potentially could be transformed into C–N bonds. Using RuCl₃·H₂O as the catalyst, the reaction occurred solely at C–H^b to produce γ -carbolinium ion **9** as the only product.^[11] In contrast, exposure of **8** to [Rh₂(esp)₂] resulted in the formation of the α -isomer as the only product.^[22] We are actively investigating the mechanistic implications of this turnover in selectivity.

To further investigate this selectivity trend, a series of *meta*-substituted pyridinium ions were submitted to reaction conditions (Table 3). Basification of the reaction mixture using Na₂CO₃ produced **11**, which was purified using silica gel chromatography. Similar to the other isomers, construction of the α -isomer tolerated both electron-donating and electron-withdrawing aryl azide substituents (entries 1–7) although the yield was diminished in the presence of a *para*-methoxy group (**8b**, entry 2). An expanded scope of α -isomer formation was observed: substitution on the pyridinium ion portion of **8** was tolerated to allow access to **11h** and **11i** (entries 8 and 9).

Because our reaction tolerated substitution on the pyridinium moiety, we anticipated that our method might facilitate access to neocryptolepine.^[23,24] This indoloquinoline alkaloid exhibits promising cytotoxicity toward cancer cells as well as strong antiplasmodial activity toward chloroquine-resistant strains.^[24f,25] Exposure of azide **8j** to [Rh₂(esp)₂] resulted in amination of only the C–H^a bond to produce neocryptolepine (**11j**) as a single regioisomer in 68% (entry 10).

In conclusion, we have developed a method to access α -, β -, or δ -carbolinium ions from aryl azides with *ortho*-pyridinium ion substituents using 1–5 mol% of [Rh₂(esp)₂]. In combination with our previous report using RuCl₃ to access γ -carbolinium ions, we believe our work demonstrates that metal-catalyzed C–H bond amination is a simple, efficient strategy to access all possible carbolinium ion isomers from readily accessible aryl azides. The synthetic utility of our method was illustrated in a four-flask synthesis of cytotoxic and antiplasmodial agent, neocryptolepine and the analgesic oxindole ($\pm$)-horsfiline. By synthesizing a chlorinated analog of horsfiline—one not readily accessible through previously reported syntheses—we demonstrated that the modular nature of our method facilitates the construction of natural and non-natural alkaloids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Selected examples of biologically active carbolines.

Scheme 1.
Synthesis of (±)-horsfiline and analog.

Table 1

Scope of Rh^{II}_{12} -catalyzed δ -carboline formation.

Entry	#	Aryl azide 1			Yield [%]	Yield [%]
		R ¹	R ²	R ³	2[a]	3[b]
1	a	H	H	H	quant.	74
2	b	Me	H	H	85	71
3	c	F	H	H	quant.	96
4	d	Cl	H	H	97	77
5	e	F ₃ C	H	H	97	78
6	f	H	Me	H	85	75
7	g	H	F ₃ C	H	98	86
8	h	H	Me	F	quant.	66

[a] As determined using ¹H NMR spectroscopy using CH₂Br₂ as an internal standard.

[b] Yield of 3 from azide 1 after silica gel chromatography. esp=α,α,α',α'-tetramethyl-1,3-benzenedipropionate; DCE=dichloroethane; Tf=trifluoromethanesulfonyl.

Table 2

Scope of Rh^{II}_2 -catalyzed tryptoline formation.

Entry	#	X ⁻	R ¹	R ²	R ³	R ⁴	Yield [%] 5 ^[a]	Yield [%] 6 ^[b]
1	a	TfO ⁻	H	H	H	H	quant.	99
2	c ^[c]	Br ⁻	allyl	H	H	H	90	60
3	c ^[c]	Br ⁻	Bn	H	H	H	89	71
4	d	TfO ⁻	Me	Me	H	Me	94	83
5	e	TfO ⁻	Me	Me	H	H	quant.	94
6	f	TfO ⁻	Me	F	H	H	quant.	71
7	g	TfO ⁻	Me	Cl	H	H	91	70
8	h	TfO ⁻	Me	F ₃ CO	H	H	quant.	88
9	i	TfO ⁻	Me	H	Me	H	quant.	90
10	j	TfO ⁻	Me	Me	F	H	quant.	>95

^[a]As determined using ¹H NMR spectroscopy using CH₂Br₂ as an internal standard.

^[b]Yield of 6 from azide 4 after silica gel chromatography.

^c1.1 equiv AgOTf added.

Table 3

Scope of Rh^{II}_2 -catalyzed α -carboline formation.

Entry	#	R ¹	R ²	R ³	R ⁴	Yield [%]
1	a	Me	H	H	H	83
2	b	MeO	H	H	H	63
3	c	H	H	H	H	80
4	d	F	H	H	H	83
5	e	Cl	H	H	H	67
6	f	F ₃ C	H	H	H	78
7	g	Me	F	H	H	64
8	h	H	H	Me	H	77
9	i	H	H	Cl	H	77
10	j	H	H	HC=CH-CH=CH	H	68

[^a] Yield of **11** from azide **8** after silica gel chromatography.