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Ruthenium-Catalyzed γ-Carbolinium Ion Formation from Aryl Azides; Synthesis of Dimebolin

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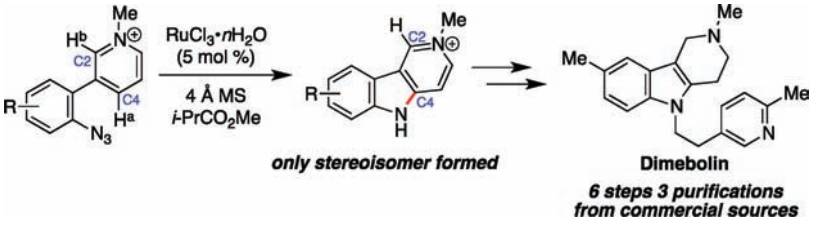
ABSTRACT



A range of γ-carbolines were produced stereoselectively from ruthenium(III)-catalyzed reactions of 3-pyridyl substituted aryl azides. Other catalysts and conditions were neither as selective nor as high-yielding. This method was used to synthesize dimebolin in a concise and efficient manner.

The synthesis of *N*-heterocycles through the formation of C−N bonds from C−H bonds improves the synthetic efficiency of the synthesis of these medicinally important molecules by eliminating functional group manipulation.[1,2] β-[3−5] and γ-carbolines[6] are particularly attractive targets for the development of C−H bond functionalization methods because they constitute the core of many biologically active compounds.[7] Dimebolin (aka latrepiridine)[8] is a γ-tetrahydrocarboline that was under

(1) For reviews, see: (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (b) Du Bois, J. *Chemtracts* **2005**, *18*, 1. (c) Agarwal, S.; Cämmerer, S.; Filali, S.; Fröhner, W.; Knöll, J.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1601. (d) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (e) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (f) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (g) Knölker, H.-J. *Chem. Lett.* **2009**, *38*, 8. (h) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (i) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831.

(2) For recent, leading reports, see: (a) (Rh) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (b) (Pd) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (c) (Cu) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (d) (Pd) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (e) (Ag) Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058. (f) (Rh) Fukumoto, Y.; Kinashi, F.; Kawahara, T.; Chatani, N. *Org. Lett.* **2006**, *8*, 4641. (g) (Rh) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 9220. (h) (Pd) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (i) Gruner, K. K.; Knölker, H.-J. *Org. Biomol. Chem.* **2008**, *6*, 3902. (j) Lu, H.; Tao, J.; Jones, J. E.; Wojtas, L.; Zhang, X. P. *Org. Lett.* **2010**, *12*, 1248. (k) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

(3) (a) Czarnocki, Z.; Siwicka, A.; Szawkalo, J. *Curr. Org. Synth.* **2005**, *2*, 301. (b) Youn, S. W. *Org. Prep. Proc. Int.* **2006**, *38*, 505. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (d) Edwankar, C. R.; Edwankar, R. V.; Namjoshi, O. A.; Rallapappi, S. K.; Yang, J.; Cook, J. M. *Curr. Opin. Drug Discuss. Dev.* **2009**, *12*, 752. (e) Alekseyev, R. S.; Kurkin, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2009**, *45*, 889. (f) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608.

(4) Recent Pictet−Spengler reports: (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (b) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (c) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485. (d) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887.

(5) β-Carbolines (non-Pictet−Spengler), see: (a) Bondzić, B. P.; Eilbracht, P. *Org. Lett.* **2008**, *10*, 3433. (b) Movassaghi, M.; Hill, M. D. *Org. Lett.* **2008**, *10*, 3485. (c) England, D. E.; Padwa, P. *Org. Lett.* **2008**, *8*, 3631. (d) Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2009**, *11*, 1979.

(6) γ-Carbolines: (a) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048. (c) Chiba, S.; Xu, Y.-J.; Wang, Y.-F. *J. Am. Chem. Soc.* **2009**, *131*, 12886. (d) Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540.

(7) (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (b) Czarwinski, K. M.; Cook, J. M. *Advances in Heterocyclic Natural Products Synthesis*; Pearson, W., Ed.; JAI Press: Greenwich, CT, 1996; Vol. III, p 217. (c) Maresh, J. J.; Giddings, L.-A.; Friedrich, A.; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stockigt, J.; Peters, B.; O'Connor, S. E. *J. Am. Chem. Soc.* **2007**, *130*, 710. (d) Luk, L. Y. P.; Bunn, S.; Liscombe, L. K.; Facchini, P. J.; Tanner, M. E. *Biochemistry* **2007**, *46*, 10153 and references therein.

(8) Shadurski, K. S.; Danusevich, I. K.; Kost, A. N.; Vinogradova E. V. U.S. Patent No. 1138164; *Chem. Abstr.* 1985, *102*, 190810.

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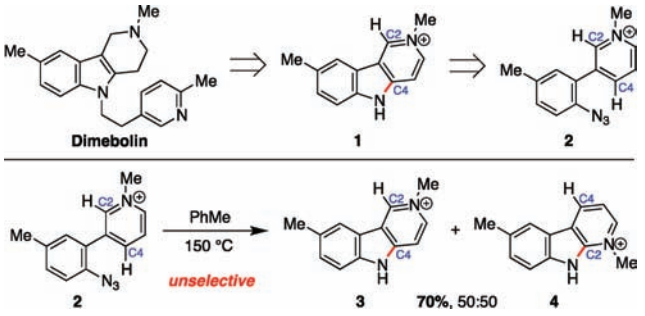
intense scrutiny because it showed promising activity for the treatment of mild to moderate cases of Alzheimer's[9] and Huntington's[10] disease.[11] Dimebolin was originally synthesized using the Fischer-indole reaction.[8] Although efficient for constructing dimebolin, this reaction is not regioselective and as a consequence this approach limits the substitution pattern on the aryl portion of the γ-tetrahydrocarboline.

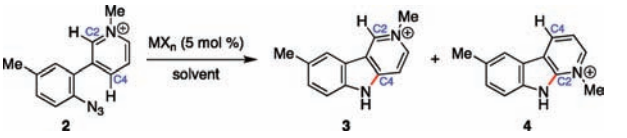
Scheme 1. Stereoselective Synthesis of γ-Carbolinium Ions from Aryl Azides



Synthesizing this *N*-heterocycle through the construction of the C−N bond from aryl azide **2** would address this limitation but presents a particular challenge because the metal intermediate must distinguish between C2 and C4. To underscore this challenge, the thermolysis of **2** provided a 1:1 mixture of **3** and **4**. Herein, we describe our efforts that culminated in a general method to access γ-carbolinium ions as single isomers from aryl azides (Scheme 1). This method enables synthesis of dimebolin from commercial starting materials in five flasks with only three purifications.

Toward our goal, transition metal complexes known to promote C−N bond formation from aryl azides were screened (Table 1). Although rhodium carboxylate complexes were found to be efficient catalysts,[12] they promoted the formation of the undesired regioisomer with modest selectivity (entries 1−3). Other metal complexes such as $[(cod)Ir(OMe)]_2$,[13] ZnI_2,[14] and $FeBr_2$[15] were found to be unreactive (entries 4−6). Selective γ-carbolinium formation was realized with ruthenium complexes.[16] In dimethoxyethane, anhydrous $RuCl_3$[16a] partially converted aryl azide **2** into carbolinium **3**. Additional screening of reaction conditions afforded the optimal conditions: 5 mol % of $RuCl_3 \cdot nH_2O$ in isopropyl acetate provided **3** as the only product (entry 8). Only partial consumption of the aryl azide was observed in isopropyl acetate in the absence of water (entry 9). The reaction could be restored in isopropyl acetate if 10 mol % of water was added to the anhydrous

Table 1. Development of Optimal Conditions for γ-Carbolinium Ion Formation from Aryl Azides



entry	MX_n	solvent	temp (°C)	yield (%)[a]	3:4
1[b]	$Rh_2(O_2C_4F_7)_4$	PhMe	90	>95	25:75
2[b]	$Rh_2(O_2C_8H_{15})_4$	DCE	80	>95	20:80
3[b]	$Rh_2(esp)_2$	DCE	60	>95	18:82
4[b]	$[(cod)Ir(OMe]_2$	*i*-$PrCO_2Me$	80	7	100:0
5[b]	ZnI_2	CH_2Cl_2	40	0	n.a.
6[b]	$FeBr_2$	PhMe	80	0	n.a.
7	$RuCl_3$	DME	80	66	100:0
8	$RuCl_3 \cdot nH_2O$	*i*-$PrCO_2Me$	80	>95	100:0
9	$RuCl_3$	*i*-$PrCO_2Me$	80	17	100:0
10[c]	$RuCl_3$	*i*-$PrCO_2Me$	80	70	100:0
11	$(cod)RuCl_2$	*i*-$PrCO_2Me$	80	23	100:0
12	Ru(TPFPP)CO	*i*-$PrCO_2Me$	80	48	100:0

[a] As determined using ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [b] 100 wt % of 4 Å MS added. [c] 10 mol % of H_2O was added.

(9) Compare (a) Okun, I.; Tkachenko, S. E.; Khavat, A.; Mitkin, O.; Kazey, V.; Ivachtchenko, A. V. *Curr. Alzheimer Res.* **2010**, *7*, 97. (b) Steele, J. W.; Kim, S. H.; Cirrito, J. R.; Verges, D. K.; Restivo, R. L.; Westaway, D.; Fraser, P.; Hyslop, P. S.; Sano, M.; Bezprozvanny, I.; Ehrlich, M. E.; Holtzman, D. M.; Gandy, S. *Mol. Neurodegener.* **2009**, *4*, 51. (c) Doody, R. S.; Gavrilova, S. I.; Sano, M.; Thomas, R. G.; Aisen, P. S.; Bachurin, B. O.; Seely, L.; Hung, D. *Lancet* **2008**, *372*, 207. (d) Ivachtchenko, I. V.; Frolov, E. B.; Mitkin, O. D.; Kysil, V. M.; Khvat, A. V.; Okun, I. M.; Tkachenko, S. E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3183.

(10) Compare (a) Kieburtz, K.; McDermott, M. P.; Voss, T. S.; Corey-Bloom, J.; Deuel, L. M.; Dorsey, E. R.; Factor, S.; Geschwind, M. D.; Hodgeman, K.; Kayson, E.; Noonberg, S.; Pourfar, M.; Rabinowitz, K.; Ravina, B.; Sanchez-Ramos, J.; Seely, L.; Walker, F.; Feigin, A. and The Dimebon in Subjects With Huntington Disease Investigators of the Huntington Study Group. *Arch. Neurol.* **2010**, *67*, 154. (b) Sabbagh, M. N; Shill, H. A. *Curr. Opin. Invest. Drugs* **2010**, *11*, 80. (c) Wu, J.; Li, Q.; Bezprozvanny, I. *Mol. Neurodegener.* **2008**, *3*, 15.

(11) (a) Pollack, A. Antihistamine Shows Promise in Treating Alzheimer's. *New York Times* June 11, 2007. (b) Hopkins, C. R. *ACS Chem. Neurosci.* **2010**, *1*, 587.

(12) (a) Stokes, B. J.; Richert, K. J.; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 6442. (b) Stokes, B. J.; Jovanović, B.; Dong, H.; Richert, K. J.; Riell, R. D.; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 3225. (c) Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056. (d) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500.

(13) Sun, K.; Sachwani, R.; Richert, K. J.; Driver, T. G. *Org. Lett.* **2009**, *11*, 3598.

(14) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191.

(15) Shen, M.; Driver, T. G. *Org. Lett.* **2008**, *10*, 3367.

(16) For leading examples of Ru-catalyzed *N*-atom transfer reactions, see: (a) Shou, W. G.; Li, J.; Guo, T.; Lin, Z.; Jia, G. *Organometallics* **2009**, *28*, 6847. (b) Fantauzzi, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Casati, N.; Macchi, P.; Cenini, S. *Chem. Commun.* **2009**, 3952. (c) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825. (d) Kawabata, H.; Omura, K.; Uchida, T.; Katsuki, T. *Chem.—Asian J.* **2007**, *2*, 248. (e) Leung, S. K.-Y.; Tsui, W.-M.; Huang, J.-S.; Che, C.-M.; Liang, J.-L.; Zhu, N. *J. Am. Chem. Soc.* **2005**, *127*, 16629.

(17) **Optimized General Procedure for γ-Tetrahydrocarboline Formation.** To a mixture of pyridinium **2a** (0.187 g, 0.5 mmol, 1.0 equiv) and $RuCl_3 \cdot nH_2O$ (0.005 g, 0.025 mmol, 0.05 equiv) was added 5 mL of isopropyl acetate (0.1 M). The resulting mixture was stirred at 80 °C for 15 h. The heterogeneous mixture was then filtered through Celite, and the filtrate was concentrated *in vacuo*. The resulting crude carbolinium ion **3a** (0.173 g) and 0.076 g of $NaBH_4$ (2.0 mmol) were dissolved in 30 mL of a 7:3 mixture of methanol and water. After 15 min, the reaction mixture was warmed to 100 °C. After 10 min, the reaction was cooled to room temperature. The mixture was diluted with 10 mL of CH_2Cl_2 ,and the resulting mixture was washed with water. The organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification using MPLC afforded tetrahydocarboline **5a**.

Table 2. Scope and Limitations of Ru(III)-Catalyzed γ-Carboline Formation

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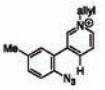
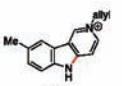
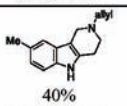
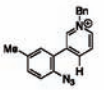
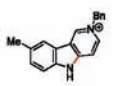
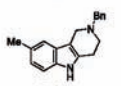
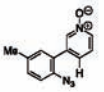
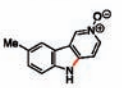
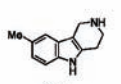
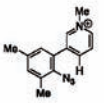
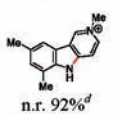
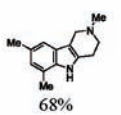
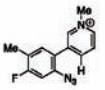
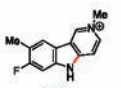
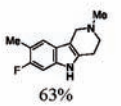
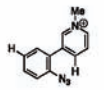
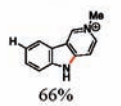
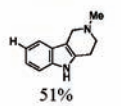
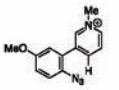
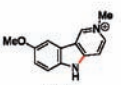
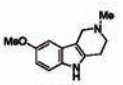
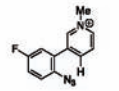
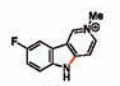
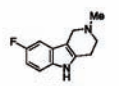
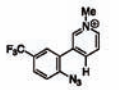
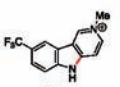
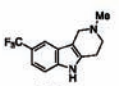
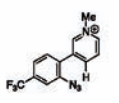
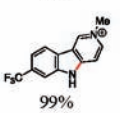
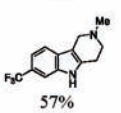
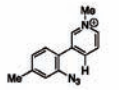
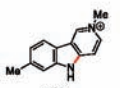
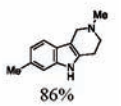
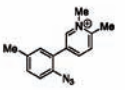
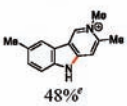
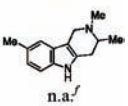
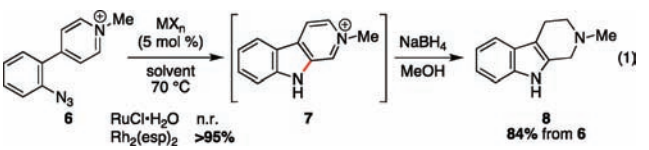
1	b		 99%	 40% 60% *N*-propyl-**5b**
2	c		 quant	 71%
3	d		 n.r.[c]	 n.a.
4	e		 n.r. 92%[d]	 68%
5	f		 81%	 63%
6	g		 66%	 51%
7	h		 87%	 67%
8	i		 60%	 37%
9	j		 77%	 73%
10	k		 99%	 57%
11	l		 76%	 86%
12	m		 48%[e]	 n.a.[f]

[a] Yield determined using ^{1}H NMR spectroscopy. [b] Yield of γ-tetrahydrocarboline **5** from aryl azide **2** after chromatography over SiO_2. [c] Other catalysts were also ineffective. [d] Use of $Rh_2(esp)_2$ (5 mol %). [e] Mesitylene, 110 °C. [f] $NaBH_4$ reduction afforded a complex mixture.

$RuCl_3$ (entry 10). Ru(II) complexes[16e] were examined and found to be poorer catalysts than $RuCl_3 \cdot nH_2O$ (entries 11 and 12). Consequently, we conclude that Ru(III) is the requisite oxidation state for the catalytic cycle.[17]

A range of 3-pyridyl substituted aryl azides were examined to determine the scope and limitations of ruthenium(III)-catalyzed γ-carbolinium formation (Table 2). The resulting ions **3** were reduced with $NaBH_4$ to obtain γ-carbolines **5** that could be purified by SiO_2 chromatography.[18] The reaction tolerated a variety of substituents on the pyridine nitrogen including allyl and benzyl groups without any loss of regioselectivity (entries 1−4). No reaction was observed with pyridine *N*-oxide **3d** or *o*-methyl substituted **3e**, revealing the sensitivity of ruthenium catalyst to strong electron-donating groups and the steric environment around the aryl azide.[19] In contrast, the reaction was insensitive to the electronic nature of the aryl azide. Substrates bearing either electron-donating or electron-withdrawing substituents produced single isomers of carbolines upon exposure to $RuCl_3 \cdot nH_2O$ (entries 6−10). While substitution on the pyridinium ion attenuated the yield, the selectivity of the reaction remained high. Our reaction enables the regioselective synthesis of γ-tetrahydrocarbolines (e.g., **5f**, **5k**, and **5l**), which cannot be made selectively using the Fischer-indole reaction.

To determine if $RuCl_3 \cdot nH_2O$ could catalyze the formation of β-carbolines, aryl azide **6** was screened (eq 1). In contrast to 3-pyridinium ions, no product was observed using 5 mol % of $RuCl_3$ hydrate. For this class of substrates, rhodium carboxylate complexes proved more effective catalysts: exposure of **6** to 5 mol % of $Rh_2(esp)_2$ afforded tryptoline **8** after $NaBH_4$ reduction.

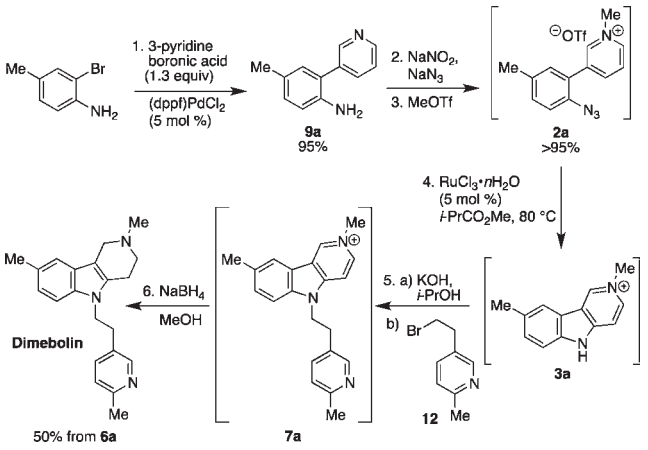


The synthetic efficiency and generality of our new method was demonstrated in a concise, stereoselective

(18) Elliott, I. W. *J. Heterocycl. Chem.* **1966**, *3*, 361.

(19) $Rh_2(esp)_2$ (5 mol %) efficiently converted biaryl azide **3e** into γ-carbolinium ion **4e**. Elucidating the unique regioselectivity exhibited by this substrate is the basis of ongoing mechanistic experiments.

Scheme 2. Synthesis of Dimebolin



synthesis of dimebolin (Scheme 2). Palladium-catalyzed Suzuki cross-coupling of *o*-bromoanilines provided biaryl **9a** in quantitative yield.[12a,b] Azidation[20] followed by alkylation of the pyridine nitrogen with methyl triflate produced **2a**, which was submitted to our ruthenium-catalyzed amination reaction without purification. Analysis of the reaction mixture using ^{1}H NMR spectroscopy indicated that carbolinium ion **3a** was formed in 91% yield. Deprotonation of the carbolinium ion followed by alkylation with **12** furnished the requisite pyridine side chain.[21] Introduction of this moiety by alternative methods, such as transition-metal-catalyzed vinylation,[22] reductive amination,[23,24] or alkylation[25] of carboline **5a** were not successful. Sodium borohydride reduction of **10a** proceeded smoothly to produce dimebolin in 48% from **9a**. This six-step synthesis required only three purifications to produce dimebolin.

In conclusion, we have demonstrated that $RuCl_3 \cdot nH_2O$ catalyzes the stereoselective formation of γ-carbolines from *ortho*-substituted aryl azides. A six-step synthesis of dimebolin validated the synthetic efficiency of our method. Future experiments will be aimed at examining the differences between the mechanism of ruthenium- and rhodium-catalyzed C−N bond formation of pyridinium ions as well as developing methods to stereoselectively functionalize the resulting carbolinium ion.

Acknowledgment. We are grateful to the National Institutes of Health NIGMS (R01GM084945) and the University of Illinois at Chicago for their generous support. We also thank Prof. L. Anderson (UIC) and Prof. D. Wardrop (UIC) for insightful discussions and Mr. Furong Sun (UIUC) for mass spectrometry data.

Supporting Information Available. Complete experimental procedures and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Smith, P. A. S.; Hall, J. H. *J. Am. Chem. Soc.* **1962**, *84*, 480.

(21) Smolyar, N. N.; Volchkov, A. S.; Yutilov, Y. M. *Pharmaceut. Chem. J.* **2001**, *35*, 514.

(22) (a) Cu-catalyzed: Liao, Q.; Wang, Y.; Zhang, L.; Xi, C. *J. Org. Chem.* **2009**, *74*, 6371. (b) Pd-catalyzed: Lebedev, A. Y.; Izmer, V. V.; Kazyul'kin, D. N.; Beletskaya, I. P.; Voskoboynikov, A. Z. *Org. Lett.* **2002**, *4*, 623.

(23) For acylation, see: (a) Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915. (b) Giri, V. S.; Maiti, B. C.; Pakrashi, S. C. *Heterocycles* **1985**, *21*, 71.

(24) For reduction, see: (a) Wattanasin, S.; Kathawala, F. G. *Synth. Commun.* **1989**, *19*, 2659. (b) Flitsch, W.; Niehoff, A. *Liebigs Ann. Chem.* **1989**, 239.

(25) Compare Khorana, N.; Purohit, A.; Herrick-Davis, K.; Teitler, M.; Glennon, R. A. *Bioorg. Med. Chem.* **2003**, *11*, 717.