Published in final edited form as:

Org Lett. 2011 May 20; 13(10): 2726–2729. doi:10.1021/ol2008268.

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

Huijun Dong, Regina T. Latka, and Tom G. Driver*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois, 60607-7061

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 -^{3,4,5} And γ -carbolines⁶ 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 latre-piridine)⁸ is a γ -tetrahydrocarboline that was under intense scrutiny because it showed promising activity for the treatment of mild- to moderate cases of Alzheimer's⁹ and Huntington's¹⁰ 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. 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. This method enables synthesis of dimebolin from commercial starting materials in five flasks with only three purifications.

Towards our goal, transition metal complexes known to promote C–N bond formation from aryl azides were screened (Table 1). While 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 [(cod)Ir(OMe)]₂,¹³ ZnI₂,¹⁴ and FeBr₂¹⁵ were found to be unreactive (entries 4 – 6). Selective γ -carbolinium formation was realized with ruthenium complexes.¹⁶ In dimethoxyethane, anhydrous RuCl₃^{16a} partially converted aryl azide **2** into carbolinium **3**. Additional screening of reaction conditions

tgd@uic.edu.

Supporting Information Available Complete experimental procedures, spectroscopic and analytical data for the products (PDF) is available free of charge via the Internet at <http://pubs.acs.org>.

afforded the optimal conditions: 5 mol % of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ 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 RuCl_3 (entry 10). Ru(II) complexes^{16c} were examined and found to be poorer catalysts than $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (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 *ortho*-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 $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (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 $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ 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 $\text{Rh}_2(\text{esp})_2$ afforded tryptoline **8** after NaBH_4 reduction.

(1)

The synthetic efficiency and generality of our new method was demonstrated in a concise, stereoselective synthesis of dimebolin (Scheme 3). Palladium-catalyzed Suzuki cross-coupling of *ortho*-bromoanilines provided biaryl **9a** in quantitative yield.^{12a,b} Azidation²⁰ 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 ^1H 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 alkylation²⁵ 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 $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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.

References

1. For reviews, see: (a) Labinger JA, Bercaw JE. *Nature*. 2002; 417:507. [PubMed: 12037558] (b) Du Bois J. *Chemtracts*. 2005; 18:1.(c) Agarwal S, Cämmerer S, Filali S, Fröhner W, Knöll J, Krah MP, Reddy KR, Knölker HJ. *Curr Org Chem*. 2005; 9:1601.(d) Godula K, Sames D. *Science*. 2006; 312:67. [PubMed: 16601184] (e) Dick AR, Sanford MS. *Tetrahedron*. 2006; 62:2439.(f) Davies HML, Manning JR. *Nature*. 2008; 451:417. [PubMed: 18216847] (g) Knölker HJ. *Chem Lett*. 2009; 38:8.(h) Chen X, Engle KM, Wang DH, Yu JQ. *Angew Chem, Int Ed*. 2009; 48:5094.(i) Driver TG. *Org Biomol Chem*. 2010; 8:3831. [PubMed: 20617243]
2. For recent, leading reports, see:(Rh) (a) Lebel H, Huard K, Lécourt S. *J Am Chem Soc*. 2005; 127:14198. [PubMed: 16218610] (Pd) (b) Tsang WCP, Zheng N, Buchwald SL. *J Am Chem Soc*. 2005; 127:14560. [PubMed: 16231894] (Cu) (c) Chen X, Hao X-S, Goodhue CE, Yu J-Q. *J Am Chem Soc*. 2006; 128:6790. [PubMed: 16719450] (Pd) (d) Thu H-Y, Yu W-Y, Che C-M. *J Am Chem Soc*. 2006; 128:9048. [PubMed: 16834374] (Ag) (e) Li Z, Capretto DA, Rahaman RO, He C. *J Am Chem Soc*. 2007; 129:12058. [PubMed: 17880068] (Rh) (f) Fukumoto Y, Kinashi F, Kawahara T, Chatani N. *Org Lett*. 2006; 8:4641. [PubMed: 16986970] (Rh) (g) Zalatan DN, Du Bois J. *J Am Chem Soc*. 2008; 130:9220. [PubMed: 18582043] (Pd) (h) Jordan-Hore JA, Johansson CCC, Gulias M, Beck EM, Gaunt MJ. *J Am Chem Soc*. 2008; 130:16184. [PubMed: 18998652] (i) Gruner KK, Knölker HJ. *Org Biomol Chem*. 2008; 6:3902. [PubMed: 18931794] (j) Lu H, Tao J, Jones JE, Wojtas L, Zhang XP. *Org Lett*. 2010; 12:1248. [PubMed: 20184343] (k) Tan Y, Hartwig JF. *J Am Chem Soc*. 2010; 132:3676. [PubMed: 20187645]
3. (a) Czarnocki Z, Siwicka A, Szawkalo J. *Curr Org Synth*. 2005; 2:301.(b) Youn SW. *Org Prep Proc Int*. 2006; 38:505.(c) Zeni G, Larock RC. *Chem Rev*. 2006; 106:4644. [PubMed: 17091931] (d) Edwankar CR, Edwankar RV, Namjoshi OA, Rallapappi SK, Yang J, Cook JM. *Curr Opin Drug Discuss Dev*. 2009; 12:752.(e) Alekseyev RS, Kurkin AV, Yurovskaya MA. *Chem Heterocycl Compounds*. 2009; 45:889.(f) Bandini M, Eichholzer A. *Angew Chem, Int Ed*. 2009; 48:9608.
4. Recent Pictet–Spengler reports: (a) Taylor MS, Jacobsen EN. *J Am Chem Soc*. 2004; 126:10558. [PubMed: 15327311] (b) Seayad J, Seayad AM, List B. *J Am Chem Soc*. 2006; 128:1086. [PubMed: 16433519] (c) Wanner MJ, van der Haas RNS, de Cuba KR, van Maarseveen JH, Hiemstra H. *Angew Chem, Int Ed*. 2007; 46:7485.(d) Klausen RS, Jacobsen EN. *Org Lett*. 2009; 11:887. [PubMed: 19178157]
5. β -Carbolines (non Pictet–Spengler), see: (a) Bondzić BP, Eilbracht P. *Org Lett*. 2008; 10:3433. [PubMed: 18642825] (b) Movassaghi M, Hill MD. *Org Lett*. 2008; 10:3485. [PubMed: 18642832] (c) England DE, Padwa P. *Org Lett*. 2008; 8:3631. [PubMed: 18627172] (d) Ohta Y, Oishi S, Fujii N, Ohno H. *Org Lett*. 2009; 11:1979. [PubMed: 19354232]
6. γ -Carbolines: (a) Zhang H, Larock RC. *Org Lett*. 2001; 3:3083. [PubMed: 11574000] (b) Zhang H, Larock RC. *J Org Chem*. 2002; 67:7048. [PubMed: 12353999] (c) Chiba S, Xu YJ, Wang YF. *J Am Chem Soc*. 2009; 131:12886. [PubMed: 19697931] (d) Ding S, Shi Z, Jiao N. *Org Lett*. 2010; 12:1540. [PubMed: 20210308]
7. (a) Cox ED, Cook JM. *Chem Rev*. 1995; 95:1797.(b) Czarwinski KM, Cook JM, Pearson W. *Advances in Heterocyclic Natural Products Synthesis*. ILLJAI PressGreenwich CT1996; :217.(c) Maresh JJ, Giddings LA, Friedrich A, Loris EA, Panjikar S, Trout BL, Stockigt J, Peters B,

- O'Connor SE. *J Am Chem Soc.* 2007; 130:710. [PubMed: 18081287] (d) Luk LYP, Bunn S, Liscombe LK, Facchini PJ, Tanner ME. *Biochemistry.* 2007; 46:10153. [PubMed: 17696451] and references therein.
8. Shadurski, KS.; Danusevich, IK.; Kost, AN.; Vinogradova, EV. US Patent No. 1138164. *Chem Abstr.* 1985; 102:190810.
 9. c.f. (a) Okun I, Tkachenko SE, Khavat A, Mitkin O, Kazey V, Ivachtchenko AV. *Curr Alzheimer Res.* 2010; 7:97. [PubMed: 19939222] (b) Steele JW, Kim SH, Cirrito JR, Verges DK, Restivo RL, Westaway D, Fraser P, Hyslop PS, Sano M, Bezprozvanny I, Ehrlich ME, Holtzman DM, Gandy S. *Mol Neurodegeneration.* 2009; 4:51.(c) Doody RS, Gavrilova SI, Sano M, Thomas RG, Aisen PS, Bachurin BO, Seely L, Hung D. *Lancet.* 2008; 372:207. [PubMed: 18640457] (d) Ivachtchenko IV, Frolov EB, Mitkin OD, Kysil VM, Khvat AV, Okun IM, Tkachenko SE. *Bioorg Med Chem Lett.* 2009; 19:3183. [PubMed: 19443217]
 10. cf. (a) Kieburts K, McDermott MP, Voss TS, Corey-Bloom J, Deuel LM, Dorsey ER, Factor S, Geschwind MD, 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. [PubMed: 20142523] (b) Sabbagh MN, Shill HA. *Curr Opin Invest Drugs.* 2010; 11:80.(c) Wu J, Li Q, Bezprozvanny I. *Mol Neurodegeneration.* 2008; 3:15.
 11. (a) Pollack, A. Antihistamine Shows Promise in Treating Alzheimer's. *New York Times*; June 11. 2007 (b) Hopkins CR. *ACS Chem Neurosci.* 2010; 1:587.
 12. (a) Stokes BJ, Richert KJ, Driver TG. *J Org Chem.* 2009; 74:6442. [PubMed: 19663433] (b) Stokes BJ, Jovanović B, Dong H, Richert KJ, Riell RD, Driver TG. *J Org Chem.* 2009; 74:3225. [PubMed: 19296584] (c) Shen M, Leslie BE, Driver TG. *Angew Chem, Int Ed.* 2008; 47:5056.(d) Stokes BJ, Dong H, Leslie BE, Pumphrey AL, Driver TG. *J Am Chem Soc.* 2007; 129:7500. [PubMed: 17523647]
 13. Sun K, Sachwani R, Richert KJ, Driver TG. *Org Lett.* 2009; 11:3598. [PubMed: 19627144]
 14. Dong H, Shen M, Redford JE, Stokes BJ, Pumphrey AL, Driver TG. *Org Lett.* 2007; 9:5191. [PubMed: 17994755]
 15. Shen M, Driver TG. *Org Lett.* 2008; 10:3367. [PubMed: 18597473]
 16. For leading examples of Ru-catalyzed N-atom transfer reactions, see: (a) Shou WG, 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. [PubMed: 17441159] (e) Leung SKY, Tsui WM, Huang JS, Che CM, Liang JL, Zhu N. *J Am Chem Soc.* 2005; 127:16629. [PubMed: 16305252]
 17. **Optimized General Procedure for γ -Tetrahydrocarboline Formation.** To a mixture of pyridinium **2a** (0.187 g, 0.5 mmol, 1.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (0.005 g, 0.025 mmol, 0.05 equiv) were 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) was dissolved in a 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 tetrahydrocarboline **5a**.
 18. Elliott IW. *J Heterocycl Chem.* 1966; 3:361.
 19. $\text{Rh}_2(\text{esp})_2$ (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.
 20. Smith PAS, Hall JH. *J Am Chem Soc.* 1962; 84:480.
 21. Smolyar NN, Volchkov AS, Yutilov YM. *Pharmaceut Chem J.* 2001; 35:514.
 22. Cu-catalyzed: (a) Liao Q, Wang Y, Zhang L, Xi C. *J Org Chem.* 2009; 74:6371. [PubMed: 19603753] Pd-catalyzed: (b) Lebedev AY, Izmer VV, Kazyul'kin DN, Beletskaya IP, Voskoboinikov AZ. *Org Lett.* 2002; 4:623. [PubMed: 11843607]

23. For acylation, see: (a) Ottoni O, Cruz R, Alves R. *Tetrahedron*. 1998; 54:13915.(b) Giri VS, Maiti BC, Pakrashi SC. *Heterocycles*. 1985; 21:71.
24. For reduction, see: (a) Wattanasin S, Kathawala FG. *Synth Commun*. 1989; 19:2659.(b) Flitsch W, Niehoff A. *Liebigs Ann Chem*. 1989; 239
25. cf. Khorana N, Purohit A, Herrick-Davis K, Teitler M, Glennon RA. *Bioorg Med Chem*. 2003; 11:717. [PubMed: 12538001]

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

Scheme 2.
Synthesis of Dimebolin.

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 ₂ C ₄ F ₇) ₄	PhMe	90	>95	25:75
2 ^b	Rh ₂ (O ₂ C ₈ H 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>i</i> -PrCO ₂ Me	80	7	100:0
5 ^b	ZnI ₂	CH ₂ Cl 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 • <i>n</i> H ₂ O	<i>i</i> -PrCO ₂ Me	80	>95	100:0
9	RuCl ₃	<i>i</i> -PrCO ₂ Me	80	17	100:0
10 ^c	RuCl ₃	<i>i</i> -PrCO ₂ Me	80	70	100:0
11	(cod)RuCl ₂	<i>i</i> -PrCO ₂ Me	80	23	100:0
12	Ru(TPFP)CO	<i>i</i> -PrCO ₂ Me	80	48	100:0

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

^b 100 wt % of 4 Å MS added.

^c 10 mol % of H₂O was added.

entry	2	aryl azide 2	γ -carbolinium 3a	γ -tetrahydro-carboline 5b
7	h			
8	i			

Org Lett. Author manuscript; available in PMC 2012 May 20.

entry	2	1	aryl azide 2	γ -carbolinium 3 ^d	γ -tetrahydro-carboline 5 ^b	
11						86%
12		m				76%
						48% ^e

Org Lett. Author manuscript; available in PMC 2012 May 20.

d Use of $\text{Rh}_2(\text{esp})_2$ (5 mol %).

e mesitylene, 110 °C. 1^e NaBH_4 reduction afforded a complex mixture.