

Iron(II) Bromide-Catalyzed Synthesis of
Benzimidazoles from Aryl Azides

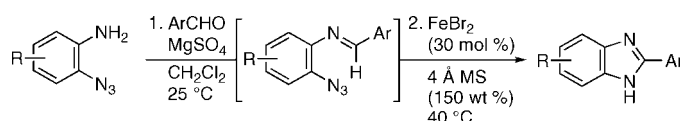
Meihua Shen and Tom G. Driver*

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

tgd@uic.edu

Received May 30, 2008

ABSTRACT



The identity of the ortho-substituent of an aryl azide influences its reactivity toward transition metals. Substitution of a vinyl group with an imine disables rhodium(II)-mediated C–H amination and triggers a Lewis acid mechanism catalyzed by iron(II) bromide to facilitate benzimidazole formation.

Controlling the reactivity of azides to provide functionalized products continues to inspire substantial research interest in the synthetic community.¹ Thermolysis or photolysis of azides produces nitrenes,^{2,3} which react with pendant olefins and C–H bonds.⁴ The nucleophilicity of azides has also been exploited to form C–N bonds selectively.^{1a,c,5} These processes, however, often proceed through highly reactive

intermediates, which can react unselectively⁶ or decompose to afford undesirable products.⁷ As a consequence, recent methods have employed transition metal catalysts to harness this reactivity to improve selectivity and diminish side reactions.^{8,9}

In the course of our studies on the reactivity of azides toward transition metals,¹⁰ we discovered that rhodium(II)

(1) For reviews, see: (a) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, 35, 146. (b) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, 44, 5188. (c) Judd, W. R.; Katz, C. E.; Aubé, J. *Sci. Synth.* **2005**, 21, 133. (d) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, 88, 297. (e) L'abbé, G. *Angew. Chem., Int. Ed.* **1975**, 14, 775.

(2) For aryl azides, see: (a) Sundberg, R. J.; Gillespie, D. W.; DeGraff, B. A. *J. Am. Chem. Soc.* **1975**, 97, 6193. (b) Sundberg, R. J.; Russell, H. F.; Ligon, W. V.; Lin, L.-S. *J. Org. Chem.* **1972**, 37, 719. (c) von E. Doering, W.; Odum, R. A. *Tetrahedron* **1966**, 22, 81. (d) Smith, P. A. S.; Hall, J. H. *J. Am. Chem. Soc.* **1962**, 84, 480. (e) Huisgen, R. *Angew. Chem.* **1955**, 67, 749. (f) Smith, P. A. S.; Brown, B. B. *J. Am. Chem. Soc.* **1951**, 73, 2435.

(3) For vinyl azides, see: (a) Moody, C. J. *Stud. Nat. Prod. Chem.* **1988**, 1, 163. (b) Henn, L.; Hickey, D. M. B.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2189. (c) Hemetsberger, H.; Knittel, D. *Monatsh. Chem.* **1972**, 103, 194. (d) Hemetsberger, H.; Knittel, D.; Weidmann, H. *Monatsh. Chem.* **1970**, 101, 161. (e) Isomura, K.; Kobayashi, S.; Taniguchi, H. *Tetrahedron Lett.* **1968**, 9, 3499.

(4) For reviews, see: (a) Söderberg, B. C. G. *Curr. Org. Chem.* **2000**, 4, 727. (b) Moody, C. J. *Comprehensive Organic Synthesis*; Trost, B. M., ; Fleming, I., ; Ley, S., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 21. (c) *Azides and Nitrenes, Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: London, 1984. (d) *Nitrenes*; Lwowski, Ed.; Wiley: New York, 1970.

(5) (a) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, 117, 10449. (b) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **1995**, 117, 8047. (c) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-k.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, 115, 10183. (d) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, 113, 8965.

(6) Thermal [3 + 2] cycloaddition reactions of azides often afford mixtures of 1,4- and 1,5-disubstituted triazoles. See: Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Pergamon: Oxford, 1984; p 1.

(7) The formation of tars and dimerization products can plague thermal reactions of azides. See: Abramovitch, R. A.; Challand, S. R.; Scriven, E. F. V. *J. Am. Chem. Soc.* **1972**, 94, 1374.

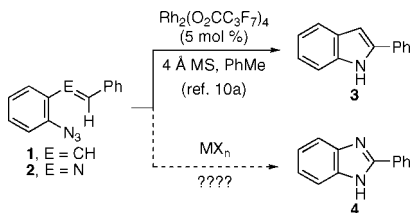
(8) For nitrogen-atom transfer reviews, see: (a) Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. *Coord. Chem. Rev.* **2006**, 250, 1234. (b) Katsuki, T. *Chem. Lett.* **2005**, 34, 1304.

(9) (a) Ruppel, J. V.; Jones, J. E.; Huff, C. A.; Kamble, R. M.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2008**, 10, 1995. (b) Bosch, L.; Vilarrasa, J. *Angew. Chem., Int. Ed.* **2007**, 41, 3926. (c) Ruppel, J. V.; Kamble, R. M.; Zhang, X. P. *Org. Lett.* **2007**, 9, 4889. (d) Chiba, S.; Wang, Y. F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, 10, 313. (e) Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.-Eur. J.* **2006**, 12, 7558. (f) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, 127, 15998. (g) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, 127, 11260. (h) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, 41, 2596. (i) Pearson, W. H.; Hutta, D. A.; Fang, W.-k. *J. Org. Chem.* **2000**, 65, 8326. (j) Bach, T.; Körber, C. *J. Org. Chem.* **2000**, 65, 2358.

(10) (a) Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, 47, 5056. (b) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, 9, 5191. (c) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, 129, 7500.

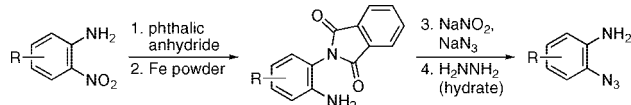
carboxylate complexes could mediate an intramolecular C–H amination reaction of 2-azidostilbene **1** to provide 2-arylin-dole **2** (Scheme 1).^{10a} At the conclusion of this study, we

Scheme 1. Examination of the Relationship between the Linker Composition and Substrate Reactivity



were interested in determining if the identity of the linker between the azide and the vinyl C–H bond influenced the reactivity of the resulting azide. In this Letter, we report that replacement of the α -carbon in **1** ($E = CH$) with a nitrogen atom (**2**, $E = N$) dramatically reduces the reactivity of the azide toward rhodium carboxylates and enables a different mechanism: Lewis acid activation of the imine, which facilitates benzimidazole formation.

Scheme 2. General Synthesis of 2-Azidoaniline Starting Materials¹²



The effect of swapping the α -carbon with a nitrogen atom on the reactivity of an aryl azide was examined using the crystalline 2-azidoarylimine **5** (Table 1).¹¹ This aldimine was formed from the condensation of 4-nitrobenzaldehyde and 2-azidoaniline, which was available from 2-nitroaniline through a four-step procedure (Scheme 2).^{12,13} Exposure of 2-azidoarylimine **5** to transition metal complexes that we had previously identified as catalysts produced unsatisfactory yields of benzimidazole **6** (entries 2–5). After extensive screening of reaction conditions,¹³ we identified the Lewis acid, aluminum chloride,¹⁴ as a competent catalyst (entry 6). Further optimization revealed the superiority of ferric and

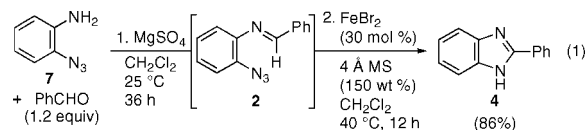
Table 1. Optimization of Benzimidazole Formation

entry	metal salt	mol %	4 Å MS ^a (wt %)	yield (%) ^b
1 ^c	none	n.a.	100	0
2 ^c	Rh ₂ (O ₂ CC ₃ F ₇) ₄	5	100	36 ^d
3 ^c	Rh ₂ (O ₂ CC ₇ H ₁₅) ₄	5	100	31
4 ^c	ZnI ₂	10	100	trace
5 ^c	Cu(OTf) ₂	10	100	trace
6 ^e	AlCl ₃	30	100	53
7 ^e	FeBr ₃	30	100	77
8 ^e	FeBr ₂	30	150 ^f	>95(91) ^g
9 ^e	FeBr ₂	10	150	55
10 ^e	FeBr ₂	30	30	62

^a Powdered. ^b As determined using ¹H NMR spectroscopy. ^c Reaction performed in PhMe. ^d Without 4 Å MS, only trace ptd. ^e Reaction performed in CH₂Cl₂ at 40 °C. ^f Recovered molecular sieves did not catalyze the reaction. ^g Isolated yield after chromatography on SiO₂.

ferrous bromide (entry 7 and 8).¹⁵ Reducing the catalyst loading of iron(II) bromide from 30 to 10 mol % had a detrimental effect on the reaction yield (compare entries 8 and 9). The reactivity of these Lewis acids starkly contrasts with our previous studies where they did not promote C–N bond formation.¹⁰ The inclusion of powdered 4 Å molecular sieves was necessary to achieve satisfactory yields reproducibly (compare entries 8 and 10). A screen of solvents revealed that benzimidazole formation occurred more efficiently in methylene chloride than in toluene to allow the reaction temperature to be lowered to 40 °C.

After identification of the optimal conditions, the scope and limitations of the reaction were examined. We soon discovered, however, that our method was severely limited by the marginal stability of the starting 2-azidoarylimine, which required purification by recrystallization due to its sensitivity toward SiO₂. To overcome this obstacle, we examined the possibility of carrying the unpurified 1-azidoarylimine **2** onto the subsequent step (eq 1). After filtration and concentration of the reaction mixture containing imine **2**,¹⁶ exposure of the resulting material to iron(II) bromide (30 mol %) and powdered 4 Å molecular sieves in methylene chloride led to an acceptable yield of benzimidazole **4**.¹⁷



With an optimized two-step procedure in hand, the impact of the aldehyde substituent on the reaction yield was

(11) For reports on the thermolysis of 2-azidoarylimines, see: (a) Wallace, J. M.; Söderberg, B. C. G.; Hubbard, J. W. *Synth. Commun.* **2006**, 36, 3425. (b) Hall, J. H.; Famm, D. R. *J. Org. Chem.* **1965**, 30, 2092. (c) Krbeček, L.; Takimoto, H. *J. Org. Chem.* **1964**, 29, 3630.

(12) (a) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2001**, 3, 4091. (b) Hall, J. H.; Patterson, E. *J. Am. Chem. Soc.* **1967**, 89, 5856.

(13) Please refer to the Supporting Information.

(14) For reactions of aryl azides promoted by stoichiometric quantities of AlCl₃, see: (a) Takeuchi, H.; Shiobara, Y.; Kawamoto, H.; Koyama, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 321. (b) Takeuchi, H.; Maeda, M.; Mitani, M.; Koyama, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 57. (c) Takeuchi, H.; Shiobara, Y.; Mitani, M.; Koyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1251. (d) Takeuchi, H.; Maeda, M.; Mitani, M.; Koyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 287.

(15) For iron-catalyzed transformations of azides, see: (a) ref 9j. (b) Bacci, J. P.; Greenman, K. L.; Van Vranken, D. L. *J. Org. Chem.* **2003**, 68, 4955. (c) Bach, T.; Schlummer, B.; Harms, K. *Chem.-Eur. J.* **2001**, 7, 2581. (d) Bach, T.; Schlummer, B.; Harms, K. *Chem. Commun.* **2000**, 287. (e) Bach, T.; Körber, C. *Tetrahedron Lett.* **1998**, 39, 5015.

(16) Concentration allowed the yield of the condensation reaction to be measured by ¹H NMR spectroscopy using an internal standard of CH₂Br₂.

examined (Table 2). While the identity of the aryl aldehyde did not affect the efficiency of the initial condensation, the

Table 2. Scope of Benzimidazole Formation

entry	RCHO	8, yield (%) ^a	9	yield (%) ^b
1		93	9a	86
2		95	9b	94
3		89	9c	49
4		80	9d	36
5		>95	9e	81
6		94	9f	61
7		>95	9g	98
8		90	9h	65
9		92	9i	92
10		>95	9j	90
11		78	9k	41
12		24	9l	dec.
13 ^c		<10	9m	n.a.

^a As determined using ¹H NMR spectroscopy. ^b Isolated yield over two steps after chromatography on SiO₂. ^c 5 equiv of propionaldehyde employed.

subsequent iron-catalyzed C–N bond formation exhibited a clear dependence on the electronic nature of the aryl moiety. Higher yields of benzimidazole **9** were obtained with more electron-deficient aryl groups (entries 1–6). The reaction tolerated sterically congested aryl groups (entries 7–10), although a diminished yield of **9h** was obtained with an *ortho*-methyl substituent (entry 8). In contrast to our previous methods, the coordinating cyano substituent in **9j** was permitted (entry 10). Poor yields of imine **8**, however, were obtained in the reaction of alkyl aldehydes with 2-azidoaniline **7** (entries 12 and 13). These results suggest that the efficiency of the reaction improves as imine **8** is rendered more electron-deficient.

The electronic nature of the starting 2-azidoaniline on the yield was interrogated by subjecting a range of aryl azides to reaction conditions (Table 3). As we previously observed, the efficiency of the condensation reaction was largely independent of the electronic- or steric nature of the starting aniline. Iron(II)-mediated C–N bond formation, however,

Table 3. Scope of Benzimidazole Formation

entry	10	11, yield (%) ^a	12	yield (%) ^b
1		66	12a	56
2		92	12b	75
3		94	12c	54
4		84	12d	82
5		>95	12b	90
6		>95	12e	92
7		81	12f	n.r.
8		74	12g	60 ^c
9		91	12h	66

^a As determined using ¹H NMR spectroscopy. ^b Isolated yield over two steps after chromatography on SiO₂. ^c 48:52 mixture of tautomers.

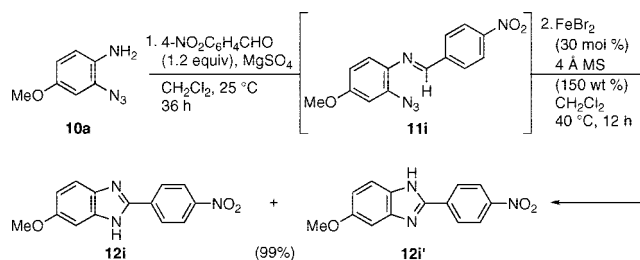
was influenced by the substituents on the resulting imine (**11**). While one electron-withdrawing group did not adversely affect the reaction outcome, the addition of a second disabled benzimidazole formation (compare entries 4 and 7). Increasing the steric nature of aniline with *ortho*-methyl substitution also had a detrimental effect on product formation (entries 8 and 9). The reaction is not stereospecific. The reaction of both 2-azido-4-methyl- and 2-azido-3-methylimine (**11b** and **11e**) afforded benzimidazole **12b** (entries 2 and 5), and 2-azido-5,6-dimethylimine (**11g**) produced nearly a 1:1 mixture of benzimidazole tautomers (entry 8). The stability of imine **11** toward the reaction conditions also impacted the reaction efficiency: substantial decomposition of imines **11a** and **11c** accompanied benzimidazole formation (entries 1 and 3).

The reduced yield observed in the condensation reaction of 4-methoxy-2-azidoaniline (**10a**) and benzaldehyde could be overcome if a more robust imine was generated (Scheme 3). Employing 4-nitrobenzaldehyde enabled formation of benzimidazole **12i** as a mixture of tautomers in 99% yield from **10a**.

While the exact mechanism remains unclear, we believe that a Lewis acid-mediated mechanism accounts for benzimidazole formation (Scheme 4).^{18,19} The reactivity trends provide evidence for this mechanism: higher conversions were observed with electron-deficient imines and electron-

(17) Attempts to perform both steps in one flask without isolation of the intermediate aryl imine were not successful.

Scheme 3. Effect of Imine Stability on Reaction Efficiency



rich azides. Therefore, coordination of iron(II) bromide to the imine nitrogen (to form **16**)²⁰ increases its electrophilicity to trigger nucleophilic attack by the pendant azide, which forms **17**. Expulsion of N₂ would generate **18**. Dissociation from the iron catalyst would provide 2*H*-benzimidazole **14**. A slow dissociation step would account for the diminished catalytic activity of more Lewis acidic reagents,²¹ such as iron(III) bromide. Tautomerization of **14** forms 1*H*-benzimidazole **15**. The intermediacy of **14** would render this transformation nonstereospecific.²²

In conclusion, we have shown that the mode of reactivity of the aryl azide is dependent on the composition of the linker between the aryl azide and the pendant C–H bond. Substitu-

(18) While iron(II) salts have been reported to catalyze nitrogen-atom transfer reactions (see refs 9j and 15), the lack of decomposition products (e.g., azo compounds, tars, anilines) suggests that a nitrenoid intermediate is not involved.

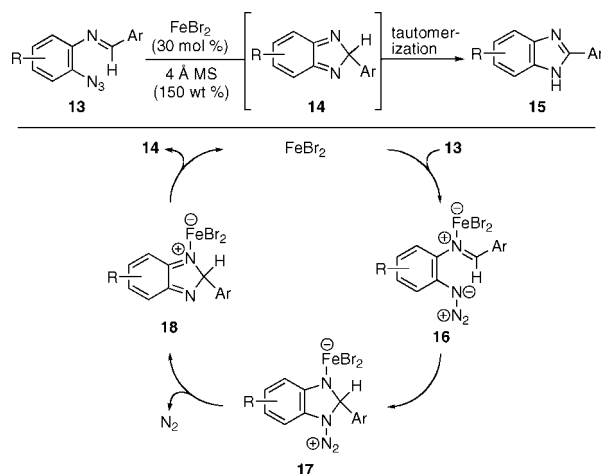
(19) For related mechanistic studies of Lewis acid-mediated additions of azides to oxocarbenium ions, see: (a) Katz, C. E.; Ribelin, T.; Withrow, D.; Basseri, Y.; Manukyan, A. K.; Bermudez, A.; Nuera, C. G.; Day, V. W.; Powell, D. R.; Poutsma, J. L.; Aubé, J. *J. Org. Chem.* **2008**, *73*, 3318. (b) Hewlett, N. D.; Aubé, J.; Radkiewicz-Poutsma, J. L. *J. Org. Chem.* **2004**, *69*, 3439.

(20) For leading reports of iron(II)-imine crystal structures, see: (a) Bart, S. C.; Lobkovsky, E.; Bill, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 5302. (b) Bouwkamp, M. W.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 9660.

(21) For leading reports, which compare the Lewis acidity of transition metals, see: (a) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817. (b) Kobayashi, S.; Busujuma, T.; Nagayama, S. *Chem.—Eur. J.* **2000**, *6*, 3491. (c) Pearson, R. G. *Inorg. Chem.* **1988**, *27*, 734.

(22) Alternatively, the 1*H*-benzimidazole product could tautomerize. For a recent review on these processes in N-heterocycles, see: Elguero, J.; Katritzky, A. R.; Denisko, O. V. *Adv. Heterocycl. Chem.* **2000**, *76*, 1.

Scheme 4. Potential Mechanism for Benzimidazole Formation



tion of the α-carbon atom with a nitrogen atom disables rhodium(II)-catalyzed amination and triggers a Lewis acid mechanism mediated by iron(II) bromide to enable benzimidazole formation from 2-azidoarylimines. Through further modification of this linker, future experiments are aimed at broadening our understanding of the reactivity of azides toward transition metals.

Acknowledgment. We are grateful to the Petroleum Research Fund administered by the American Chemical Society (46850-G1) and the University of Illinois at Chicago for their generous support. We thank Mr. Furong Sun (UIUC) for mass spectrometry data. The 70-VSE mass spectrometer (UIUC) was purchased in part with a grant from the Division of Research Resources, National Institutes of Health (RR 04648).

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

OL801227F