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Nonconventional Carbon Additions to Azomethines. Aryl Amination/Indoline Synthesis by Direct Aryl Radical Addition to Azomethine Nitrogen

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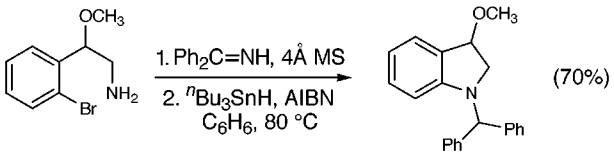
ABSTRACT



The generality of a new method for aryl amination has been defined. Ketimines derived from *o*-bromophenethylamine cyclize to the *N*-substituted indoline when treated with $^{n}Bu_3SnH$ and a radical initiator. The pH-neutral conditions tolerate base- and acid-sensitive functionality. The observed regioselectivity is nonconventional for addition reactions involving carbon radicals and carbon–heteroatom π-bonds.

The development of methods that effect aryl amination is a challenge of broad interest due to the prevalence of the aniline subunit within biologically active natural products and medicinal agents.[1] Significantly, indole alkaloid syntheses frequently commence from one of many available aniline or indole derivatives. Although this strategy is inherently limited, its popularity is perhaps due to the fact that there are few methods available for forming aryl−nitrogren bonds. Moreover, existing technology generally fails to offer the mild conditions necessary for the highest possible degree of chemoselectivity. Transition metal-mediated aryl amination has revolutionized this area in recent years by providing a catalytic means to form aryl−nitrogen bonds under generally alkaline conditions.[2,3]

From the standpoint of indoline/indole synthesis, both transition metal[4] and radical[5] chemistry have proven their efficacy in making the nitrogen−C2 and various carbon−carbon bonds of the dihydropyrrolidine/pyrrole ring. However, the aryl−nitrogen bond construction is only rarely evaluated for lack of mild methods to execute its formation.[2a,6,7] Methods developed to form the aryl−nitrogen bond must appreciate the facility with which the product indolines are known to aromatize to the indole. The importance of aryl amination and its products is motivation to discover additional chemical solutions that complement known methods. In contrast to recent progress in this area,[3] we approached this problem with the conviction that a conceptually and operationally distinct solution might also form the basis for a new chemical strategy. As such, we are developing methods that utilize activation of a π_{N-C} bond in the amine component as opposed to a σ_{N-H} bond.

(1) *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 50.

(2) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. F. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417−1423. (c) López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **1995**, *60*, 5678.

(3) Lam, P. Y. S.; Duedon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600.

(4) Leading reference: Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662.

(5) (a) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. Radical Cyclization Reactions. *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1996; Vol. 48, Chapter 2. (b) Kobayashi, Y.; Fukuyama, T. *J. Heterocycl. Chem.* **1998**, *35*, 1043.

(6) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394.

(7) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

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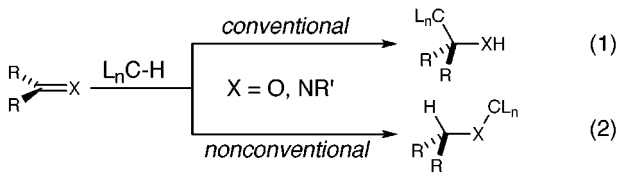
Carbanion and carbon radical species add to the carbon−heteroatom π-bond with complete regioselectivity for carbon−carbon bond formation (eq 1).[5a,8] To our knowledge, there are only a few examples in which the addition regioselectivity is reversed (eq 2).[9−11,13] The most notable of these exceptions

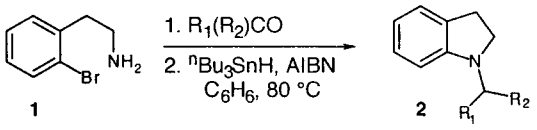


is the generality with which acyl radicals add to the heteroatom of a carbonyl or azomethine.[10,11] In contrast, nonpolarized carbon radicals generally enter into bond formation with the carbon of these functional groups. When an aldimine is the acceptor, aryl radicals cyclize 6-*endo*-carbon in preference to 5-*exo*-nitrogen.[12] The aryl−nitrogen bond-forming pathway has been successfully tapped through the implementation of a ketimine or amidate, but the predominant if not exclusive product remains that of direct aryl radical reduction by the hydrogen atom source.[13]

On the basis of these reports, it has been concluded that it is not possible to effect free radical aryl−nitrogen bond formation in any acceptable yield. In the context of aryl amination, we communicate the highly regioselective aryl radical addition to a pendant azomethine in which amination uniformly predominates over the direct reduction pathway.

Our initial studies are limited to 5-*exo* cyclizations of *o*-bromophenethylamine ketimines. Using the acetophenone ketimine, the reductive cyclization was optimized without artificially limiting trialkyltin hydride concentration. In the event, a 0.01 M solution of the ketimine derived from condensation of *o*-bromophenethylamine (**1**) with acetophenone was transformed to indoline **2a** in 82% isolated yield (two steps). Inspection of the crude reaction mixture by 400 MHz ^{1}H NMR suggested that *only* the product of direct reduction (ArBr (**1**) → ArH (**3**)) was competitively formed (**2a**:**3a** = 5:1); no evidence of the regioisomeric tetrahydroisoquinoline was observed. Using traditional slow addition techniques, the ratio of **2a**:**3a** was further improved to >10:1 and 87% isolated yield (Table 1, entry 1). Evidence that the chain propagation was reasonably efficient was gathered by demonstrating complete conversion of starting material using only 2.5 mol % of AIBN at 80 °C.[14]

Table 1. Reductive 5-*Exo* Aryl Radical Cyclizations to Ketimines[a]



entry	R_1	R_2	product	**2**:**3**[b]	yield (%)[c]
1	Ph	CH_3	**2a**	10:1	87
2	Ph	CF_3	**2b**	>12:1	77
3	Ph	Ph	**2c**	10:1	86
4	4-Me_2NPh	CH_3	**2d**	9:1	90
5	4-CF_3Ph	CH_3	**2e**	9:1	72
6	CH_3	CF_3	**2f**	14:1	83
7	CH_3	CH_3	**2g**	1:1	30

[a] Trialkyl tin hydride and AIBN were added as a benzene solution over 3 h. All reactions were carried out in C_6H_6 (0.01 M in substrate, 80 °C) and proceeded to complete conversion. [b] Measured by 400 MHz ^{1}H NMR of untreated reaction mixture by comparison to an authentic sample of **3** (ArH) formed from phenethylamine and the ketone. [c] Isolated yield (two steps) of **2** after chromatography.

These conditions proved to be quite general in determining the reaction scope (Table 1). In contrast to previous reports,[13] substrates were cyclized with uniform efficiency when the nascent α-amino carbon radical carried at least one radical-stabilizing substituent, regardless of its electronic character. Aryl radical cyclizations to dialkyl ketimines were significantly affected by electronic factors (cf. entries 6−7). Despite the apparent stabilizing nature of a phenyl substituent, no noticeable improvement was observed when the benzophenone ketimine was used.[15]

As expected, substitution of the phenethylamine backbone only increased the cyclization efficiency, presumably through conformational influence (Table 2). Alkyl substitution at the benzylic position methodically increased the proportion of cyclization to direct reduction (**6**), from 10:1 to 46:1. Substitution at the aminomethyl carbon might be expected to sterically deter aryl radical attack at the nitrogen, but no significant decrease in efficiency was observed. When a formidable leaving group was positioned at the benzylic carbon, the 3-methoxy indoline product (**5f**) was formed with comparable efficiency; *no evidence for elimination to the indole was observed in the crude reaction mixture*.

Substitution of the aryl ring by electronically diverse functionality should not adversely affect the chemistry of the derived radicals due to the localization of the unpaired electron to a σ-orbital.[16] This expectation was confirmed by

(8) (a) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. (b) Kim, S.; Kee, I. S.; Lee, S. *J. Am. Chem. Soc.* **1991**, *113*, 9882.

(9) Carbanion addition to carbonyl oxygen. Chi, S.; Heathcock, C. H. *Org. Lett.* **2000**, *1*, 1.

(10) (a) Rust, F. F.; Seubold, F. H.; Vaughan, W. E. *J. Am. Chem. Soc.* **1948**, *70*, 3258. (b) Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 1833. (c) Urry, W. H.; Nishihara, A.; Niu, J. H. Y. *J. Org. Chem.* **1967**, *32*, 347. (d) Mendenhall, G. D.; Protasiewicz, J. D.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1994**, *116*, 1718.

(11) Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838−5839.

(12) (a) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315. (b) Tomaszewski, M. J.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123. (c) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369. (d) Ryu, I.; Ogura, S.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 1515.

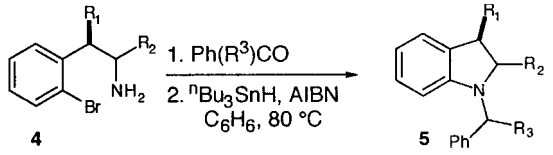
(13) (a) Takano, S.; Suzuki, M.; Ogasawara, K. *Heterocycles* **1994**, *37*, 149. (b) McClure, C. K.; Kiessling, A. J.; Link, J. S. *Tetrahedron* **1998**, *54*, 7121. (c) 5-*Endo*-nitrogen cyclization. Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 307.

(14) Followed by ^{1}H NMR in C_6D_6. No attempt was made to further decrease the initiator.

(15) Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148.

(16) Suehiro, T.; Suzuki, A.; Tsuchida, Y.; Yamazaki, J. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3324.

Table 2. Reductive 5-*Exo* Aryl Radical Cyclizations to Ketimines[a]

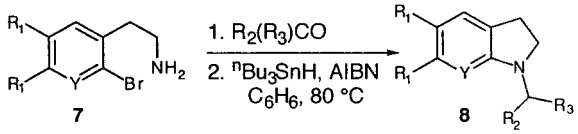


entry	R_1	R_2	R_3	product	**5**:**6**[b]	yield (%)[d]
1	CH_3	H	CH_3	**5a**	42:1	86
2	H	CH_3	Ph	**5b**	>20:1[c]	78
3	CH_3	*cis*-CH_3	Ph	**5c**	13:1	84
4	CH_3	*trans*-CH_3	Ph	**5d**	>200:1	79
5	*gem*-$(CH_3)_2$	H	CH_3	**5e**	46:1	73
6	CH_3O	H	Ph	**5f**		70

[a] All reactions were carried out in C_6H_6 (0.01 M in substrate, 80 °C) and proceeded to complete conversion. [b] Measured by GC/MS analysis of the untreated reaction mixture. [c] Undetectable by 400 MHz ^{1}H NMR. [d] Isolated yield (two steps) after chromatography.

the generality with which electron rich/deficient aryl rings/ketimines could be paired and cyclized (Table 3).

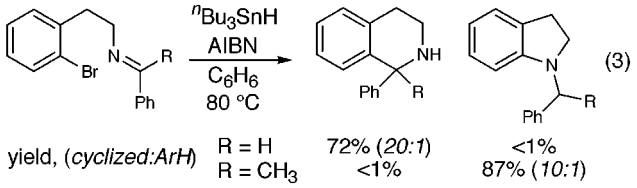
Table 3. Reductive 5-*Exo* Aryl Radical Cyclizations to Ketimines[a]



entry	R_1/Y	R_2	R_3	**8**:**9**[b]	yield (%)[c]
1	CH_3O/CH	Ph	CH_3	9:1	83
2	CH_3O/CH	Ph	CF_3	9:1	89
3	CH_3O/CH	Ph	Ph	12:1	64
4	H/N	Ph	Ph		50

[a] All reactions were carried out in C_6H_6 (0.01 M in substrate, 80 °C) and proceeded to complete conversion. [b] Relative amount of direct aryl reduction (**9**) measured by 400 MHz ^{1}H NMR of the untreated reaction mixture. [c] Isolated yield (two steps) after chromatography.

Using our standard protocol, we confirmed that an aryl radical will cyclize 6-*endo*-carbon with simple aromatic aldimines (eq 3). Our findings demonstrate that an aryl radical will undergo intramolecular cyclization selectively



(3)

to the nitrogen terminus of an azomethine bond even in the absence of any substrate conformational bias or artificial manipulation of the reaction conditions. Although it is now clear that both steric and electronic factors are influential in determining regioselectivity and cyclization rate (relative to direct aryl radical reduction), we are currently working to delineate the extent to which each of these control elements can be orchestrated to further generalize these nonconventional additions. This question is of fundamental importance since it is generally accepted that known formal nonconventional additions mimic Lewis acid−carbonyl complexation.[11] In this regard, these aryl radical additions are truly radical cyclizations and not cyclizations of a radical.[17] This study documents that *direct* carbon radical additions to the nitrogen of an azomethine can be an efficient and general process.

The absence of acid or base in this protocol appears to offer the mildest method yet for effecting aryl−nitrogen bond formation. In the context of alkaloid synthesis, this feature offers significant flexibility for synthesis design. Although we are currently developing cyclizations to nonaromatic imines, the benzylamine products reported in this study are easily deprotected under a variety of mild conditions to furnish the parent indolines.[18]

In summary, we have demonstrated the generality with which aryl amination can be effected using free radical intermediates. The convergent manner in which the nitrogen substituent and phenethylamine fragment are connected through a condensation sets the stage for the development of solid phase and combinatorial use of this methodology. These applications will be the subject of future reports.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For an excellent discussion and leading references, see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.
(18) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 579−583.