J|A|C|S
ARTICLES
Published on Web 12/11/2002

Free Radical-Mediated Aryl Amination and Its Use in a Convergent [3 + 2] Strategy for Enantioselective Indoline α-Amino Acid Synthesis

Rajesh Viswanathan, Erode N. Prabhakaran, Michael A. Plotkin, and Jeffrey N. Johnston*

Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47405-7102

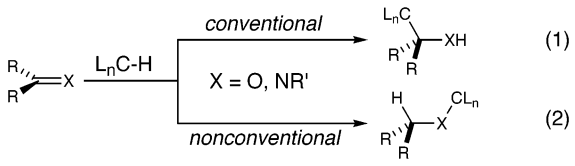
Received September 6, 2002; E-mail: jnjohnst@indiana.edu

Abstract: The scope of aryl radical additions to the nitrogen of azomethines is described. Aryl, trifluoromethyl alkyl, and α,β-unsaturated ketimines engage in regioselective aryl−nitrogen bond formation via 5-*exo* cyclizations of an aryl radical to azomethine nitrogen. Selectivity for carbon−nitrogen over carbon−carbon bond formation is generally high (>95:5) and competes only with direct aryl radical reduction by stannane (0−10%). α-Ketoimines are a promising new class of carbon radical acceptors for which no competitive aryl radical reduction is observed. The reaction conditions are pH-neutral and are therefore among the mildest methods available for amination of an aromatic ring. The ketimines examined did not suffer from competitive reduction by stannane, offering an advantage over the use of diazo and azide functional groups as nitrogen sources for carbon radicals. The free radical-mediated aryl amination was sequenced with the O'Donnell phase transfer-catalyzed enantioselective alkylation strategy of glycinyl imine to provide either enantiomer of indoline α-amino acids with high ee. These new constrained phenyl alanine derivatives are now readily available for evaluation across a variety of applications.

Introduction

The carbonyl is often touted as one of the, if not the most, useful functional groups in organic synthesis due to facile 1,2-addition of heteroatom and carbon nucleophiles across the π-bond (eq 1, X = O). Commercially available compounds containing a C=O unit are abundant, and the products of addition reactions are valued both as synthetic intermediates and in their own right. The aza derivatives of carbonyls contain an azomethine (C=N) that behaves analogously to the carbonyl, but with slight differences resulting from the attenuated electronegativity of nitrogen as compared to oxygen.

The regiochemical course of carbon radical additions to azomethines has been the object of study for many years.[1] Both intra- and intermolecular variants have been dominated by examples regioselective for carbon−carbon bond formation (eq 1, X = NR′),[2] or *conventional addition*, and the value of these additions is generally recognized.[1,3]



However, exceptions to this regiochemical addition mode were noted by several investigators who identified the regioisomeric carbon−nitrogen bond-forming pathway (eq 2, X = NR′) representative of a *nonconventional addition*.[4,5] Independently, Takano[6] and Warkentin[7] first identified products resulting from aryl radical addition to the nitrogen of ketimines (eq 3). These reports established the feasibility of the process, but the low yields (2−59%) for three substrates and identification of intermolecular hydrogen atom transfer to the aryl radical as the competing, if not predominant, reaction pathway[8,9] suggested

(1) (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. (c) Ollivier, C.; Renaud, P. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 93−112.

(2) (a) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. (b) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631. (c) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633.

(3) For leading references, see: Hart, D. J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 279−302.

(4) There are also reports of nonradical carbon additions to heteroatoms: azomethine nitrogen: Lin, J.-M.; Koch, K.; Fowler, F. W. *J. Org. Chem.* **1986**, *51*, 167; carbonyl oxygen: Chi, S.; Heathcock, C. H. *Org. Lett.* **2000**, *2*, 1.

(5) Acyl radical addition to carbonyl: Rust, F. F.; Seubold, F. H.; Vaughan, W. E. *J. Am. Chem. Soc.* **1948**, *70*, 3258. (a) Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 1833. (b) Urry, W. H.; Nishihara, A.; Niu, J. H. Y. *J. Org. Chem.* **1967**, *32*, 347. (c) Harrison, D. A.; Schwartz, R. N.; Kagan, J. *J. Am. Chem. Soc.* **1970**, *92*, 5793. (d) Mendenhall, G. D.; Protasiewicz, J. D.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1994**, *116*, 1718. (e) Yamamoto, Y.; Ohno, M.; Eguchi, S. *J. Org. Chem.* **1996**, *61*, 9264. To azomethine: (f) Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838. For an excellent review of acyl radical chemistry, see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(6) (a) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315. (b) Takano, S.; Suzuki, M.; Ogasawara, K. *Heterocycles* **1994**, *37*, 149.

(7) (a) Tomaszewski, M. J.; Warkentin, J. *Tetrahedron Lett.* **1992**, 2123. (b) Tomaszewski, M. J.; Warkentin, J.; Werstiuk, N. H. *Aust. J. Chem.* **1995**, *48*, 291.

(8) Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 307.

(9) McClure, C. K.; Kiessling, A. J.; Link, J. S. *Tetrahedron* **1998**, *54*, 7121.

that this mode of addition is synthetically inefficient. One exception is an example of carbon radical addition to azomethine nitrogen observed in the Frey[10] and Bowman[11] cases of sp^3-hybridized carbon radical additions to azomethine nitrogen.[1c,12]

Our interest in this chemistry resulted from a desire to develop conceptually unique approaches to the aryl amination problem.[13] This longstanding objective of methods development witnessed great advance during the past decade by the groups of Buchwald, Hartwig, and others.[14] Historically, solutions to this problem strategically target the N−H σ-bond for activation, often requiring an added base to facilitate this process. Additionally, significant electronic effects are observed in metal-mediated (and other) couplings, thereby underscoring a potential difficulty when developing a method based upon a "polar" disconnection.

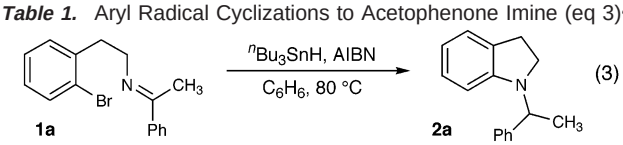
We have reinvestigated aryl radical additions to azomethines with the expectation that use of a C−N π-bond would provide a base-free aryl amination method expected to be relatively insensitive to electronic effects.[15] We provide here a systematic study, including several examples previously reported to be inefficient, of aryl radical additions to azomethines that validates this approach. The necessary characteristics of the azomethine component are described experimentally. Finally, the development of an enantioselective indoline amino acid synthesis demonstrates the synthetic utility of the method.

Results

o-Bromophenethylamine was prepared and condensed (activated 4 Å molecular sieves) in benzene with acetophenone to provide the stereoisomerically enriched (*E*)-ketimine (>95:5, ^{1}H NMR). Without purification, the imine was subjected to tributylstannane and a free radical initiator (AIBN) over a range of substrate concentrations in independent experiments (Table 1, entries 1−3). In these and all other reactions, the only identifiable side product was that of direct aryl radical reduction by stannane (ArH(**3**)). The products of direct reduction were obtained by independent synthesis, and their formation during cyclization was quantified by GC/MS and used as an internal standard to measure relative cyclization efficiency. Over the range of concentrations studied, cyclization predominated by a significant margin (5:1 to 10:1), and the indoline was isolated consistently in good yield. Not unexpectedly, at the optimal substrate concentration (0.01 M), addition of stannane by syringe pump further minimized the product of direct reduction, and the indoline was isolated in 87% yield.[16]

The optimal protocol (0.4 equiv of AIBN, 1.2 equiv of ^{n}Bu$_3$SnH added over 3 h to a 0.01 M solution of substrate) was

Table 1. Aryl Radical Cyclizations to Acetophenone Imine (eq 3)[a]

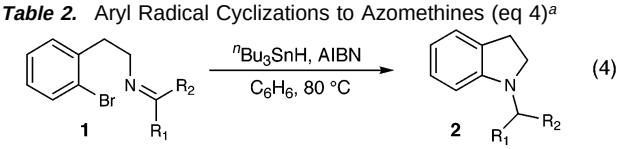


(3)

entry	[**1a**]	^{n}Bu$_3$SnH (addn time, h)	**2a**:ArH[b]	yield (%)[c]
1	0.1	—[d]	1.6:1	60
2	0.01	—[d]	5:1	82
3	0.001	—[d]	4:1	75
4	0.01	1	4:1	64
5	0.01	2	6.7:1	77
6	0.01	3	10:1	87
7	0.01	4	6.5:1	81

[a] See Supporting Information for complete experimental details. [b] Measured by GC/MS using an authentic sample of the phenethylimine derivative (ArH, **3**). [c] Isolated yield. Mass balance is **3**. [d] No slow addition.

Table 2. Aryl Radical Cyclizations to Azomethines (eq 4)[a]



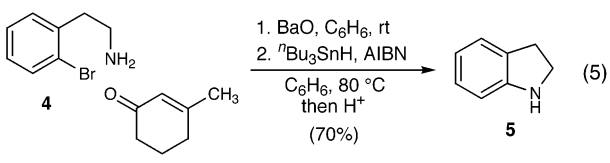
(4)

entry	R_1	R_2	product	**2**:**3**[b]	yield (%)[c]
1	Ph	CH_3	**2a**	10:1	87
2	Ph	Ph	**2b**	10:1	86
3	4-Me_2NPh	CH_3	**2c**	9:1	90
4	4-CF_3Ph	CH_3	**2d**	9:1	72
5	3,4,5-F_3Ph	CH_3	**2e**	11:1	65
6	2,6-$(MeO)_2$Ph	CH_3	**2f**	3:1	27
7	Ph	CF_3	**2g**	>12:1	77
8	CH_3	CF_3	**2h**	14:1	83
9	CH_3	CH_3	**2i**	1:1	30
10	C_2H_5	C_2H_5	**2j**	nd	40
11	Ph	H	**2k**		8[d]

[a] See Supporting Information for complete experimental details. [b] Measured by GC/MS using an authentic sample of phenethylimine derivative (ArH, **3**). [c] Isolated yield. [d] The isoquinoline resulting from aryl−carbon bond formation is the major product (67%).

then applied to a range of ketimines to determine the scope of the imine component (Table 2). Throughout this exercise, aldimines were avoided because they are known to engage almost exclusively in aryl radical addition to the azomethine carbon.[1,15] Hence, ketone derivatives of diverse electronic nature were compared under these conditions. Aryl alkyl ketones of varying electronic character behave without significant difference whether it be the aryl or alkyl substituent bearing the electron-withdrawing group. Moreover, one radical stabilizing substituent (additional to the nitrogen) was found to be enabling, whereas a second neither enhanced nor diminished the cyclization efficiency (cf. **2i**, **2a**, **2b**). The low yielding cyclization of an *o*,*o*-disubstituted aryl ketone suggested that significant resonance between the aryl ring and azomethine is critical (Table 2, entry 6).

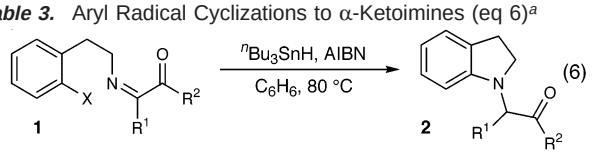
Stabilization by a vinyl substituent was demonstrated by cyclization of a 3-methylcyclohexenone imine (eq 5).



(5)

(10) Han, O.; Frey, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 8982.
(11) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369.
(12) Tanner's report of an apparent 5-*endo* carbon radical cyclization to azomethine nitrogen predates these studies: Tanner, D. D.; Rahimi, P. M. *J. Org. Chem.* **1979**, *44*, 1674.
(13) Leading references: (a) Copper-promoted: Lindley, J. *Tetrahedron* **1984**, *40*, 1433. 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. Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (b) Nucleophilic aromatic substitution: Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. Hattori, T.; Sakamoto, J.; Hayashizaka, N.; Miyano, S. *Synthesis* **1994**, 199. (c) Electrophilic nitroarenes: Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390.
(14) Palladium-mediated amination, leading references: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
(15) Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009.
(16) Takano reported a 12% yield for this cyclization (ref 6).

Table 3. Aryl Radical Cyclizations to α-Ketoimines (eq 6)[a]



entry	X	R^1	R^2	product	AIBN (equiv/ addn time, h)	yield (%)[b]
1	Br	CH_3	CH_3	**2l**	0.4/3	0[c]
2				**2l**	0.4/1	12[c]
3				**2l**	0.8/1	41[c]
4	I	CH_3	CH_3	**2m**	0.4/1	44
5				**2m**	1.5/8	82
6	I	C_6H_5	C_6H_5	**2n**	1.5/8	65
7	I	CH_3	OCH_3	**2o**[d]	1.5/4	75
8	I	H	OC_2H_5	**2p**	1.5/4	<5[e]

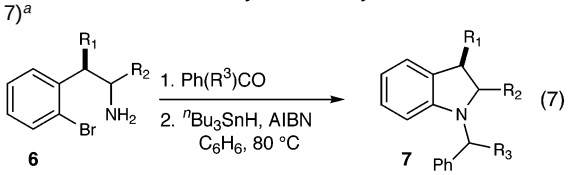
[a] See Supporting Information for complete experimental details. [b] Isolated yield, mass balance is **1**. No product of direct aryl radical reduction detected in these experiments by GC/MS. [c] Conversions of 0, 15, and 50 for entries 1−3, respectively. [d] Intermediate Schiff base contains 60% enamine tautomer. [e] Major product is tetrahydroisoquinoline (55%).

The condensation step for this substrate class is often complicated by competitive amine conjugate addition. In the present case, this was overcome by use of activated barium oxide identified through a broad screen of desiccants, thereby providing the desired imine with >90% purity. Subsequent cyclization of the unpurified α,*β*-unsaturated ketimine provided indoline (**5**) upon workup. It is unclear whether allylic amine (produced directly) and/or enamine (via tautomerization) is the first product, but the overall yield compares favorably with aryl ketimines.

α-Ketoimines. The trend identified in Table 2 led us to examine the effect of an acyl substituent on the ketimine. Initial attempts to effect aryl radical cyclizations to α-ketoimines (eq 6) returned only starting aryl bromide when subjected to conditions optimized for **1a** and other aryl ketimines (Table 3). This result was unexpected because conversion to the arene (**3**) is observed with substrates not amenable to aryl−nitrogen bond formation (**1i** and **j**). Conversions at the 15 and 45% level were possible by increasing the amount and rate of AIBN addition (Table 3, entries 2, 3). Significantly, these substrates were unique in their ability to transform selectively (>200:1 cyclized:ArH) to the product of amination. Upon utilization of the analogous aryl iodide **1m**, we found that complete and selective conversion to indoline **2m** was possible. This protocol readily extended to α-ketoimines of varying reductive potential. Unfortunately, the aldimine of glyoxal furnished the corresponding tetrahydroisoquinoline at the expense of the amination product (Table 3, entry 8).

Backbone Substitution. The transformations in Table 4 reveal the favorable effect that substitution of the phenethylamine backbone imparts to the cyclization efficiency. Although substitution of the chain might be expected to increase amounts of more rapidly cyclizing conformers, we were uncertain whether strain resident in the indoline ring might counteract this effect and allow direct aryl radical reduction to predominate. Furthermore, substitution on the nitrogen-bearing carbon might slow attack at the nitrogen. A comparison of the ratios of indoline:ArH reveals that these systems behave strictly in accord

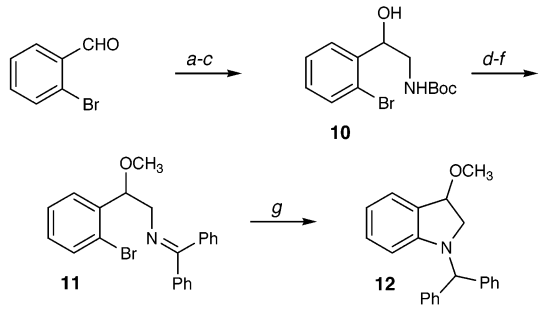
Table 4. Reductive 5-*Exo* Aryl Radical Cyclizations to Ketimines (eq 7)[a]



entry	R_1	R_2	R_3	6/7	7:3[b]	yield (%)[d]
1	CH_3	H	CH_3	**a**	42:1	86
2	H	CH_3	Ph	**b**	>20:1[c]	78
3	CH_3	*cis*-CH_3	Ph	**c**	13:1	84
4	CH_3	*trans*-CH_3	Ph	**d**	>200:1	79
5	*gem*-$(CH_3)_2$	H	CH_3	**e**	46:1	80

[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.

Scheme 1 [a]



[a] Reagents and conditions: (a) TMSCN, ZnI_2, CH_2Cl_2. (b) $LiAlH_4$, Et_2O, 0 °C. (c) $(Boc)_2O$, CH_2Cl_2 (65%, three steps). (d) NaH, Me_2SO_4, DMF, 0 °C. (e) CF_3CO_2H, CH_2Cl_2. (f) $Ph_2C{=}NH$, C_6H_6, room temperature (70%, three steps). (g) ^{n}Bu_3SnH, AIBN, C_6H_6, 80 °C (70%).

with expected ground state conformational influences.[17] Both unsubstituted (**2a**) and a *cis*-2,3-disubstituted indoline (**6c**) were formed with comparable efficiency (10:1 indoline:ArH), and this was further improved to the >200:1 level for *trans*-disubstituted indoline **7d**. The remaining variations (**7a**,**b**,**e**) provided interim ratios of indoline:ArH, all with synthetically useful isolated yields.

Electronic Effects. A characteristic of most metal-mediated aminations is a sensitivity of the catalyst to electronic variations in both coupling components (aryl halide and amine). Radical intermediates are not immune to these effects,[18] although the use of an aryl radical in these additions was expected to be advantageous owing to its weakly nucleophilic polar character.[19] Cyclizations of electronically neutral aryl radicals to ketimines of varying electron density are described in Table 2 (entries 1, 3−5). Additionally, all iterations of electron-rich/neutral/deficient aryl radical cyclizations to electron-rich/neutral/deficient ketimine were examined (Table 5). Dopamine-derived ketimines **8a**−**e** were cyclized to their respective indolines **9a**−**e** with comparable ease (Table 5, entries 1−5). Similarly, electron-deficient pyridyl radicals formed from **8f**−**h** produced azain-

(17) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305. (c) Chatgilialoglu, C.; Ingold, K. U.; Tse-Sheepy, I.; Warkentin, J. *Can. J. Chem.* **1983**, *61*, 1077. (d) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.
(18) Review: Tedder, J. M. *Tetrahedron* **1982**, *38*, 313. For a selected recent example, see: Della, E. W.; Kostakis, C.; Smith, P. A. *Org. Lett.* **1999**, *1*, 363.
(19) Suehiro, T.; Suzuki, A.; Tsuchida, Y.; Yamazaki, J. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3324.

Table 5. Reductive 5-*Exo* Aryl Radical Cyclizations to Ketimines (eq 8)[a]

8 9

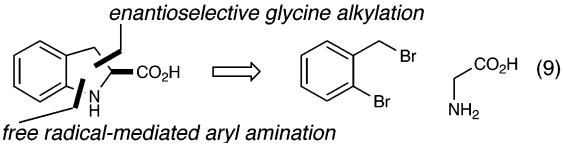
entry	R^1/Y	R^2	R^3	8/9	9:3[b]	yield (%)[c]
1	CH_3O/CH	Ph	CH_3	**a**	9:1	83
2	CH_3O/CH	Ph	CF_3	**b**	9:1	89
3	CH_3O/CH	Ph	Ph	**c**	12:1	64
4	CH_3O/CH	*o*-MeOPh	CH_3	**d**	nd	52
5	CH_3O/CH	*p*-MeOPh	Ph	**e**	5:1	47
6	H/N	Ph	Ph	**f**	4:1	60
7	H/N	*p*-CF_3Ph	CH_3	**g**	5.5:1	76
8	H/N	*p*-MeOPh	CH_3	**h**	5:1	55

[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 radical reduction measured by 400 MHz ^{1}H NMR of the untreated reaction mixture. [c] Isolated yield (two steps) after chromatography.

dolines **9f**−**h** in uniformly good yield (Table 5, entries 6−8). In these examples, the cyclization efficiency differed at most by a factor of 3.

To determine the viability of the present method for acid- or base-sensitive substrates, we targeted indoline **12** for synthesis (Scheme 1). The ketimine precursor was synthesized from *ortho*-bromobenzaldehyde through a sequence of cyanohydrin formation, reduction, and Boc protection to **10** followed by *O*-methylation, Boc deprotection, and transimination to arrive at the requisite benzophenone ketimine **11**. In the event, the radical-mediated amination proceeded cleanly to the 3-methoxy indoline **12**. Spectroscopic ananlysis (^{1}H NMR) of the crude reaction mixture did not reveal the presence of any *N*-diphenylmethyl indole. The desired indoline was purified by chromatography on neutral alumina, providing **12** in 70% yield. Complete conversion of **12** to *N*-diphenylmethyl indole occurred upon standing when exposed to air overnight.

Enantioselective Synthesis of Indoline α-Amino Acids. Indoline alkaloids have long been the target of total synthesis due to their prevalence in nature and their associated diverse biological activity.[20] This interest has driven the development of methods to construct or, more commonly, functionalize the indoline backbone. The importance of, and continuing need for, enantioselective indoline annulation protocols is clear from the impact that enantioselective Heck cyclizations[21] have recently had on alkaloid total synthesis.[22] To fill this void and demonstrate the utility of free radical-mediated aryl amination, we developed a new indoline annulation protocol that can be rendered stereoselective and utilizes nonaniline precursors (eq 9).



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

We first targeted protected indoline α-amino acid (**13a**),[23] a constrained form of the endogenous alkaloids phenyl alanine and proline. In the latter capacity, it was used in the development of the ACE inhibitor Pentopril.[24] *cyclo*-Dopa,[25] the constrained form of L-Dopa, occurs naturally in betanidin, a member of the betalain natural products. Additionally, reduction and deprotection of **13a** furnish an amino alcohol that has been used in asymmetric synthesis, an application that requires the availability of both enantiomers to access both product antipodes (Table 6).[26−28]

The requirement of an azomethine is common to the aminations described here and the immediate products of phase transfer-catalyzed alkylation (PTCA) of glycinyl imines pioneered by O'Donnell.[29] Recent advances in enantioselective variants of PTCA suggested a high probability of success.[30]

The *ortho*-bromobenzyl bromides required for the alkylation step were prepared by radical bromination of commercially available *ortho*-bromotoluene derivatives. Using the Corey protocol for alkylation, we found that the cinchonidinium salt (**A**, Table 4) provided the resulting (*S*)-phenyl alanine derivatives in uniformly good yield and high enantiomeric excess. In our hands, catalysts **A** and **B** obtained by large-scale synthesis provided products of higher ee if the ammonium salt was first chromatographed (silica gel, 2% MeOH/CH_2Cl_2).

Exposure of the aryl halides to tri-*n*-butyltin hydride in the presence of AIBN furnished the products of cyclization in good yield without the need for slow addition of ^{n}Bu_3SnH. Despite the possibility for direct aryl radical reduction by stannane, no evidence for this product was detected by GC/MS. It is not until an 8-fold excess of stannane is used that intermolecular aryl radical reduction becomes significant (5:1 cyclized:reduced).

(21) Asymmetric Heck cyclizations are generally limited to cyclic or 1,1-disubstituted olefins, although exceptions exist: (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (b) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. (c) Review: Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 8G.

(22) Representative examples: (a) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702. (b) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500. (c) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398. (d) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477. (e) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949.

(23) Two syntheses of **13** congeners were reported recently, both involving asymmetric hydrogenation (functionalization): (a) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451. (b) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614. For recent interest in Captopril-inspired ACE inhibitors, see: (c) wa Mutahi, M.; Nittoli, T.; Guo, L.; Sieburth, S. McN. *J. Am. Chem. Soc.* **2002**, *124*, 7363.

(24) Gruenfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, J. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277.

(25) There are no asymmetric syntheses of *cyclo*-Dopa; however, its synthesis from 3,4-dihydroxy phenylalanine has been reported: (a) Buchi, G.; Fliri, H.; Shapiro, R. *J. Org. Chem.* **1978**, *43*, 4765. (b) Hermann, K.; Dreiding, A. S. *Helv. Chim. Acta* **1975**, *58*, 1805.

(26) CBS-type catalysts and their derivatives: (a) Martens, J.; Danelsberg, C.; Behnen, W.; Wallbaum, S. *Tetrahedron: Asymmetry* **1992**, *3*, 347. (b) Jones, G. B.; Heaton, S. B.; Chapman, B. J.; Guzel, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3625. (*S*)-Indoline α-amino acid has been used further in asymmetric synthesis after transformation to the derived amino alcohol: (c) hydrogenation − Pasquier, C.; Naili, S.; Mortreux, A.; Agbossou, F.; Pelinski, L.; Brocard, J.; Eilers, J.; Reiners, I.; Peper, V.; Martens, *J. Organomet. Chem.* **2000**, *19*, 5723. (d) Asymmetric additions to aldehydes: Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4165.

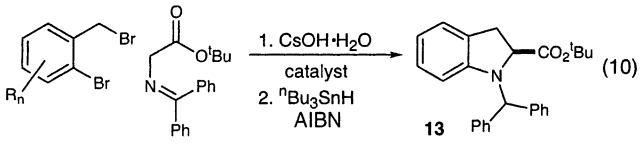
(27) Given the unavailability of *ent*-**13**, its octahydroindoline derivative is necessarily used to generate the enantiomeric products: Kim, Y. H. *Acc. Chem. Res.* **2001**, *34*, 955.

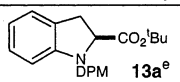
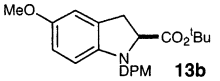
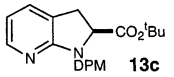
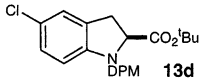
(28) Acquisition of *ent*-**10** and related derivatives has relied solely on resolution techniques.

(29) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 10.

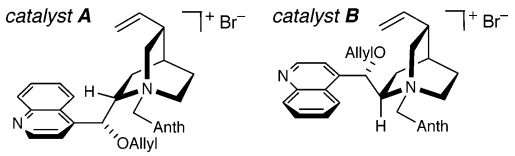
(30) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

Table 6. Enantioselective Indoline α-Amino Acid Synthesis (eq 10)[a]



entry	catalyst	product[b]	alkylation yield[c] (%ee)[d]	cyclization yield[c] (%)
1	A	 **13a**[e]	89 (96)	69
2	B	ent-**13a**	81 (93)	70
3	A	 **13b**	81 (94)	45[e]
4	B	ent-**13b**	74 (91)	55[e]
5	A	 **13c**	77 (96)	71
6	B	ent-**13c**	76 (86)	60
7	A	 **13d**	74 (93)	55
8	B	ent-**13d**	71 (94)	60

[a] See Supporting Information for complete experimental procedure. [b] Absolute configuration of **13a** is assigned by chemical correlation and is consistent with previous studies (ref 28); **13b**−**d** assigned by analogy. [c] Isolated yield. [d] Determined by HPLC using a chiral stationary phase. [e] **13b**: 91% ee, *ent*-**13b**: 87% ee.



Using this two step sequence, we cyclized electronically neutral (**13a**), rich (**13b**), and deficient (**13c**,**d**) aryl halides. In all cases, the enantiomeric indolines were synthesized with comparable ee by implementation of the analogous cinchonine catalyst.[31]

Discussion

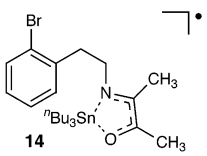
To achieve good ratios of indoline:ArH, the conditions must account for slowly propagating radicals. The cyclization manifold produces an α-methylbenzyl radical that is more sensitive to the effective stannane concentration because the radical is only weakly propagating (that is, hydrogen atom transfer from stannane to the α-methylbenzyl radical is slow vis-à-vis transfer to the aryl radical).[32] Hence, a survey of both stannane concentration and addition time (if necessary) enabled individual reaction optimization. Radical reactions in which acetophenone was present were not difficult to maintain, but benzophenone frequently complicated the cyclization, resulting in low yields of indoline and misleading results (lower **2**:ArH (**3**) ratios). Notwithstanding, benzophenone ketimine derivatives were advantageous practically because they are uniquely amenable to chromatography (neutral alumina), and residual benzophenone imine (or benzophenone from ketimine hydrolysis by adventitious water) could be separated in most cases.

In contrast to previous reports, production of the reduced aryl halide is minimal (<10%) in aryl radical cyclizations to acetophenone imine derivatives, but it was typically possible to measure its presence by GC/MS (comparison to an authentic sample).[6,7] The cyclizations described in Table 2 were effected using identical conditions, and ratios of **2**:ArH (**3**) were measured from the unpurified reaction mixture to gauge relative efficiency of cyclization. The relative yields are not always reliable for this purpose, but even though these conditions were only optimized for **2a**, yields for the remaining indolines under these circumstances are synthetically useful.

We considered the possibility that substitution of the ethylamine carbons might eventually slow the 5-*exo*-nitrogen cyclization so as to allow either 6-*endo*-carbon cyclization or direct aryl radical reduction to predominate. However, as Table 4 reveals, substitution increased the cyclization rate in accord with the Thorpe−Ingold effect.[17] It is notable that even substitution at the amine-bearing carbon does not increase the amount of tetrahydroisoquinoline product to the limit of detection. The least favorable substitution effect was observed in cyclization to a *cis*-2,3-dimethyl indoline, yet even the 13:1 ratio of indoline (**7c**):ArH was equal to the case in which there is no substitution (**2a**).

Cyclizations of aryl radicals to α-ketoimines were distinct in two respects: (1) they yield *only* indoline product − the reduced aryl halide could not be identified in the crude reaction mixture (>200:1), and (2) they provided the only indication of competitive stannyl radical addition to the azomethine. This latter aspect is significant in the greater context of nitrogen sources for carbon radical amination. Competitive direct reduction of the nitrogen functional groups by stannane has limited broader application of carbon radical amination. In fact, stannanes have long been used to reduce carbon−heteroatom π-bonds even in the absence of a radical initiator. Reports on the use of diarylazo[33] and azide[34] functional groups have acknowledged that direct reduction is a complicating factor, forcing the use of more reactive carbon radical precursors (alkyl iodide) and/or silanes ($(TMS)_3SiH$).

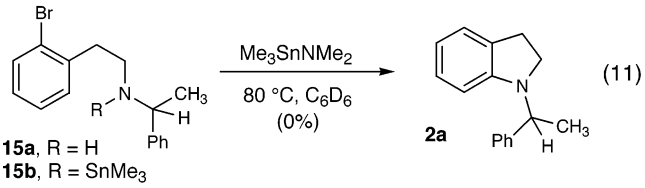
In our studies, the corresponding amine that would result from either radical or nonradical reduction of the ketimine was observed only in attempts to use fluorenone ketimine, as noted previously by Takano.[6] However, even with substrates possessing similar reduction potentials to fluorenone imine, no direct reduction to the amine could be detected.[35] The anomalous behavior of α-ketoimines indicates the possibility of *reversible* stannane addition to the ketimine (to either C=O or C=N) to form radical **14**, consistent with its exceptional radical accepting capabilities. The adduct of a stannyl radical with various *ortho*-quinones has been characterized by ESR spectroscopy and supports this possibility.[36] At low concentrations of stannyl radical, we suspect that **14** decomposes by release of $^nBu_3Sn^\bullet$ to a nonpropagative reaction. However, alongside this nonpro-



(31) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595.
(32) Crich, D.; Mo, X.-S. *J. Am. Chem. Soc.* **1998**, *120*, 8298.
(33) (a) Alberti, A.; Bedofni, N.; Benaglia, M.; Leardini, R.; Nanni, D.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Org. Chem.* **1992**, *57*, 607. (b) Leardini, R.; Lucarini, M.; Nanni, D.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Org. Chem.* **1993**, *58*, 2419. (c) Benati, L.; Placucci, G.; Spagnolo, P.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1684.

ductive pathway, stannyl radical reaction with aryl iodide can occur at higher AIBN/stannane ratios and addition rates. Once formed, the aryl radical then adds rapidly and selectively to the azomethine nitrogen.

The contention that reductive amination is not operative en route to indoline is supported by both the extreme hydrolytic sensitivity of a putative stannamide intermediate and Warkentin's observation that stannamides react rapidly (<30 min) at even 25 °C with stannane to form the amine and bistributyltin.[7b]



15a, R = H
15b, R = $SnMe_3$

2a (11)

We attempted to prepare **2a** from stannamide **15b** under conditions similar to the reactions described here (eq 11), but no indoline was observed after extended heating.

Conclusion

Direct addition of aryl radicals to the nitrogen of an azomethine is a more efficient, synthetically useful process than previously suggested. Significantly, these cyclizations differ from acyl radical and other carbon radical additions in that alternative cyclizations or mechanisms (electron transfer) to formally achieve the same goal are not possible. Moreover, the examples described here unequivocally demonstrate that polarization effects in the transition state are not essential for carbon−nitrogen bond formation.

A complementary aspect of this approach is the resiliency of the ketimines examined toward competitive direct reduction by stannane that is often problematic when using azo or azide nitrogen sources. The use of a ketimine also merges well with glycine catalytic asymmetric alkylation chemistry, providing streamlined access to enantioenriched indoline α-amino acids. The examples described here are the most efficient free radical-mediated aryl aminations reported to date and validate the utility of this approach for synthetic purposes. The mildness of the conditions is notable for an aryl amination, and studies are underway to determine its applicability to natural product total synthesis.[37]

Acknowledgment. This work was supported by NIGMS (GM-63577-01). E.N.P. thanks Boehringer-Ingelheim Pharmaceuticals for a postdoctoral fellowship. Acknowledgment is made to Indiana University and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

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

JA0284308

(34) Kin, S.; Joe, S. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521.
(35) Direct reduction of Schiff bases by $^{n}Bu_3SnH$ under thermal or free radical conditions is a well-established reaction: (a) Newmann, W. P.; Heymann, E. *Liebigs Ann. Chem.* **1965**, *683*, 249. (b) Werry, J.; Stamm, H.; Lin, P.-Y.; Falkenstein, R.; Gries, S.; Irngartinger, H. *Tetrahedron* **1989**, *45*, 5015.
(36) Alberti, A.; Hudson, A.; Pedulli, G. *J. Chem. Soc., Faraday Trans. 2* **1980**, *76*, 948.
(37) Cox, A. L.; Johnston, J. N. *Org. Lett.* **2001**, *3*, 3695.