J|A|C|S
ARTICLES
Published on Web 03/02/2004

Synthesis of Medium Ring Nitrogen Heterocycles via a Tandem Copper-Catalyzed C−N Bond Formation−Ring-Expansion Process

Artis Klapars, Sean Parris, Kevin W. Anderson, and Stephen L. Buchwald*

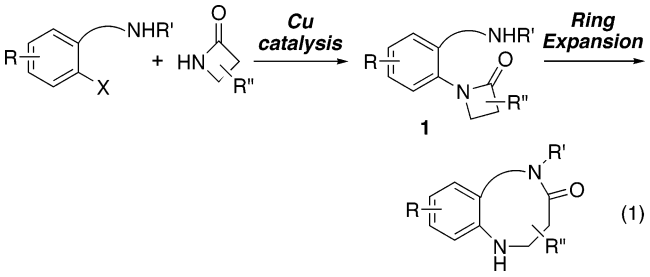
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received September 17, 2003; E-mail: sbuchwal@mit.edu

Abstract: A simple method for the preparation of medium ring heterocycles (7-, 8-, 9-, and 10-membered) has been developed. The process employs a Cu-catalyzed coupling of a β-lactam with an aryl bromide or iodide followed by intramolecular attack of a pendant amino group. In some instances, the intermediate β-lactam is observable but can be converted to the aza-heterocycle by catalysis. Acetic acid was found to be superior to transition metal complexes as a catalyst for this ring-expansion process.

Introduction

Medium ring heterocycles are often encountered in biologically active natural products as well as drug candidates. However, medium sized rings are difficult to prepare due to enthalpic and entropic reasons, and direct cyclization methods are ineffective unless certain conformational restraints are present in the acyclic precursor.[1] A potential solution to the formation of medium ring heterocycles is to employ a ring expansion of a β-lactam with a neighboring nitrogen nucleophile. Banfi and co-workers have elegantly demonstrated such a possibility for the preparation of 7-membered heterocycles.[2] Their work focused on a specific goal related to enzyme chemistry and required a lengthy synthesis to obtain the needed substrate.[2,3] We felt that *N*-arylated β-lactams **1** could be readily accessible using our recently developed copper-catalyzed aryl amidation reaction, which tolerates a wide range of functional groups including aliphatic amines, anilines, and certain secondary amides.[4,5] Herein, we report a general coupling/ring-expansion route to 7-, 8-, 9-, and 10-membered nitrogen heterocycles.



(1)

Results and Discussion

We set out to test our proposal using 2-bromobenzylamine and 2-azetidinone as the coupling partners (Table 1, entry 1). Gratifyingly, the desired 8-membered heterocycle was isolated in 96% yield and none of the *N*-arylated β-lactam **1** was observed, indicating that a facile domino process involving the C−N coupling and the subsequent ring expansion (eq 1) had taken place. Interestingly, no ligand was required for the coupling reaction in entry 1. Presumably, the amino group in 2-bromobenzylamine binds the copper(I) precatalyst, activating the aryl bromide toward oxidative addition. Although not investigated in every case, the addition of a diamine ligand, *N*,*N*′-dimethylethylenediamine, was nevertheless found beneficial for many cases in Table 1, particularly when *N*-substituted bromobenzylamines were used as coupling partners.

As shown in Table 1, the reaction tolerates substituents on the β-lactam ring (entry 2), electron-donating groups in the aryl bromide (entry 3), and an aliphatic OH group (entry 4). If a norephedrine-derived aryl bromide containing a relatively bulky *N*-substituent was used (entry 5), a mixture of the desired product and the β-lactam intermediate **1** was obtained. To address this problem, we briefly explored a means to catalyze the ring-expansion step, which essentially is a transamidation

(1) Reviews: (a) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125. (b) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (c) Evans, P. A.; Holmes, B. *Tetrahedron* **1991**, *47*, 9131. Selected examples: (d) Lindström, U. M.; Somfai, P. *Chem.-Eur. J.* **2001**, *7*, 94. (e) Bieräugel, H.; Jansen, T. P.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2002**, *4*, 2673. (f) Derrer, S.; Davies, J. E.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2957.

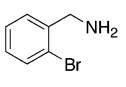
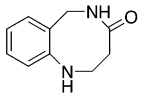
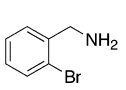
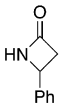
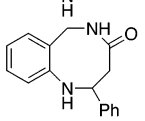
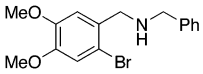
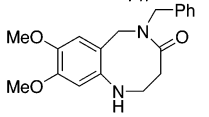
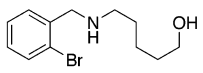
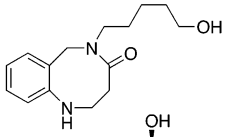
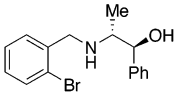
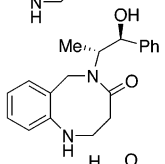
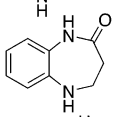
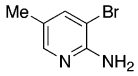
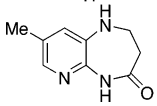
(2) (a) Banfi, L.; Guanti, G.; Rasparini, M. *Tetrahedron Lett.* **1998**, *39*, 9539. (b) Banfi, L.; Guanti, G.; Rasparini, M. *Eur. J. Org. Chem.* **2003**, 1319.

(3) For a different ring-expansion method that utilizes β-lactams to prepare 7−9-membered ring azaheterocycles: Begley, M. J.; Crombie, L.; Daigh, D.; Jones, R. C. F.; Osborne, S.; Webster, R. A. B. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2027.

(4) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(5) Examples of the use of β-lactams as intermediates in organic synthesis: (a) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383. (b) Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599. (c) Lee, H. K.; Kim, E.-K.; Pak, C. S. *Tetrahedron Lett.* **2002**, *43*, 9641 and references therein. (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813. (e) Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237.

Table 1. Preparation of 7- and 8-Membered Nitrogen Heterocycles[a]

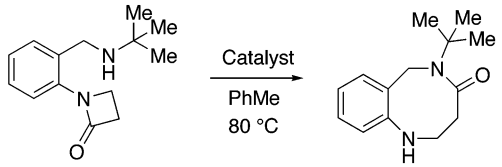
Entry	Aryl Halide	Lactam	Product	Yield[b]
1				96%[c]
2				88%
3				83%
4				90%
5				72%[d]
6				92%[e,f]
7				59%[f]

[a] Performed with 5.0 mol % CuI, 10 mol % *N*,*N*′-dimethylethylenediamine, and 2 equiv of K_2CO_3 in PhMe at 110 °C for 22−24 h. [b] Isolated yields (average of two runs); >95% purity as determined by GC and ^{1}H NMR. [c] Coupling reaction performed without the ligand. [d] Transamidation conditions: 2 equiv of AcOH, THF, 60 °C, 4 h. [e] Coupling reaction was performed at 100 °C, 5 h. [f] Transamidation conditions: 50 mol % $Ti(OiPr)_4$, dioxane, 110 °C, 24 h.

reaction (eq 1). Several Lewis acid catalysts for intermolecular transamidation reactions have been recently disclosed by Gellman and Stahl.[6] We found that two of these catalysts, $Sc(OTf)_3$ and $Ti(NMe_2)_4$, indeed accelerated the ring-expansion reaction in a model system (Table 2, entries 2−5). We also found that acetic acid turned out to be even more effective than the Lewis acidic metal catalysts and slightly better than the 2:1 Et_3N/HOAc that had previously been employed (Table 2, entries 6−8).[7] Using 2 equiv of AcOH in THF for 4 h at 60 °C, we were able to convert the crude mixture of the C−N coupling reaction products obtained in entry 5 (Table 1) into the desired ring-expanded product.

A relatively slow ring-expansion step was also encountered in the preparation of 7-membered heterocycles starting with 2-haloanilines (Table 1, entries 6−7); less than 5% of the desired ring expanded product was observed at the end of the copper-catalyzed coupling reaction. Fortunately, the desired 7-membered heterocycles could be obtained if the crude mixture of the coupling reaction products was treated with 50 mol % of

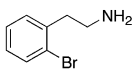
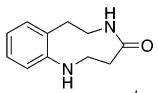
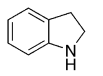
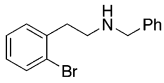
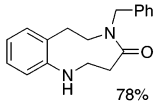
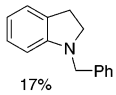
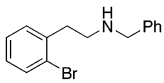
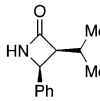
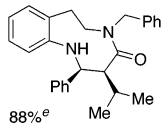
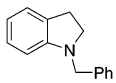
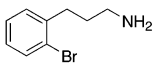
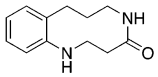
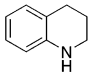
Table 2. Catalysts for the Ring-Expansion Reaction



entry	catalyst	amount of catalyst	time	conversion	yield[a]
1	none	none	24 h	19%	7%
2	$Sc(OTf)_3$	50 mol %	24 h	64%	55%
3	$Sc(OTf)_3$	5 mol %	24 h	20%	<5%
4	$Ti(NMe_2)_4$	50 mol %	24 h	96%	<5%
5	$Ti(NMe_2)_4$	5 mol %	24 h	78%	27%
6	AcOH	50 mol %	3.5 h	>99%	94%
7	AcOH	5 mol %	16 h	>99%	98% (95%)
8	AcOH/TEA	5/10 mol %	20 h	>99%	92%

[a] GC yield (isolated yield).

Table 3. Preparation of 9- and 10-Membered Nitrogen Heterocycles[a]

Entry	Aryl Bromide	Lactam	Product[b]	Sideproduct[c]
1			 68%,[d] 48%[c]	 18%,[d] 37%
2			 78%	 17%
3			 88%[e]	 3%
4			 68%[f]	 13%, 48%[d]

[a] Performed with 5.0 mol % CuI, 10 mol % *N*,*N*′-dimethylethylenediamine, and 2 equiv of K_2CO_3 in PhMe at 110 °C for 22−24 h. [b] Isolated yields (average of two runs); >95% purity as determined by GC and ^{1}H NMR. [c] GC yield. [d] Coupling reaction was performed without the ligand. [e] Transamidation conditions: 10 equiv of AcOH, 10 equiv of NEt_3, dioxane, 110 °C, 24 h. [f] Transamidation conditions: 2 equiv of AcOH, THF, 60 °C, 4 h.

$Ti(OiPr)_4$ in toluene at 110 °C. Interestingly, different catalysts are optimal for the transamidation reaction of the aniline and alkylamine nucleophiles, which is most likely due to the differences in the relative basicity of anilines and alkylamines.

The C−N coupling−ring-expansion reaction could also be extended to the preparation of 9- and 10-membered rings. However, direct cyclization of the aryl bromide substrate providing either an indoline or a tetrahydroquinoline competed with the desired process (Table 3).[8] The ratio of the desired medium ring product to the undesired 5- or 6-membered ring side-product exhibited an interesting dependence on the diamine ligand. Thus, the *N*,*N*′-dimethylethylenediamine ligand increased the yield of the undesired 5-membered heterocycle (Table 3, entry 1) while decreasing the amount of the undesired 6-membered heterocycle (Table 3, entry 4). Formation of the 5-mem-

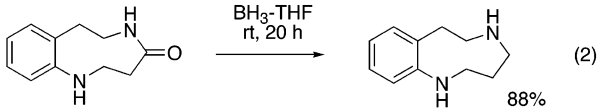
(6) (a) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422. See also: (b) Cheng, J.; Deming, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 9457.

(7) It is important to note that we are only comparing intramolecular transamidation processes, which are relatively facile as compared to intermolecular ones. Thus, the dependence on the nature of the catalyst easily could be different for these two classes of this reaction.

(8) For intramolecular Cu-catalyzed aryl amination reactions, see: Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231.

bered ring side-product was also diminished for an *N*-benzylated aryl bromide substrate (Table 3, entries 2 and 3).

Presumably, the *N*-benzyl substituent decreases the propensity of the amine to coordinate to the active copper catalyst, thus preventing the direct cyclization. In some cases (Table 3, entries 3[9] and 4), the ring-expansion step was relatively slow, and therefore acetic acid was successfully employed again as a catalyst. Finally, the structural diversity of the heterocyclic products accessible via this method could be further expanded using borane−THF reduction of the amide group (eq 2).



(2)

Conclusion

In summary, we have developed a procedure for the preparation of 7-, 8-, 9-, and 10-membered nitrogen heterocycles via a domino process involving a copper-catalyzed C−N coupling reaction followed by a ring-expansion step proceeding through an intramolecular transamidation reaction. The simplicity of the process and the relative lack of methods to prepare 7−10-membered nitrogen heterocycles should render this method of great use to synthetic chemists. We have also found that the transamidation reaction can be efficiently catalyzed by acetic acid (in the case of alkylamine substrates) or $Ti(OiPr)_4$ (for aniline substrates). We believe that these catalysts offer a significant advantage over the previously reported transamidation catalysts in the case of intramolecular processes.

Experimental Section

The following are select procedures for the Cu-catalyzed C−N bond formation−ring-expansion process. A full account of the reaction conditions and characterization of substrates and products can be found in the Supporting Information.

2,3,5,6-Tetrahydro-1*H*-benzo[*b*][1,5]diazocin-4-one (Table 1, Entry 1). A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol %), 2-azetidinone (177 mg, 1.20 mmol), and K_2CO_3 (280 mg, 2.03 mmol), evacuated, and backfilled with argon. 2-Bromobenzylamine (125 μL, 1.00 mmol) and toluene (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve, and the reaction mixture was stirred at 110 °C for 24 h in a preheated oil bath. After the resulting green-brown suspension was allowed to reach room temperature, dodecane (46 μL, internal GC standard) and CH_2Cl_2 (3 mL) were added, and the supernatant solution was analyzed by GC to indicate >99% conversion of the aryl bromide starting material. The reaction mixture was filtered through a silica gel plug (0.5 × 0.5 cm) eluting with 10:1 CH_2Cl_2−MeOH (50 mL), the filtrate was concentrated, and the residue was purified by column chromatography on silica gel (CH_2Cl_2−MeOH 20:1) to provide the desired product as a pale yellow solid (167 mg, 95% yield). mp: 109−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16−7.09 (m, 2H), 6.90 (td, J = 7.6, 1.2 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.40 (br s, 1H), 4.37 (d, J = 7.7 Hz, 2H), 3.94 (br s, 1H), 3.40−3.33 (m, 2H), 2.87−2.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 148.9, 130.9, 129.7, 129.2, 122.3, 121.5, 45.7, 45.3, 39.1. IR (neat, cm^{-1}): 3319, 1653, 1604, 1485, 1409, 1093, 756. Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86. Found: C, 68.42; H, 6.94.

2-Phenyl-2,3,5,6-tetrahydro-1*H*-benzo[*b*][1,5]diazocin-4-one (Table 1, Entry 2). A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol %), (*rac*)-4-phenyl-2-azetidinone (177 mg, 1.20 mmol), and K_2CO_3 (280 mg, 2.03 mmol), evacuated, and backfilled with argon. *N*,*N*′-Dimethylethylenediamine (11 μL, 0.10 mmol, 10 mol %), 2-bromobenzylamine (125 μL, 1.00 mmol), and toluene (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve, and the reaction mixture was stirred at 110 °C for 25 h in a preheated oil bath. The resulting yellow suspension was allowed to reach room temperature, transferred to a solution of 30% aqueous NH_3 (5 mL) in water (20 mL), and extracted with ethyl acetate (3 × 75 mL). The combined organic layers were dried (Na_2SO_4) and concentrated by rotary evaporation. The residue was dissolved in hot ethyl acetate (∼10 mL). To this solution was added hot hexane (∼10 mL), and the product was allowed to crystallize from the solution in the refrigerator overnight. The supernatant solution containing some yellow, gelatinous precipitate was decanted, and the white crystals remaining in the flask were dried under vacuum to provide the desired product (230 mg, 92% yield). mp: 170−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.30 (m, 5H), 7.20−7.08 (m, 2H), 6.97 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.33 (br s, 1H), 4.56 (dd, J = 15.4, 8.6 Hz, 1H), 4.41 (dd, J = 15.4, 6.8 Hz, 1H), 4.26 (dd, J = 9.8, 2.3 Hz, 1H), 3.71 (s, 1H), 3.30 (dd, J = 14.0, 9.8 Hz, 1H), 2.94 (dd, J = 14.0, 2.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 147.4, 144.9, 130.3, 129.2, 128.9, 128.0, 126.2, 122.7, 122.5, 60.7, 45.8, 45.2. IR (neat, cm^{-1}): 3293, 1654, 1472, 1457, 757, 731, 699. Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39. Found: C, 76.20; H, 6.45.

5-[(1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-2,3,5,6-tetrahydro-1*H*-benzo[*b*][1,5]-diazocin-4-one (Table 1, Entry 5). A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol %), 2-azetidinone (86 mg, 1.21 mmol), and K_2CO_3 (280 mg, 2.03 mmol), evacuated, and backfilled with argon. A solution of (1*S*,2*R*)-*N*-(2-bromobenzyl)-norephedrine (325 mg, 1.01 mmol) in PhMe (1.0 mL) was added under argon followed by *N*,*N*′-dimethylethylenediamine (11 μL, 0.10 mmol, 10 mol %). The Schlenk tube was sealed with a Teflon valve, and the reaction mixture was stirred at 110 °C for 23 h in a preheated oil bath. The resulting tan suspension was allowed to reach room temperature, transferred to a solution of 30% aqueous NH_3 (5 mL) in water (20 mL), and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product mixture was dissolved in THF (10 mL) and, using a syringe, was transferred to a Schlenk tube filled with argon and capped with a rubber septum. Acetic acid (115 μL, 2.01 mmol) was added to the Schlenk tube, the rubber septum was replaced with a Teflon valve, and the sealed Schlenk tube was placed in an oil bath preheated to 110 °C. After being stirred at 60 °C for 4 h, the resulting pale yellow solution was allowed to reach room temperature, poured into 1 M aqueous Na_2CO_3 (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography on silica gel (CH_2Cl_2−MeOH 30:1). The product was dissolved in CH_2Cl_2 (10 mL) and concentrated to ∼2 mL followed by addition of hexane (∼15 mL). The resulting crystals were collected and dried to give the desired product (215 mg, 69% yield) as fine, white needles. mp: 213-215 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.14 (m, 4H), 7.10−7.05 (m, 3H), 6.87 (td, J = 7.8, 1.4 Hz), 6.71 (dd, J = 7.8, 1.4 Hz), 5.82 (s, 1H), 4.79 (s, 1H), 4.66 (d, J = 16.0 Hz, 1H), 4.32 (d, J = 16.0 Hz, 1H), 4.13 (br t, J = 5.3 Hz, 1H), 3.60−3.45 (m, 2H), 3.34−3.27 (m, 1H), 3.10−2.93 (m, 2H), 1.12 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 149.4, 142.9, 131.5, 129.2, 128.0, 126.9, 125.9, 123.0, 120.3, 118.9, 76.4, 65.9, 54.7, 44.2, 39.5, 9.6. IR (neat, cm^{-1}): 3355, 3215, 1618, 1604, 1489, 1472, 1037, 767, 704. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14. Found: C, 73.22; H, 7.13.

8-Methyl-1,2,3,5-tetrahydropyrido[3,4-*b*][1,4]diazepin-4-one (Table 1, Entry 7). A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol %), 2-amino-3-bromo-5-methylpyridine (188 mg, 1.01 mmol), 2-azetidinone (86 mg, 1.21 mmol), and K_2CO_3 (280 mg, 2.03 mmol), evacuated, and backfilled with argon. *N*,*N*′-Dimethylethylene-

(9) The stereochemistry of the product in Table 3, entry 3, was determined to be as shown by X-ray crystallography (see Supporting Information).

diamine (11 μL, 0.10 mmol, 10 mol %) and toluene (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve, and the reaction mixture was stirred at 110 °C for 23 h in a preheated oil bath. The resulting brown-black suspension was allowed to reach room temperature, filtered through a silica gel plug (0.5 × 0.5 cm) eluting with 10:1 CH_2Cl_2−MeOH (50 mL), and the red filtrate was concentrated. The semisolid residue in the evaporation flask (ca. 155 mg) was transferred to a Schlenk tube, which was then evacuated, backfilled with argon, and sealed with a rubber septum. The evaporation flask was rinsed with warm toluene (2 + 2 × 1.5 mL) under argon, and the washings were transferred to the Schlenk tube using a syringe. $Ti(OiPr)_4$ (148 μL, 0.501 mmol) was added to the Schlenk tube under argon, the septum on the Schlenk tube was replaced with a Teflon valve under a stream of argon, and the sealed Schlenk tube was placed in an oil bath preheated to 110 °C. After being stirred at 110 °C for 24 h, the reaction mixture was allowed to reach room temperature and then filtered through a silica gel plug (0.5 × 0.5 cm) eluting with 10:1 CH_2Cl_2−MeOH (50 mL). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (CH_2Cl_2−MeOH 20:1) to provide the desired product as a pink solid (106 mg, 59% yield). mp: 192−194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 7.72 (s, 1H), 6.80 (s, 1H), 3.95 (br s, 1H), 3.58−3.49 (m, 2H), 2.86−2.80 (m, 2H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 139.0, 136.6, 133.3, 129.5, 126.6, 41.9, 38.3, 17.4. IR (neat, cm^{-1}): 3354, 3324, 1653, 1605, 1533, 1491, 1394, 1283, 855. Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26. Found: C, 60.72; H, 6.24.

5-*tert*-Butyl-2,3,5,6-tetrahydro-1*H*-benzo[*b*][1,5]diazocin-4-one (Table 2, Entry 6: Effect of Various Transamidation Catalysts on the Ring-Expansion Reaction). Two of eight Schlenk tubes were charged with the following amounts of $Sc(OTf)_3$: 12.3 mg (0.025 mmol, 5 mol %) and 123 mg (0.25 mmol, 50 mol %). All eight Schlenk tubes were evacuated and backfilled with argon. A solution of 1-[2-(*tert*-butylaminomethylphenyl]-2-azetidinone (116 mg, 0.500 mmol) and dodecane (225 μL, internal GC standard) in toluene (2.5 mL) was added to each Schlenk tube under argon followed by the following catalysts in five of the Schlenk tubes: acetic acid, 1.4 μL (0.025 mmol, 5 mol %) and 14 μL (0.25 mmol, 50 mol %); acetic acid/triethylamine, 1.4 μL of acetic acid (0.025 mmol, 5 mol %)/7.0 μL of triethylamine (0.050 mmol, 10 mol %); and $Ti(NMe_2)_4$, 5.8 μL (0.025 mmol, 5 mol %) and 58 μL (0.25 mmol, 50 mol %). The Schlenk tubes were sealed with Teflon valves, and the reaction mixtures were stirred in a preheated oil bath at 80 °C and monitored by GC analysis. Ethyl acetate (3 mL) and 1 M aqueous Na_2CO_3 (2 mL) were added to each Schlenk tube, and the organic layer was analyzed by GC. The results are presented in Table 2. The combined organic layers (Table 2, entry 6) were dried (Na_2SO_4) and concentrated by rotary evaporation, and the residue was purified by column chromatography on silica gel (CH_2Cl_2−MeOH 10:1) to provide the desired product as a white solid (110 mg, 95% yield). mp: 195−198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05−7.09 (m, 2H), 6.79 (td, *J* = 7.4, 0.9 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 4.68 (s, 2H), 4.05 (br s, 1H), 3.51 (m, 2H), 3.02 (m, 2H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 150.4, 131.7, 128.2, 124.3, 119.5, 118.6, 57.7, 49.1, 44.6, 41.1, 28.6. IR (neat, cm^{-1}): 3426, 1630, 1473, 1415, 1357, 1342, 756. Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68. Found: C, 72.38; H, 8.75.

***cis*-5-Benzyl-3-isopropyl-2-phenyl-1,2,3,5,6,7-hexahydrobenzo[*f*]-[1,5]diazonin-4-one (Table 3, Entry 3).** A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol %), (*rac*)-*cis*-3-isopropyl-4-phenyl-2-azetidinone (226 mg, 1.20 mmol), and K_2CO_3 (280 mg, 2.03 mmol), evacuated, and backfilled with argon. *N*-Benzyl-2-(2-bromophenyl)ethylamine (227 μL, 1.00 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.10 mmol, 10 mol %), and toluene (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve, and the reaction mixture was stirred at 110 °C for 24 h in a preheated oil bath. The resulting dark purple-gray suspension was allowed to reach room temperature, transferred to a solution of 30% aqueous NH_3 (5 mL) in water (20 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. NMR analysis of the crude product indicated >99% conversion of the aryl bromide with ∼90% formation of the unexpanded *cis*-*N*-[2-(2-benzylamino)-ethylphenyl]-3-isopropyl-4-phenyl-2-azetidinone, ∼3% yield of *N*-benzylindoline, and only ∼2% yield of the desired 5-benzyl-3-isopropyl-2-phenyl-1,2,3,5,6,7-hexahydrobenzo[*f*][1,5]diazonin-4-one. The crude product mixture was dissolved in dioxane (10 mL) and, using a syringe, was transferred to a Schlenk tube filled with argon and capped with a rubber septum. Acetic acid (0.58 mL, 10 mmol) and Et_3N (1.4 mL, 10 mmol) were added to the Schlenk tube, the rubber septum was replaced with a Teflon valve, and the sealed Schlenk tube was placed in an oil bath preheated to 110 °C. After being stirred at 110 °C for 23 h, the resulting tan solution was allowed to reach room temperature, poured into 1 M aqueous Na_2CO_3 (50 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography on silica gel (hexanes−ethyl acetate 4:1). The product was recrystallized from hot hexane (∼5 mL) to provide the desired *cis*-5-benzyl-3-isopropyl-2-phenyl-1,2,3,5,6,7-hexahydrobenzo[*f*][1,5]diazonin-4-one (351 mg, 88% yield) as colorless cubes. mp: 108−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.20 (m, 11H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 5.33 (d, *J* = 14.4 Hz, 1H), 4.70 (s, 1H), 4.18 (d, *J* = 14.4 Hz, 1H), 3.62−3.45 (m, 3H), 3.10 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.78 (dd, *J* = 15.5, 8.2 Hz, 1H), 2.69 (dd, *J* = 10.6, 4.0 Hz, 1H), 2.00−1.86 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 146.6, 139.7, 137.6, 134.1, 130.4, 128.7, 128.5, 128.3, 127.6, 127.4, 127.32, 127.26, 123.4, 123.0, 66.3, 53.3, 50.1, 48.2, 34.2, 27.1, 21.9, 20.4. IR (neat, cm^{-1}): 3368, 1637, 1496, 1447, 757, 731, 699. Anal. Calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.59. Found: C, 81.38; H, 7.89.

2,3,5,6,7,8-Hexahydro-1*H*-benzo[*f*][1,5]diazecin-4-one (Table 3, Entry 4). A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol %), 2-azetidinone (86 mg, 1.21 mmol), and K_2CO_3 (280 mg, 2.03 mmol), evacuated, and backfilled with argon. 3-(2-Bromophenyl)-propylamine (160 μL, 1.00 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.10 mmol, 10 mol %), and toluene (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve, and the reaction mixture was stirred at 110 °C for 23 h in a preheated oil bath. The resulting tan suspension was allowed to reach room temperature, transferred to a solution of 30% aqueous NH_3 (5 mL) in water (10 mL), and extracted with CH_2Cl_2 (3 × 15 mL). GC analysis of the extract indicated >99% conversion of the aryl bromide with ∼13% yield of 1,2,3,4-tetrahydroquinoline. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product mixture was dissolved in THF (10 mL) and, using a syringe, was transferred to a Schlenk tube filled with argon and capped with a rubber septum. Acetic acid (115 μL, 2.01 mmol) was added to the Schlenk tube, the rubber septum was replaced with a Teflon valve, and the sealed Schlenk tube was placed in an oil bath preheated to 110 °C. After being stirred at 60 °C for 4 h, the resulting pale yellow solution was allowed to reach room temperature, poured into a solution of 30% aqueous NH_3 (10 mL) in water (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography on silica gel (CH_2Cl_2−MeOH 20:1) to provide the desired product (140 mg, 69% yield) as a white solid. mp: 161−163 °C. The ^{1}H and ^{13}C NMR spectra displayed two sets of signals due to rotamers of the cyclic amide in a 2:3 ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19−7.06 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 0.4H), 6.94 (d, *J* = 8.0 Hz, 0.6H), 6.87−6.79 (m, 1H), 5.78 (br s, 0.4H), 4.91 (br s, 0.6H), 4.00−3.86 (m, 0.6H), 3.80−3.50 (m, 3.4H), 3.15−2.90 (br m, 1H), 2.80−2.64 (br m, 0.8H), 2.60−2.45 (br m, 1.8H), 2.28 (t, *J* = 5.8 Hz, 1.2 Hz), 2.30−1.82 (br m, 1.8H), 1.74−1.62 (br m, 0.4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 173.5, 147.2, 145.6, 132.5, 131.6, 130.8, 129.0, 128.4, 127.8, 121.5, 121.0, 118.2, 117.2, 45.8, 42.5, 40.9, 40.4, 37.2, 32.4, 32.3, 31.1, 26.9, 24.3. IR (neat, cm^{-1}):

3372, 3291, 1652, 1583, 1505, 1457, 743. Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89. Found: C, 70.41; H, 8.03.

Acknowledgment. This paper is dedicated to the memory of our friend and colleague, Professor Satoru Masamune, in honor of his seminal contributions to the field of organic chemistry. We thank the National Institutes of Health (GM 45906) for supporting this work. We are grateful to Pfizer, Merck, Novartis, Lundbeck, and Rhodia. We thank the Cambridge-MIT Institute for support of S.P. and Pharmaceutical solutions for additional funds. We thank Mr. Timothy Barder for determining the crystal structure of the product in Table 3, entry 3.

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

JA038565T