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Concise Copper-Catalyzed Synthesis of Tricyclic Biaryl Ether-Linked Aza-Heterocyclic Ring Systems

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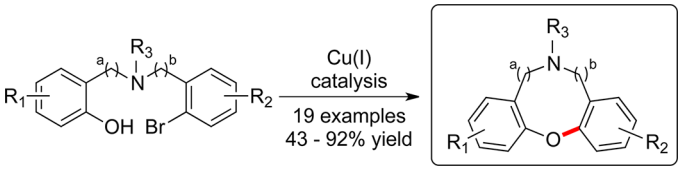
ABSTRACT



A new method for the synthesis of tricyclic biaryl ether-linked ring systems incorporating seven-, eight-, and nine-membered ring amines is presented. In the presence of catalytic quantities of copper(I), readily accessible acyclic precursors undergo an intramolecular carbon−oxygen bond-forming reaction facilitated by a "templating" chelating nitrogen atom. The methodology displays a broad substrate scope, is practical, and generates rare and biologically interesting tricyclic heteroaromatic products that are difficult to access by other means.

Tricyclic aza-hetereocyclic ring systems incorporating a biaryl ether motif are present in a number of biologically active and pharmaceutically relevant compounds and thus constitute very attractive synthetic targets. For example, the dibenzooxazepinones[1] and dibenzooxazepines[2] have been shown to exhibit significant biological activities (Figure 1). The dibenz[*b*,*g*][1,5]oxazocines, which contain a tricyclic biaryl ether-linked ring system incorporating an eight-membered ring amine, are comparatively much less well studied, but some are known to be CNS active and are used for the treatment of pain and/or inflammation.[3] Despite these interesting biological properties, examples are relatively rare; analogous compounds containing seven- and nine-membered amine ring systems are extremely scarce. Consequently, compounds of this sort (indeed, seven-nine membered cyclic biaryl ethers in general) are under-represented in current small molecule screening libraries. This can mainly be attributed to synthetic difficulties; for example, there are notable problems associated with medium ring synthesis, with medium ring biaryl scaffolds representing especially challenging targets.[4,5] Overall, there are a lack of

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(1) For examples, see: (a) Wang, L.; Sullivan, G. M.; Hexamer, L. A.; Hasvold, L. A.; Thalji, R.; Przytulinska, M.; Tao, Z.; Li, G.; Chen, Z.; Xiao, Z.; Gu, W.; Xue, J.; Bui, M.; Merta, P.; Kovar, P.; Bouska, J. J.; Zhang, H.; Park, C.; Stewart, K. D.; Sham, H. L.; Sowin, T. J.; Rosenberg, S. H.; Lin, N. *J. Med. Chem.* **2007**, *50*, 4162. (b) Klunder, J. M.; Hargrave, K. D.; West, M.; Cullen, E.; Pal, K.; Behnke, M. L.; Kapadia, S. R.; McNeil, D. W.; Wu, J. C.; Chow, G. C. *J. Med. Chem.* **1992**, *35*, 1887. (c) Lu, S. M.; Maggi, C. A.; Gensini, M.; Bigioni, M.; Parlani, M.; Giolitti, A.; Fratelli, M.; Valli, C.; Terao, M.; Garattini, E. *ACS Med. Chem. Lett.* **2010**, *1*, 411. For Sintamil, see, for example: (d) David, J.; Grewal, R. S. *Indian J. Exp. Biol.* **1974**, *12*, 225.

(2) For examples, see: (a) Jiang, X. L.; Lee, G. T.; Prasad, K.; Repic, O. *Org. Process Res. Dev.* **2008**, *12*, 1137. (b) Sakaki, J.; Konishi, K.; Kishida, M.; Gunji, H.; Kanazawa, T.; Uchiyama, H.; Fukaya, H.; Mitani, H.; Kimura, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4808. (c) Ebisawa, M.; Umemiya, H.; Ohta, K.; Fukasawa, H.; Kawachi, E.; Christoffel, G.; Gronemeyer, H.; Tsuji, M.; Hashimoto, Y.; Shudo, K.; Kagechika, H. *Chem. Pharm. Bull* **1999**, *47*, 1778. For Loxapine, see for example: (d) Chakrabarti A.; Bagnall, A. M.; Chue, P.; Fenton, M.; Palaniswamy, V.; Wong, W.; Xia, J. Loxapine for schizophrenia. *Cochrane Database of Systematic Reviews* 2007, Issue 4, Art. No. CD001943.

(3) (a) Ouyang, X.; Chen, Z.; Liu, L.; Dominguez, C.; Kiselyove, A. S. *Tetrahedron* **2000**, *56*, 2369. (b) Ouyang, X.; Kiselyove, A. S. *Tetrahedron Lett.* **1999**, *40*, 5827. See, for example: (c) Ohgog, T.; Tanaka, S.; Fujimoto, M.; Kitahara, A. *Yakugaku Zassi* **1977**, *97*, 24. (d) Tanaka, S.; Hashimoto, K. 6-substituierte 6,7-dihydro-5H-dibenzo b.g. 1.5 Oxazocine und Thiazocine und Verfahren zu deren Herstellung. *Ger. Offen.* DE 2044508, May 1971. (e) Joergensen, T. K.; Andersen, K. E.; Andersen, H. S.; Hohlweg, R.; Madsen, P.; Olsen, U. B. *Novel Heterocyclic Compounds.* WO 9631497 A1, October 1996.

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efficient, concise, and flexible strategies toward diversely substituted dibenz[*b*,*g*][1,5]oxazocines and equivalent biaryl ethers with seven- and nine-membered ring amines. New methodology of broad utility for the synthesis of these scaffolds is needed so that their biological usefulness can be investigated and exploited further.

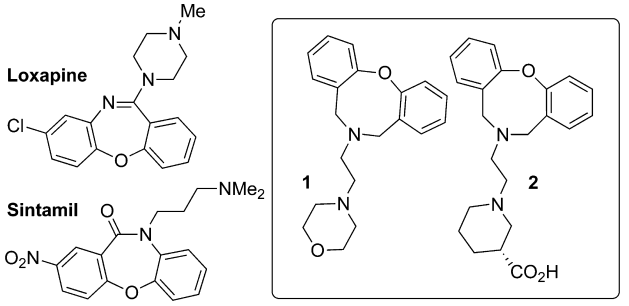
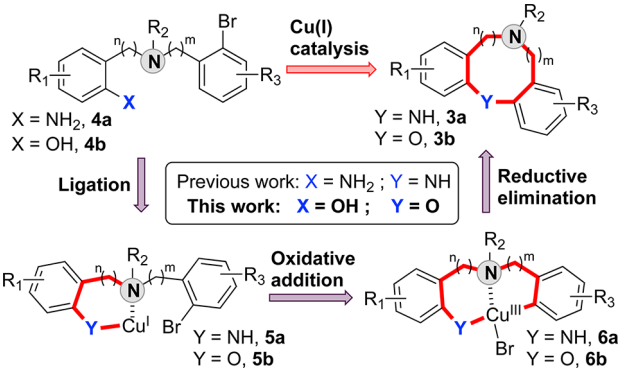


Figure 1. Examples of biologically active compounds based around *O*-linked medium-ring biaryl scaffolds. Loxapine[2d] (a dibenzooxazepine) is used in the treatment of schizophrenia, and Sintamil[1d] (a dibenzooxazepinone) has antidepressive activity. Compounds **1** and **2** are dibenz[*b*,*g*][1,5]oxazocines; **1** has antidepressive activity[3d], and **2** has potential for the treatment of pain and/or inflammation.[3e]

Recently, we reported the development of a novel copper-catalyzed strategy for the synthesis of medium ring nitrogen-linked biaryl systems **3a** (Scheme 1).[6] Our approach was based around the direct *N*-arylation of acyclic precursors of the general form **4a**, which incorporated a "templating" aliphatic nitrogen atom in addition to an aniline nitrogen and aryl bromide. Our mechanistic hypothesis is that both the aniline nitrogen and aliphatic templating nitrogen atom bind to the copper atom, forming a species, **5a**, in which the copper metal is incorporated in a chelate with the substrate. This ligation is followed by oxidative addition to the aryl halide, forming **6a**, and subsequent reductive elimination yields the cyclized product. The presence of the templating nitrogen atom was found to be crucial for cyclization.[7] We envisaged that the same mechanistic blueprint could be applied to a carbon–oxygen bond formation manifold, which would enable access to oxygen-linked biaryl oxazacine systems **3b** from acyclic precursors **4b**. The validity of this approach had been established in our previous study; the synthesis of one oxygen-linked medium ring biaryl ether was accomplished by direct cyclization of a phenolic acyclic precursor using a slightly modified version of the optimized reaction conditions employed for the synthesis of nitrogen-linked biaryls.[6] However, the yield of the desired cyclic product was extremely low, which clearly limited the utility of this method.

Scheme 1. Mechanistic Blueprint for the Copper(I)-Catalyzed *N*- and *O*-Linked Biaryl Cyclization Process[a]



[a] The "templating" aliphatic nitrogen atom is circled. Possible ancilliary ligands omitted for clarity.

Herein we describe the development of a new, concise, and efficient protocol of broad applicability for the preparation of a range of compounds based around rare and biologically interesting tricyclic biaryl ether-linked scaffolds incorporating seven-, eight-, and nine-membered ring amines.[8] Application of this methodology should allow the sampling of attractive regions of chemical space that are under-exploited in current drug discovery efforts.[9]

Initial optimization studies were directed toward the ring-closure of acyclic precursor **7**, readily generated by a three-step sequence (Scheme 2). Reductive amination of (2-bromo)benzylamine **8** and salicylaldehyde **9** led to the formation of amine **10**. Subsequent treatment of this crude product material with formaldehyde yielded cyclic hemiaminal **11**, and reduction in acid provided **7** in a high overall yield, with chromatography required only at the final stage.[10] This proved to be a general and robust route to a wide variety of cyclization substrates (see the Supporting Information).

(4) (a) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777. (b) Surry, D.; Su, X.; Fox, D. J.; Franckevicius, V.; Macdonald, S. J. F.; Spring, D. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 1870. (c) Surry, D. S.; Spring, D. R. *Chem. Soc. Rev.* **2005**, 2589. See also ref 6.

(5) Selected examples of the main strategies used for the formation of dibenz[*b*,*g*][1,5]oxazocines from acyclic precursors: Reaction of primary amines with biaryl ethers disubstituted with alkyl bromides: (a) Tanaka, S.; Hashimoto, K.; Tanaka, S.; Hashimoto, K. *Yakugaku Zassi* **1973**, *93*, 1003. (b) Tanaka, S.; Hashimoto, K.; Wantanabe, H. *Chem. Pharm. Bull.* **1973**, *21*, 1683. (c) Tanaka, S.; Hashimoto, K. US Patent 3803143, April 1974.Intramolecular amide formation in biaryl ethers followed by amine reduction: (d) Lieb, F.; Eiter, K. *Liebigs Ann. Chem* **1976**, *93*, 203. Intramolecualr S_NAr reaction of aliphatic amines: ref 3a,3b.

(6) Kenwright, J. L.; Galloway, W. R. J. D.; Blackwell, D. T.; Isidro-Llobet, A.; Hodgkinson, J.; Wortmann, L.; Bowden, S. D.; Welch, M.; Spring, D. R. *Chem.—Eur. J.* **2011**, *17*, 2981.

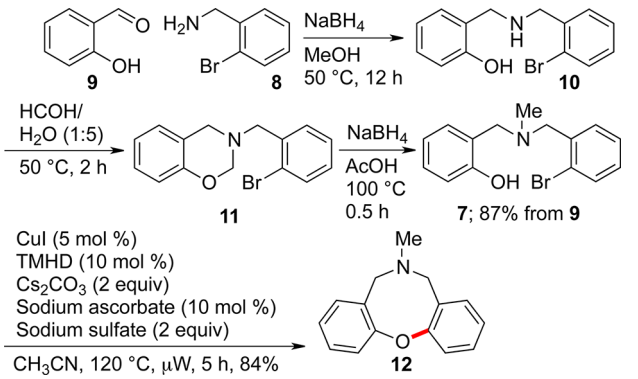
(7) It was proposed that internal co-ordination of the diamine moiety to the copper (I) catalyst yields a highly reative copper chelate bringing the aryl halide bond into close proximity to the reactive copper metal which may facilitate the subsequent oxidative addition step; chelation may also stabilize the postulated copper (III) intermediate so formed, lowering the energy barrier associated with its generation. See ref 6.

(8) A similar chelate effect for enabling medium-ring biaryl synthesis using carbon–hydrogen coupling has previously been reported; see: Pintori, D. G.; Greaney, M. F. *J. Am. Chem. Soc.* **2010**, *133*, 1209.

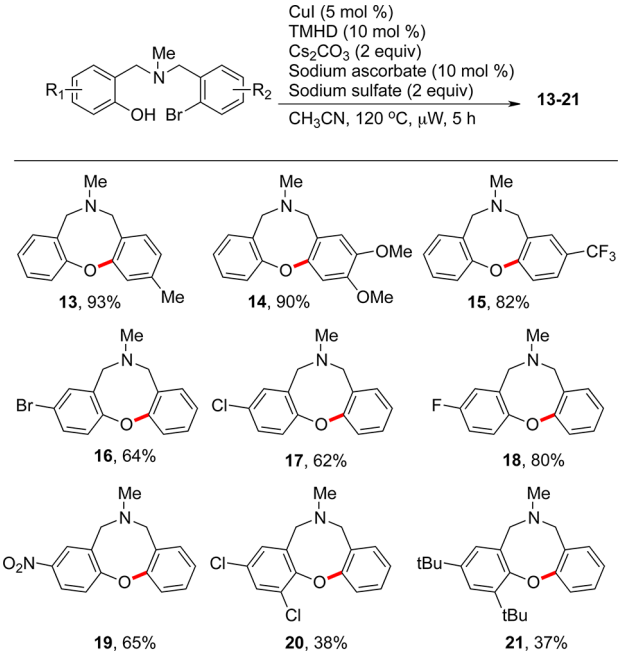
(9) For recent dicussions of chemical space coverage and bioactive molecule discovery, see: (a) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nature Commun.* **2010**, *1*, 80. (b) Eberhadt, L.; Kumar, K.; Waldmann, H. *Curr. Drug Targets* **2011**, *12*, 1531.

(10) Wei, H.; Yin, L.; Luo, H.; Li, X.; Chan, A. S. C. *Chirality* **2011**, *23*, 222.

Scheme 2. Synthesis of Substrate **5** and Cyclization to **6a**



Scheme 3. Scope of Substrates for the Formation of Substituted *N*-Methylated Dibenz[*b*,*g*][1,5]oxazocines



A selection of solvents, copper salts, bases, and 1,3-dicarbonyl ligands were screened for the cyclization of **7** to form **12**.[11] The optimized conditions used a combination of copper(I) iodide, 2,6-tetramethylheptanedione (TMHD),[12] cesium carbonate, sodium ascorbate, and sodium sulfate in acetonitrile at a substrate concentration of 0.2 M,[13] heated under microwave irradiation (sealed tube, under nitrogen) at 120 °C (Scheme 2).[14]

With these optimized conditions established, the cyclization of various other acyclic precursors was examined (Scheme 3). Electron donation (**13** and **14**) and electron withdrawal (**15**) were well tolerated in the halide portion of the substrates. With regard to the phenolic portion, an electron-withdrawing nitro group *ortho* to the reactive phenolic oxygen was tolerated (**19**). Different halogen atoms could also be successfully incorporated into the product scaffolds (**16**–**18**, **20**). These provide possible synthetic handles for postcyclization elaboration around the biaryl core via other transition-metal-catalyzed processes. Large groups placed *ortho* to the coupling oxygen did bring about a drop in yield (e.g., **21**). However, copper-catalyzed carbon–oxygen bond formation is known to be more challenging with *ortho*-substituted coupling partners.

We next examined the synthesis of different sized oxazacines bearing a biaryl ether motif. Pleasingly, seven-membered derivative **22** could be generated from substrate **23** in a high yield (Scheme 4).[15] Nine-membered rings (**24** and **25**) could also be obtained using the optimized conditions (from **26** and **27** respectively), albeit with a reduced yield (Scheme 4). Heterocyclic functionality was incorporated into one product, **25**, further demonstrating the value of the methodology in the context of the generating pharmaceutically relevant products.

The attempted ring closing of secondary amine **10** to **28** failed under the optimized cyclization conditions. However we have developed an alternative route to **28** (Scheme 5). An allyl group is easily appended to the secondary nitrogen of **10** to give **29**. Cylization then proceeded smoothly to generate **30**. The allyl group was removed in high yield using Wilkinson's catalyst, thus furnishing **28**. The amine of **28** provides a handle for further functionalization around the biaryl core.

We hypothesize that the success of these cyclization reactions is due to the presence of a "templating" nitrogen atom in the acyclic substrates, which chelates the copper catalyst and thereby facilitates ring-closure. Consequently, it was expected that acylation of the templating nitrogen would diminish the reactivity of the system, since the lone pair of electrons could then be delocalized into the carbonyl bond and thus would not be as available for co-ordination to a copper species. Indeed, it was found that

(11) See the Supporting Information for details regarding the optimization studies.

(12) The use of this ligand in the formation of diaryl ethers has previously been reported. See, for example: Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623.

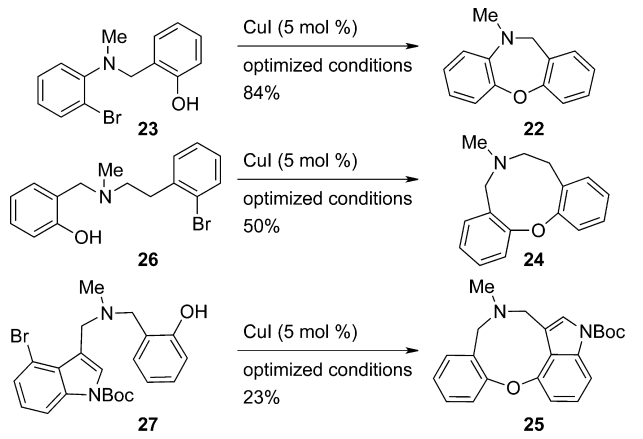
(13) There was no evidence of any competitive intermolecular couplings, despite the relatively high concentration used. Medium ring formations from acyclic precursors frequently require the use of more dilute reaction conditions. See ref 6 and references cited therein.

(14) The reaction of **7** to **12** (Scheme 2) proceeds in 74% yield at 80 °C in the absence of both the sodium ascorbate and sodium sulfate. Microwave heating to 120 °C and addition of sodium ascorbate were both shown to increase the yield of this reaction. Further research into the basis for this effect is ongoing. The addition of sodium sulfate was found to have a minimal impact upon the maximum yield obtained for this cyclization. However, in the absence of sodium sulfate, the yields for this process were found to be quite variable and observed to change with the age of the cesium carbonate base used. This effect was ascribed to the variable moisture content of the base, and the addition of sodum sulfate (which presumably acts as a drying agent) was found to improve the reliability of the reaction.

(15) As seven-membered ring formation is often faster than for equivalent eight-membered rings, we sought confirmation that the aliphatic chelating nitrogen was still playing a part in facilitating the cyclization process. To that end we synthesized an all carbon equivalent of the acyclic precursor leading to **24** and subjected it to the optimized cyclization conditions. As expected, there was no evidence for the formation of the corresponding cyclic product (see the Supporting Information for synthesis details).

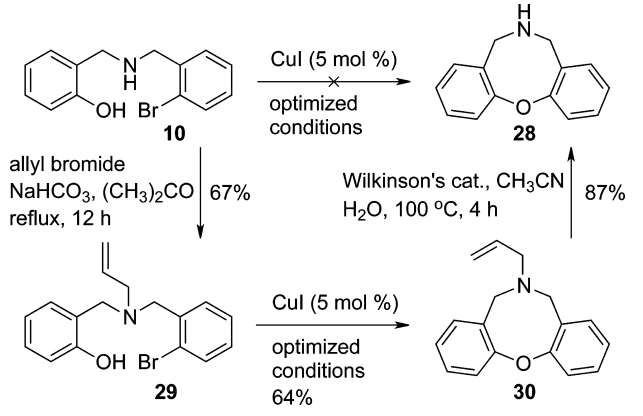
N-Boc protected substrate **31** would not cyclize under our optimized conditions (Scheme 6).[16]

Scheme 4. Formation of Biaryl Ethers Incorporating Seven- and Nine-Membered Ring Amines[a]



[a] Optimized reaction conditions: CuI (5 mol %), TMHD (10 mol %), Cs_2CO_3 (2 equiv), sodium ascorbate (10 mol %), sodium sulfate (2 equiv), CH_3CN, 120 °C, microwave, 5 h.

Scheme 5. Synthesis of Dibenz[*b*,*g*][1,5]oxazocine with Free Secondary Amine Group[a–c]



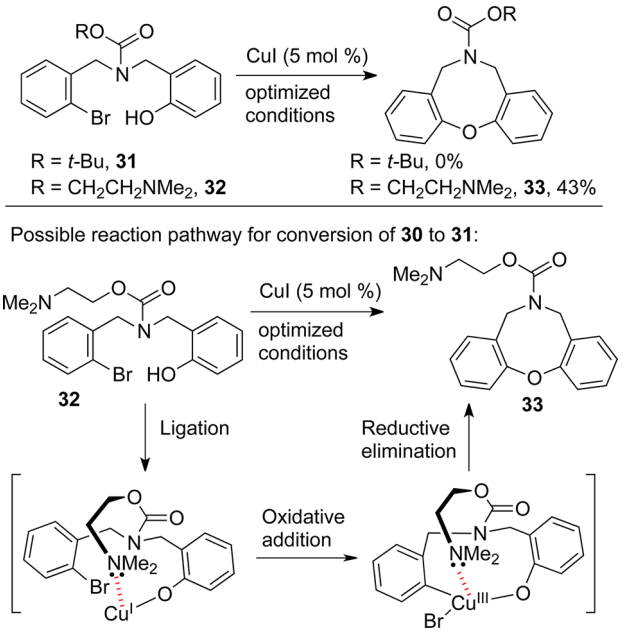
[a] Optimized reaction conditions: CuI (5 mol %), TMHD (10 mol %), Cs_2CO_3 (2 equiv), sodium ascorbate (10 mol %), sodium sulfate (2 equiv), CH_3CN, 120 °C, microwave, 5 h. [b] Yield of **29** over two steps from **8** and **9** (Scheme 2). [c] Wilkinson's cat. = chlorotris(triphenylphosphine)rhodium(I).

We decided to investigate whether addition of a further amine could restore reactivity (Scheme 6).

Gratifyingly, exocyclic amine functionality tethered via an aliphatic linkage to the linear substrate (compound **32**) allowed successful cyclization to form **33**. We propose that this exocyclic tether is flexible enough to bind the copper. It is striking that this proposed 11-membered chelate is able to so dramatically affect the coupling process. Conceivably, this

(16) Similar obervations were made during our studies into the synthesis of nitrogen-linked medium-ring biaryls (see ref 6).

Scheme 6. "Remote Activation" by an Exocyclic Tether[a]



[a] Optimized reaction conditions: CuI (5 mol %), TMHD (10 mol %), Cs_2CO_3 (2 equiv), sodium ascorbate (10 mol %), sodium sulfate (2 equiv), CH_3CN, 120 °C, microwave, 5 h.

"remote activation" concept could be leveraged in the synthesis of alternative series of oxidized dibenzoxazocine-type scaffolds, extending the scope of the cyclization strategy.

In conclusion, we have developed a new, concise, and general protocol for the synthesis of compounds based around tricyclic biaryl ether-linked scaffolds incorporating seven-, eight-, and nine-membered ring amines, including the dibenz[*b*,*g*][1,5]oxazocines class of heterocycles. The process displays a broad substrate scope, uses an inexpensive copper catalyst, and generates rare and biologically interesting heteroaromatic products that would be difficult to synthesize by other methods. We envisage that this approach should prove useful for the exploration of hitherto under-investigated scaffolds and thereby the discovery of new molecules of medicinal interest. Compounds synthesized in this program are currently being screened for biological activity. Further mechanistic investigation is underway in our laboratories to clarify the activating effect of the "templating" nitrogen. The results of these studies will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra.This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.