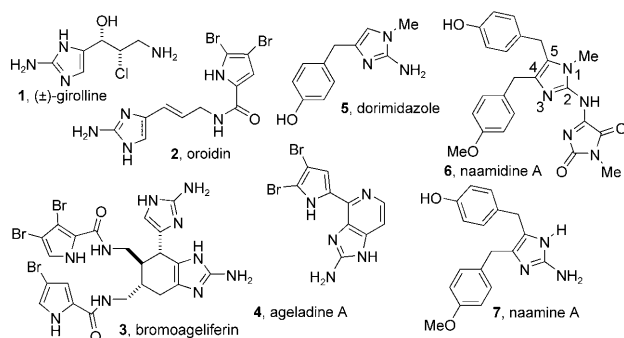


Addition–Hydroamination Reactions of Propargyl Cyanamides: Rapid Access to Highly Substituted 2-Aminoimidazoles**

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In memory of Albert I. Meyers

The 2-aminoimidazole moiety is emerging as a valuable pharmacophore for biomedical research.^[1] This pharmacophore has been shown to have an effect on the activity of compounds, alter their selectivity for enzyme isoforms,^[2] and improve important physiochemical properties, such as lipophilicity,^[3] blood–brain-barrier passage,^[4] cell permeability,^[5] and bioavailability.^[6] These effects are a consequence of predictable pK_a -value changes and the diverse hydrogen-bond topologies of enzyme complexes with compounds containing the 2-aminoimidazole moiety. Marine sponges have proven to be a valuable source of medicinally relevant 2-aminoimidazole natural products. Compounds **1–4** were isolated from organisms of the class Demospongiae,^[7] and compounds **5–7** from organisms of the class Calcarea^[8] (Scheme 1). These natural products display a range of

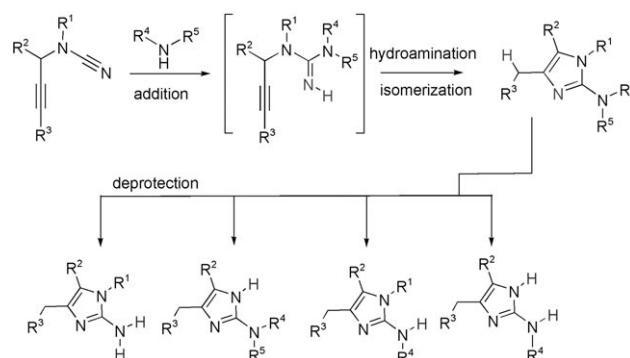


Scheme 1. Representative 2-aminoimidazole natural products.

substitution and hydrogen-bond-donor/acceptor patterns. Given the potential impact of this motif in small-molecule discovery, it is imperative that a streamlined strategy is created for its preparation.

There are currently two predominant strategies to access the 2-aminoimidazole motif.^[7] The first originates with the

condensation of an α -aminoketone with cyanamide or an α -halo ketone with an acetylated guanidine derivative.^[9,10] This strategy relies on unstable precursors and is applicable to the preparation of minimally substituted cores. The second approach involves the decoration of an imidazole scaffold.^[11,12] Although highly substituted 2-aminoimidazoles can be prepared by this strategy, multiple steps are required to protect the imidazole, introduce substituents, activate C2 for the introduction of the amine (usually by lithiation), and deprotect the final product. We felt that the addition of a guanidine N–H bond across a C–C π system would be a powerful reaction for the preparation of these challenging heterocycles (Scheme 2). The development of amine–alkene/



Scheme 2. A general approach to the 2-aminoimidazole core.

alkyne hydroamination chemistry has provided an invaluable approach to the construction of nitrogen-based heterocycles.^[13] The extension of this methodology to guanidines, however, remains largely underdeveloped.^[14] To the best of our knowledge, Esser et al. have provided the only examples of the addition of a guanidine N–H bond across an alkyne.^[15] This alkali-metal-catalyzed process requires forcing conditions and delivers the cyclized product in low to moderate yields. Herein, we report a facile La^{III} -initiated guanidine–alkyne hydroamination sequence, which leads ultimately to the 2-aminoimidazole core.

With the preparation of several target structures in mind, we hypothesized that we could expand the utility of a hydroamination approach to this heterocyclic core by intercepting a guanidine derivative in situ (Scheme 2). The addition of an amine to a cyanamide would generate the propargyl guanidine and be followed by the addition of the N–H bond across the tethered alkyne. Isomerization should

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follow to generate the imidazole core. Although the addition of amines to cyanamides under neutral or basic conditions has been shown to be reversible,^[16] we considered the possibility that the hydroamination step might serve as an efficient trap for the neutral guanidine moiety. Importantly, the propargyl cyanamides can be constructed by a three-component iminium–acetylide addition (3-CC), which relies on stable precursors (an aldehyde, an amine, and an alkyne) to generate skeletal diversity. This strategy would permit substitution at every position on the 2-aminoimidazole (i.e. substituents R¹–R⁵) in just three steps and thus streamline the preparation of the 2-aminoimidazole core. The judicious introduction of a removable group R¹, R⁴, or R⁵ would ultimately enable access to every possible substitution/hydrogen-bond pattern of the 2-aminoimidazole core.

We began by addressing the preparation of the propargyl cyanamides (Table 1). The addition of an acetylide to an iminium ion is well-known.^[17] This reaction has become a

Table 1: Three-component coupling.

Entry	Components	9
1	ArCH ₂ NHMe Ph≡ PhCH ₂ CHO	<p>9a</p> <p>8a, Ar = PMB (94%) 8a', Ar = 2,4-DMB (61%) 8a'', Ar = 3,4-DMB (95%)</p> <p>87% from 8a ~quant from 8a' 74% from 8a''</p>
2	PMB ₂ NH Ph≡ HCHO	<p>9b</p> <p>8b 99%</p> <p>9b 94%</p>
3	PMBNHallyl PMP≡ HCHO	<p>9c</p> <p>8c 99%</p> <p>9c 94%</p>
4	PMBNHBn Bun≡ HCHO	<p>9d</p> <p>8d 94%</p> <p>9d 90%</p>
5	PMBNHMe Ph≡ nBuCHO	<p>9e</p> <p>8e 91%</p> <p>9e 91%</p>
6	PMBNHMe PMP≡ 4-BnOPhCH ₂ CHO	<p>9f</p> <p>8f 98%</p> <p>9f 76%</p>

a) For **8a,f**: CuBr (10 mol %), MeCN, 80 °C, 12 h. b) For **8b–e**: CuBr (10 mol %), MeCN, room temperature. c) CNBr (3.0 M in CH₂Cl₂), K₂CO₃, dioxane. Bn = benzyl, PMB = *p*-methoxybenzyl, PMP = *p*-methoxyphenyl.

Table 2: Lanthanide-initiated addition–hydroamination sequence.

Entry	Substrate	Catalyst ^[a]	10 (yield [%])	Yield of 11 [%]
1	9a	none	–	–
2	9a	Zn(OTf) ₂ (2 equiv)	10a (45)	32
3	9a	Zn(OTf) ₂ (30 mol %)	10a (32)	18
4	9a	CuBr ₂ (30 mol %)	10a (15)	21
5	9a	La(OTf) ₃ (30 mol %)	10a (75)	–
6	9b	La(OTf) ₃ (30 mol %)	10b (91)	–
7	9b	Y(OTf) ₃ (30 mol %)	10b (78)	–
8	9b	Sc(OTf) ₃ (30 mol %)	10b (66)	–

[a] Tf = trifluoromethanesulfonyl.

powerful tool following asymmetric and practical advances by the research groups of Knochel and Carreira.^[18,19]

In contrast to literature reports that primary amines can participate in this reaction, we found them to be problematic substrates and often isolated dimeric propargyl amines derived from further reaction of the newly created secondary amine.^[20] However, the copper(I)-catalyzed addition of alkynes to iminium ions generated from secondary amines is quite general and high-yielding; with both aromatic and aliphatic alkynes and aldehydes, the products are typically obtained in more than 90 % yield (Table 1, entries 1–5). Reactions involving an aryl acetaldehyde (Table 1, entries 1 and 6) required slightly more forcing conditions to generate a useful equilibrium concentration of the iminium ion from the enamine. Typically these reactions were conducted at 80 °C and required approximately 12 h to reach completion; however, they still provided the tertiary propargyl amines in greater than 90 % yield.


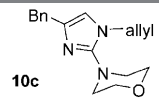

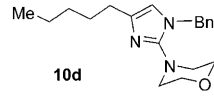

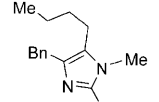
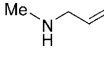
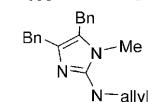

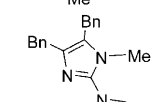
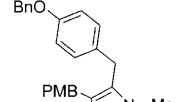
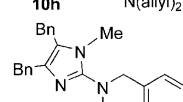
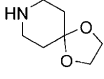
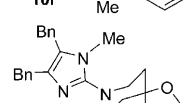
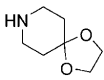
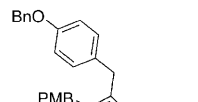

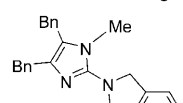
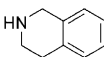
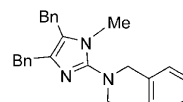
After installation of the requisite tertiary amine, a von Braun sequence was used to introduce the cyanamide.^[21] Initial attempts with symmetric *N,N*-dialkyl propargyl amines (e.g. *N,N*-dimethyl propargyl amines) led exclusively to the propargyl bromide. Not surprisingly, quaternization of the tertiary amine was followed by cleavage of the more labile propargylic C–N bond. We found that the use of a *p*-methoxybenzyl group reversed this selectivity to give the desired cyanamides (i.e. **8**→**9**). We have observed that an increase in electron density at the propargylic C–N bond leads to competitive cleavage to give small amounts of the corresponding propargyl bromide (ca. 10 %). The 2,4- and 3,4-dimethoxybenzyl (DMB) groups can both overcome this competing reaction pathway (see Table 1, entry 1, **8a,a'**→**9a**); however, substrates with the PMB group still deliver synthetically useful amounts of material, and these substrates can be prepared more readily or are commercially available. For example, **8f**, the PMB-activated propargyl amine precursor substrate for *n*-amine A, has two electron-rich aromatic groups flanking

the C–N bond, and the desired cyanamide was obtained in 76% yield. When two benzylic groups were present on the nitrogen atom of the propargylic amine (in **8d**), exclusive cleavage of the more-electron-rich substituent was observed (Table 1, entry 4). This reaction sequence generated the propargyl cyanamides in good yields in most cases. The 3-CC can be followed directly by the von Braun sequence without purification to give the cyanamides in equally high yields (e.g. **9b**, 94%, 2 steps).

Having successfully generated the cyanamide precursors, we next explored their conversion into 2-aminoimidazoles. The thermal addition–hydroamination sequence gave the desired heterocycles in moderate yield with only a few cyclic secondary amines, including pyrrolidine and piperidine. The use of secondary acyclic amines led to much lower yields, if the reaction proceeded at all (data not shown). These initial experiments enabled us to make three important observations: 1) The reaction proceeded without the isolation of the intermediate propargyl guanidine, which suggests that the hydroamination was quite facile; 2) the five-membered heterocycles were formed exclusively; and 3) both the yields of the isolated products and the reaction rates follow the general trend of amine nucleophilicity, that is, pyrrolidine > Et₂NH > NH₃.^[22] Taken together, these results suggest that addition to the cyanamide may be rate-limiting,^[23] and that catalysis of this step would be crucial to diversify nucleophile participation.

We therefore examined catalysts to promote the addition of the amine to the cyanamide. We anticipated that diallylamine could serve as an –NH₂ surrogate after deprotection; however, it did not participate in the thermal addition reaction (no reaction at 150 °C for 120 h). This challenging nucleophile served as our test for catalysis (Table 2). Zn^{II} and Cu^{II} salts both catalyzed the formation of the 2-

Table 3: Lanthanide-initiated addition–hydroamination sequence.

$ \begin{array}{c} \text{R}^1 \\ \\ \text{N} \equiv \text{N} \\ \\ \text{R}^2 - \text{C} \equiv \text{C} - \text{R}^3 \end{array} \xrightarrow[\text{Conditions}]{\text{amine, La(OTf)}_3} \begin{array}{c} \text{R}^2 \\ \\ \text{N} \\ \\ \text{R}^1 \\ \\ \text{N} \\ \\ \text{R}^4 \\ \\ \text{R} \end{array} $					
Entry	Amine	9	Conditions ^[a]	10	Yield [%]
1		9c	A		83
2		9d	A		64
3		9e	A		82
4		9a	A		85
5		9a	A		93
6	(allyl) ₂ NH	9f	A		89
7	BnNHMe	9a	B		81
8		9a	B		96
9		9f	B		76
10		9a	B		89
11		9a	B C		81 54

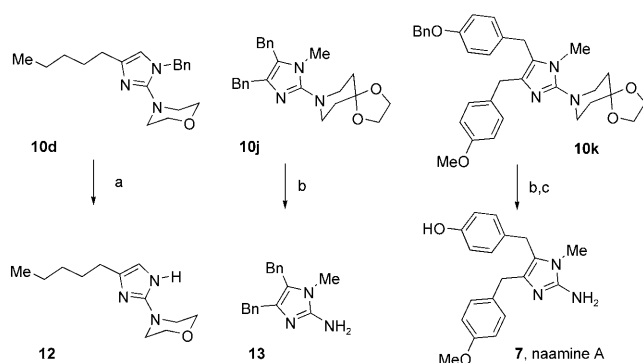
[a] Reaction conditions: A) amine (neat), La(OTf)₃ (30 mol %), 95 °C, 24 h; B) amine (3–5 equiv), La(OTf)₃ (30 mol %), iPrOH, 95 °C, 24–48 h; C) amine (5 equiv), La(OTf)₃ (10 mol %), iPrOH, 95 °C, 24 h.

aminoimidazole **10a** from **9a** but also produced the previously unobserved product **11** (Table 2, entries 2–4), which arises from decyanation of the propargyl cyanamide. $\text{La}(\text{OTf})_3$ was found to catalyze the addition–hydroamination–isomerization sequence to provide **10a** and **10b** in good yields (76 and 91 %, respectively). Interestingly, the yield of isolated **10b** decreased as the size of the lanthanide/Group-III-metal ion decreased (Table 2, entries 6–8). These lanthanum(III)-initiated reactions proceeded smoothly at 95 °C.

The optimized conditions were applied to a number of substrate/nucleophile combinations under solvent-free conditions (Table 3). Both cyclic and acyclic secondary amines reacted well to give the 2-aminoimidazoles **10c–10h** in good yields (Table 3, entries 1–6). In terms of enthalpy, the hydroamination of alkynes is greatly favored over that of the corresponding alkenes, as observed in the selective formation of **10c** (Table 3, entry 1), although an alkene and an alkyne are present in equivalent positions with respect to the guanidine moiety in the acyclic intermediate.

For more-complex amines that cannot be used under solvent-free conditions, typically those with a higher molecular weight, 2-propanol can serve as an acceptable solvent. Thus, treatment of the cyanamide **9f** with the amine (3–5 equiv) and $\text{La}(\text{OTf})_3$ (30 mol %) gave the 2-aminoimidazoles **10i–m** in good yields (Table 3, entries 7–11). The catalyst loading can also be decreased to 10 mol % (Table 3, entry 11); however, the relatively low cost of $\text{La}(\text{OTf})_3$ permits a higher catalyst loading for convenience.

We next examined the potential to remove substituents and provide access to alternate hydrogen-bond-donor/acceptor topologies (Scheme 3). Unfortunately, standard



Scheme 3. Deprotection of amine groups: a) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 (60 psi), MeOH, AcOH, 87%; b) HCl, MeCN, then JandaJel- NH_2 , NH_4Cl , EtOH, 70% for **13**; c) 10% Pd/C, H_2 (1 atm), 63% from **10k**.

deallylation conditions failed to remove both allyl groups from the imidazole core. Building blocks with a benzyl group at N1, such as **10d**, can be hydrogenated to give the corresponding mono-unsubstituted 2-aminoimidazoles, such as **12**. Treatment of the ketal **10j** with HCl/MeCN followed by aminomethylated JandaJel in a procedure modified slightly from the protocol described by Carreira and co-workers^[19] delivered **13**, with a free 2-amino group, in good yield. This

procedure was also applied to the synthesis of naamine A (**7**) from **10k**; in a subsequent step, the phenol was liberated by hydrogenolysis. This experimental approach proved useful, as the purification of these compounds is simplified to filtration.

In summary, the described three-step sequence offers a highly concise and convergent route to selectively substituted 2-aminoimidazoles.^[24] The lanthanum(III)-initiated hydroamination–isomerization sequence permits a unique disconnection for rapid access to more-complex natural product skeletons. We are currently studying the role of lanthanum(III) in the hydroamination process, so that catalysts can be developed for the further expansion of this transformation.

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- [1] J. D. Sullivan, R. L. Giles, R. E. Looper, *Curr. Bioact. Compd.* **2009**, 5, 39–78.
- [2] R. M. Keenan, W. H. Miller, C. Kwon, F. A. Ali, J. F. Callahan, R. R. Calvo, S.-M. Hwang, K. D. Kopple, C. E. Peishoff, J. M. Samanen, A. S. Wong, C.-K. Yuan, W. F. Huffman, *J. Med. Chem.* **1997**, 40, 2289–2292.
- [3] a) W. W. Wilkerson, S. Dax, W. W. Cheatham, *J. Med. Chem.* **1997**, 40, 4079–4088; b) D. A. Nugiel, K. Jacobs, L. Cornelius, C.-H. Chang, P. K. Jadhav, E. R. Holler, R. M. Klabe, L. T. Bacheler, B. Cordova, S. Garber, C. Reid, K. A. Louge, L. J. Gorey-Feret, G. N. Lam, S. P. Seitz, *J. Med. Chem.* **1997**, 40, 1465–1474.
- [4] S. A. Munk, D. A. Harcourt, P. N. Arasasingham, J. A. Burke, A. B. Kharlamb, C. A. Manlapaz, E. U. Padillo, D. Roberts, E. Runde, *J. Med. Chem.* **1997**, 40, 18–23.
- [5] U. Bickmeyer, A. Grube, K. W. Klings, M. Koeck, *Biochem. Biophys. Res. Commun.* **2008**, 373, 419–422.
- [6] S. Ahmad, K. Ngu, D. W. Combs, S. C. Wu, D. S. Weinstein, W. Liu, B.-C. Chen, G. Chandrasena, C. R. Dorso, M. Kirby, K. S. Atwal, *Bioorg. Med. Chem. Lett.* **2004**, 14, 177–180.
- [7] For a recent review of the chemistry and biology of the Demospongiae alkaloids, see: a) S. M. Weinreb, *Nat. Prod. Rep.* **2007**, 24, 931–948; for girroline, see: b) F. Lavelle, A. Zerial, C. Fizames, B. Rabault, A. Curaudeau, *Invest. New Drugs* **1991**, 9, 233–244; for oroidin, see: c) S. R. Kelly, E. Garo, P. R. Jensen, W. Fenical, J. R. Pawlik, *Aquat. Microb. Ecol.* **2005**, 40, 191–203; d) J. J. Richards, T. E. Ballard, C. Melander, *Org. Biomol. Chem.* **2008**, 6, 1356–1363; for bromoageliferin, see: e) A. Yamada, H. Kitamura, K. Yamaguchi, S. Fukuzawa, C. Kamijima, K. Yazawa, M. Kuramoto, G. Y. S. Wang, Y. Fujitani, D. B. Uemura, *Bull. Chem. Soc. Jpn.* **1997**, 70, 3061–3069; f) R. W. Huigens III, J. J. Richards, G. Parise, T. E. Ballard, W. Zeng, R. Deora, C. Melander, *J. Am. Chem. Soc.* **2007**, 129, 6966–6967; for ageladine A, see: g) M. Fujita, Y. Nakao, S. Matsunaga, M. Seiki, Y. Itoh, J. Yamashita, R. W. M. van Soest, N. Fusetani, *J. Am. Chem. Soc.* **2003**, 125, 15700–15701.
- [8] For dorimidazole, see: a) K. A. Alvi, P. Crews, D. G. Loughhead, *J. Nat. Prod.* **1991**, 54, 1509–1515; for naamidine A and naamine A, see: b) S. Carmely, Y. Kashman, *Tetrahedron Lett.* **1987**, 28, 3003–3006; c) S. Carmely, M. Ilan, Y. Kashman, *Tetrahedron* **1989**, 45, 2193–2200; d) R. D. James, D. A. Jones, W. Aalbersberg, C. M. Ireland, *Mol. Cancer Ther.* **2003**, 2, 747–751.
- [9] For cyanamide condensations, see: a) A. Lawson, *J. Chem. Soc.* **1956**, 307–310; b) G. C. Lancini, E. Lazzari, *J. Antibiot. Ser. A*

- 1966, 3, 152–154; for condensations of *N*-acetyl guanidines, see: c) T. L. Little, S. E. Webber, *J. Org. Chem.* **1994**, 59, 7299–7305.
- [10] For examples in target-oriented synthesis, see: a) N. K. Garg, R. Sarpong, B. M. Stoltz, *J. Am. Chem. Soc.* **2002**, 124, 13179–13184; b) P. S. Baran, A. L. Zografos, D. P. O'Malley, *J. Am. Chem. Soc.* **2004**, 126, 3726–3727.
- [11] S. Daninos, A. Al Mourabit, A. Ahond, M. B. Zurita, C. Poupat, P. Potier, *Bull. Soc. Chim. Fr.* **1994**, 131, 590–599.
- [12] For examples in target-oriented synthesis, see: a) S. Ohta, N. Tsuno, S. Nakamura, N. Taguchi, M. Yamashita, I. Kawasaki, M. Fujieda, *Heterocycles* **2000**, 53, 1939–1955; b) M. L. Meketa, S. M. Weinreb, *Org. Lett.* **2006**, 8, 1443–1446.
- [13] a) T. E. Muller, M. Beller, *Chem. Rev.* **1998**, 98, 675–704; b) M. Norbis, B. D. Hölscher, *Angew. Chem.* **2001**, 113, 4105; *Angew. Chem. Int. Ed.* **2001**, 40, 3983.
- [14] C. H. Hövelmann, J. Streuff, L. Brelot, K. Muniz, *Chem. Commun.* **2008**, 2334–2336.
- [15] F. Esser, K. H. Pook, A. Carpy, *Synthesis* **1990**, 72–76.
- [16] R. Klingner, *Hoppe-Seyler's Z. Physiol. Chem.* **1926**, 155, 206–239.
- [17] For a recent review, see: L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263–4275.
- [18] a) C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, 114, 2651–2654; *Angew. Chem. Int. Ed.* **2002**, 41, 2535–2538; b) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, 115, 5941–5944; *Angew. Chem. Int. Ed.* **2003**, 42, 5763–5766.
- [19] P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org. Lett.* **2006**, 8, 2437–2440.
- [20] L. W. Bieber, M. F. da Silva, *Tetrahedron Lett.* **2004**, 45, 8281–8283.
- [21] J. von Braun, *Ber. Dtsch. Chem. Ges.* **1900**, 33, 1438.
- [22] F. Brotzel, Y. C. Chu, H. Mayr, *J. Org. Chem.* **2007**, 72, 3679–3688.
- [23] B. B. Snider, S. M. O'Hare, *Tetrahedron Lett.* **2001**, 42, 2455–2458.
- [24] For other approaches to the naamidine alkaloids, see: a) S. Ohta, N. Tsuno, S. Nakamura, N. Taguchi, M. Yamashita, I. Kawasaki, M. Fujieda, *Heterocycles* **2000**, 53, 1939–1955; b) N. S. Aberle, G. Lessene, K. G. Watson, *Org. Lett.* **2006**, 8, 419–421; c) D. S. Ermolat'ev, V. L. Alifanov, V. B. Rybakov, E. V. Babaev, E. V. Van der Eycken, *Synthesis* **2008**, 2083–2088.