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Synthesis of Bicyclic Guanidines via Cascade Hydroamination/Michael Additions of Mono-*N*-acryloylpropargylguanidines

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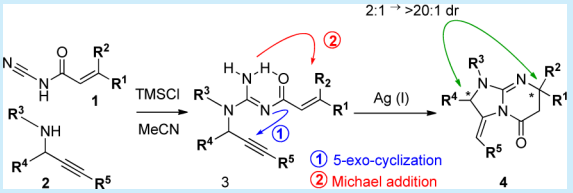
Supporting Information

ABSTRACT: A cascade silver(I)-catalyzed hydroamination/Michael addition sequence has been developed to deliver highly substituted bicyclic guanidines. This transformation gives rise to geometrically and constitutionally stable ene−guanidines and generates a remote stereocenter with moderate to high diastereoselectivity.

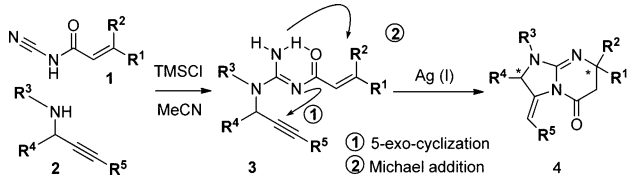


Polycyclic guanidinium ion natural products exhibit a broad spectrum of biological activity and embed an important structural unit that is critical for medicinal chemistry and for broader discovery-based applications.[1] Unnatural polycyclic guanidines have also been employed as competent organocatalysts with unique coordination arrangements and an array of donor/acceptors.[2,3] Given their broad utility, a variety of synthetic methods have been developed to access this class of compounds. Some of these methods include the cyclization of propargylguanidines,[4] intermolecular diamination of alkenes,[5] reaction of unsaturated molecules with aziridines and diazirenes,[6] intramolecular alkylation of guanidines,[7] and radical cascade cyclizations,[8] among others.[9] Very recently, titanium amides have been shown to catalyze the synthesis of cyclic guanidines from diamines and carbodiimides in a single step.[10] Unfortunately, most of these synthetic routes require multistep synthesis or preparation of highly functionalized precursors. The development of advanced, efficient, and facile methods to access these compounds thus remains an important goal for synthetic chemists.[11] Herein, we report a one-step Ag(I)-catalyzed hydroamination/Michael addition sequence of mono-*N*-acryloylpropargylguanidines yielding bicyclic guanidines with complete regiocontrol and modest to high levels of 1,5-asymmetric induction.

The synthesis of unsymmetrical guanidines has been intensively investigated, and a variety of guanylating agents are available.[12] We recently reported the chlorotrimethylsilane activation of acylcyanamides as an efficient method for the synthesis of mono-*N*-acylguanidines via a reactive *N*-silylcarbodiimide intermediate.[14]

This discovery prompted us to consider new types of guanylating agents, capable of engaging cascade reactivity which could lead to the formation of bicyclic guanidines. We became interested in the unsaturated *N*-cyanoacylamide **1** as a guanylating agent and precursor for bicyclic guanidines (Scheme 1). Upon reaction with TMSCl, *N*-cyanoacylamide **1** should generate an *N*-silylcarbodiimide intermediate capable of reaction with a propargylamine **2**. Acryloylguanidines (e.g., **3**) themselves

Scheme 1. Synthetic Strategy for the Bicyclic Guanidines



do not undergo intramolecular cyclization due to internal hydrogen bonding by the NH_2 group to the carbonyl, locking it in an unproductive *s-cis* conformer. We envisioned that initial 5-*exo* selective cyclization of the guanidine on a tethered alkyne would generate an intermediate that can undergo rapid *s-cis* → *s-trans* isomerization by the introduction of significant pseudo-A[1,3] strain. This would then allow the formation of the 6-membered ring via Michael addition with the unsubstituted guanidine nitrogen (N^2) (Scheme 1). If successful, this would provide access to highly substituted 5,6-membered bicyclic guanidines.

To execute this strategy, we first examined the direct activation of the *N*-cyanoacrylamides **1a−h** and their reaction with propargylamine **2a** (Table 1). The reaction of both **1a** and **1b** with **2a** yielded products **3a**/**b** in moderate yields (entries 1 and 2). The reaction of more electron-deficient cinnamoyl derivatives (**1c−e**) with **2a** gave better yields of propargylguanidines **3c−e** (entries 3−5). Conversely, the more electron-rich *N*-cyanoacrylamide (**1f**) gave its corresponding propargylguanidine in attenuated yield (entry 6). The reactivity of these intermediate *N*-silylcarbodiimides appears to be acutely sensitive to the electronic nature of the *N*-cyanoacrylamides. For example, the more electron-rich substrates **1g**/**h**, which are *β*-disubstituted, fail to react with **2a** (entries 7 and 8).

Having synthesized the required substrates, we next investigated the cascade cyclization−Michael addition sequence. Indeed, Ag(I) initiated a highly selective 5-*exo* cyclization

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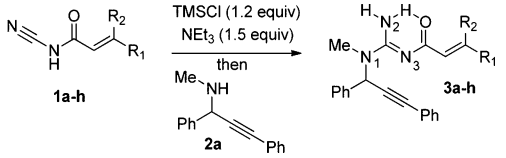
Table 1. Survey of Guanylation Activity with *N*-Cyanoacrylamides[a]

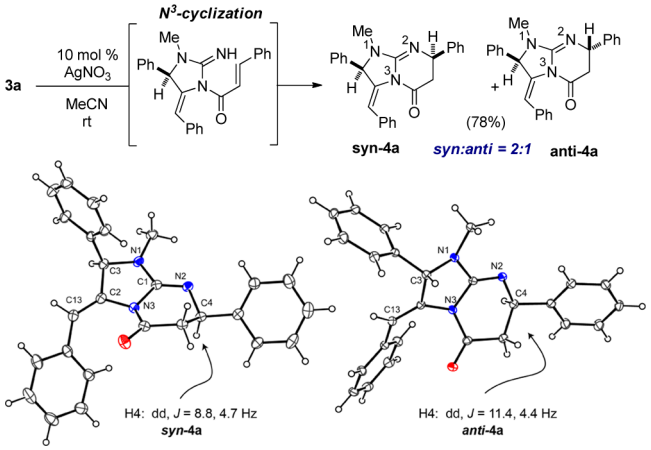


entry	cyanamide (**1**)	products (**3**)	yield[b] (%)
1	R^1 = H, R^2 = Ph (**1a**)	**3a**	63
2	R^1 = H, R^2 = 2-naphthyl (**1b**)	**3b**	60
3	R^1 = H, R^2 = C_4H_6-*o*-Br (**1c**)	**3c**	83
4	R^1 = H, R^2 = C_4H_6-*m*-CF_3 (**1d**)	**3d**	78
5	R^1 = H, R^2 = C_4H_6-*p*-Br (**1e**)	**3e**	73
6	R^1 = H, R^2 = 1,3-benzodioxolyl (**1f**)	**3f**	36
7	R^1 = Me, R^2 = Me (**1g**)	**3g**	0
8	R^1 = Me, R^2 = Ph (**1h**)	**3h**	0

[a]Reaction conditions: cyanamide (1.0 mmol), amine (1.0 mmol), TMSCl (1.2 equiv), NEt_3 (1.5 equiv), CH_2Cl_2 (10 mL), 8 h. [b]Isolated yield. TMSCl = chlorotrimethylsilane, NEt_3 = triethylamine.

guanidine as previously reported.[5a−c] Accordingly, treatment of **3a** in the presence of $AgNO_3$ (10 mol %) in acetonitrile at room temperature provided **4a** in good chemical yield as a mixture of two diastereoisomers that were readily separable by chromatography (78% yield, dr = 2:1) (Scheme 2). It is important to note

Scheme 2. Synthesis of Bicyclic Guanidines from Propargylguanidines and Confirmation of Their Stereochemistry by X-ray Crystallography



that the initial hydroamination proceeds with excellent regiochemical control via attack by the imino-nitrogen (N^3), as drawn. After the stereochemistry of *syn*-**4a** and *anti*-**4a** was confirmed by X-ray crystallography, it became straightforward to identify the relative configurations of these products by the larger diaxial ^3J coupling between H_4 and the neighboring methylene group in the *anti*-diastereomer. As expected from an *anti*-aminometalation pathway, the products are formed as single geometric isomers the C−C double bond. The fact that this transformation proceeded with modest diastereoselectivity was surprising, given that the two stereocenters are five atoms apart and separated by an almost planar 5,6-fused heterocyclic system. When the crystal structures of *syn*/*anti*-**4a** were evaluated, it was noted that the *anti*-diastereomer had considerable torsional strain about the C^2−C^3 bond. The alkene is bent significantly out of the plane with N^3, deconjugating the alkene from the guanidine, allowing us to intuitively assign the *syn*-diastereomer as the thermodynamically favored product. Prior to the Michael addition, torsional strain between R^3−R^4−R^5 might preferentially position the Michael acceptor above or below the plane of the cyclic guanidine depending on the relative torsion this interaction imparted to the N^3−carbonyl bond. Examples of Ag(I)-catalyzed Michael additions of amines are rare,[15] and we were doubtful that catalysis of this step would significantly impact the reaction outcome. Probing these torsional effects on the reaction outcome guided our substrate analysis.

We first examined substrates where R^4 = aryl, anticipated to behave as a large substituent (Figure 1). All substrates in this

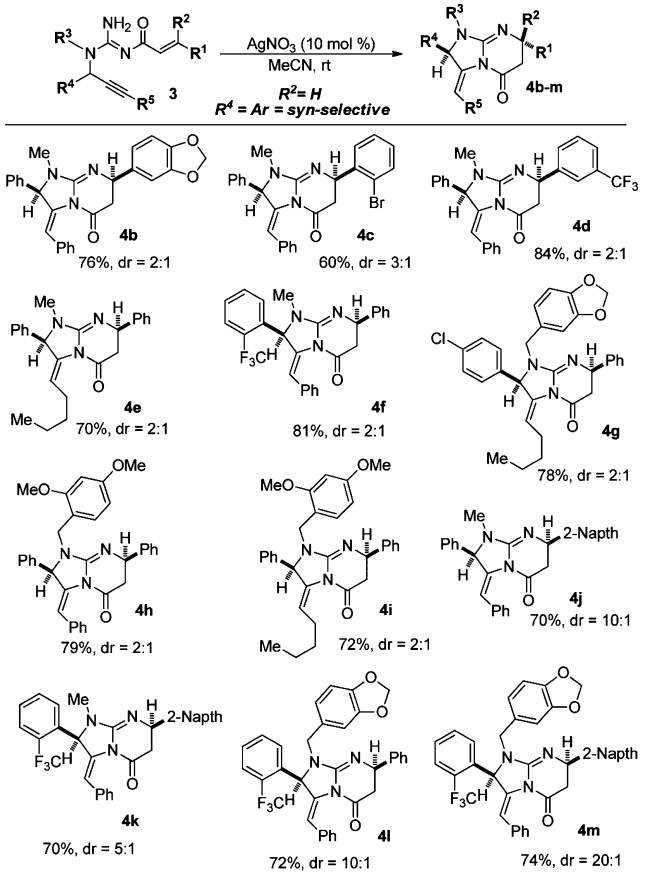


Figure 1. Substrate scope for the cyclization/Michael addition catalyzed by $AgNO_3$ where R^4 = aryl. Reaction conditions: substrate (0.3 mmol), $AgNO_3$ (10 mol %), MeCN (0.1 M), 8 h. The diasteromeric ratios were determined by ^{1}H NMR analysis of the crude mixture.

series were tolerated, giving the products in good chemical yield and similar diastereoselectivities. Examples **4b−d** demonstrate that a variety of electron-withdrawing and -donating groups on the acryloylguanidine are tolerated to give the products in good chemical yield and similar diastereoselectivities. Substitution of the alkyne substituent (R^5) to a smaller alkyl group also had no effect on diastereoselectivity (**4e**). Introduction of a larger *o*-substituted aryl group (**4f**) or a larger group at N^1 was also inconsequential (**4g−i**). Unexpectedly, we found that the 2-naphthyl-substituted acryloylguanidines cyclized with enhanced diastereoselectivity 10:1 dr for **4j** and 5:1 dr for **4k**. While independently the interaction R^3−R^4−R^5 is critical for selectivity, the interactions do appear to be additive. For example, a large substituent at N^1 and C^3 (e.g., *m*-(trifluoromethyl)phenyl) improves the selectivity to 10:1 dr (**4l**). Inclusion of the 2-

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naphthyl group enhances the diastereoselectivity of the product **4m** to >20:1 by ^{1}H NMR.

We next examined substrates where R^4 = alkyl or α-branched, anticipated to behave as a small group by virtue of their ability to orient a methyne hydrogen toward the alkene (Figure 2). Quite

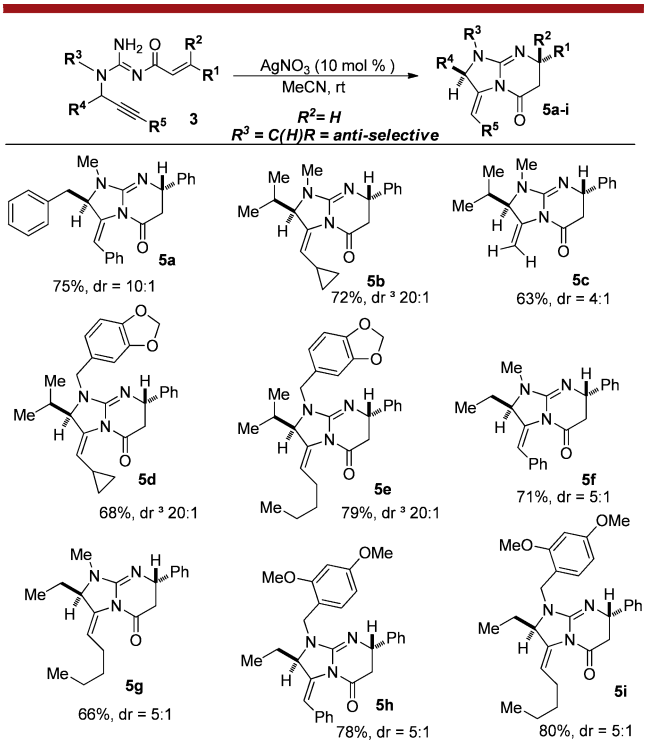


Figure 2. Substrate scope for the cyclization/Michael addition catalyzed by $AgNO_3$ where R^4 = alkyl. Reaction conditions: substrate (0.3 mmol), $AgNO_3$ (10 mol %), MeCN (0.1 M), 8 h. The diastereomeric ratios were determined by ^{1}H NMR analysis of the crude mixture.

to our surprise, all of these substrates cyclized with higher diastereoselectivity but favored the *anti*-diastereomer. The substrates where R^4 = benzyl or isopropyl gave *anti*-**5a** and *anti*-**5b** in good diastereoselectivity (10:1 dr or >20:1 dr, respectively). Deletion of a substituent on the alkyne did lower the diastereoselectivity to 4:1 dr as seen with **5c**. Other substituent interchanges still delivered the products (**5d**–**i**) with good levels of *anti*-diastereoselectivity ranging from 5:1 to >20:1 dr.

In the context of delivering a small collection of this new scaffold for initial biological evaluation, we also examined this cascade reaction on substrates lacking a substituent at R^4 (Figure 3). A variety of substituents on the N^1 guanidine nitrogen were well tolerated, generating the corresponding bicyclic products in good chemical yield (**6a**–**i**). More electron-rich alkyne substituents were also tolerated (**6e**). All of the Michael acceptors examined were also tolerated (**6f**–**i**). Notably, this synthetic procedure is scalable and practical providing **6d** in 67% yield when performed on a 2.5 mmol scale.

These architectures comprise other functional groups that can be engaged. For example, reduction of the ene–guanidine in **6d** cleanly provides the saturated tetrahydroimidazolpyrimidone **7** (Scheme 3a). Attempts to isomerize the alkene and generate the dihydroimidazolpyrimidone under acidic conditions were unsuccessful. Exposure of **6d** to 1:1 CH_2Cl_2:TFA returned the starting material with the alkene both constitutionally and geometrically intact. We did, however, observe that the alkene

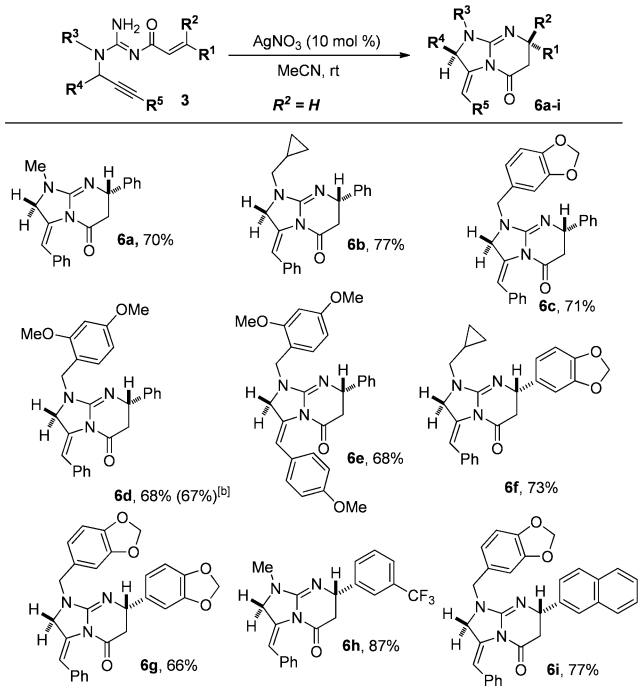
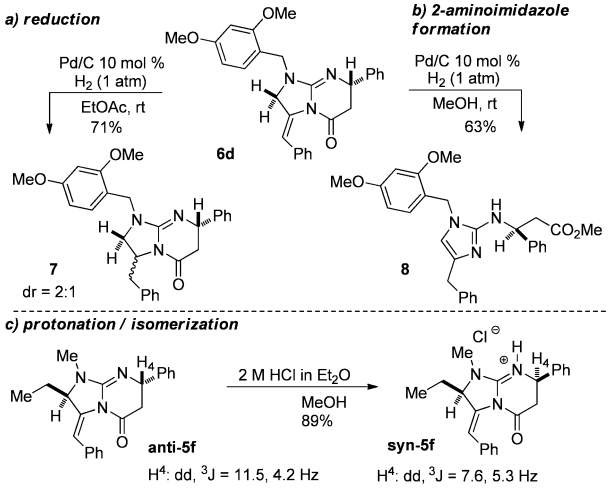


Figure 3. Substrate scope for the cyclization/Michael addition catalyzed by $AgNO_3$ where R^4 = H. Reaction conditions: substrate (0.3 mmol), $AgNO_3$ (10 mol %), MeCN (0.1 M), 8 h. The diastereomeric ratios were determined by ^{1}H NMR analysis of the crude mixture. [b] Performed on a 2.5 mmol scale.

Scheme 3. Transformation of the Resultant Bicyclic Guanidines



could be isomerized under hydrogenolysis conditions. In the presence of a nucleophilic solvent, the ring-opened methyl ester **8** can be obtained, representing an interesting entry to *N*-imidazolyl-β-amino ester (Scheme 3b). Interestingly, attempts to isomerize the alkene in *anti*-**5f** with HCl/Et_2O/MeOH did not affect the alkene (Scheme 3c). Instead, epimerization occurred at C^4, as evidenced by the smaller diaxial ^3J coupling to H^4, suggesting that the Michael addition is reversible under acidic conditions and that the *syn*-diastereomer is indeed thermodynamically preferred. It should be noted that resubjection of the isolated diastereomers or mixtures thereof to the original Ag-catalyzed reaction conditions does not change the product ratio, suggesting that the initial product ratio is kinetic.

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An initial evaluation of the biological activities of these intriguing scaffolds identified several members to be inhibitory toward the growth of an attenuated strain of *Mycobacterium tuberculosis* H37Ra. For example, compound **6d** inhibited growth with an IC_{50} = 7.7 μM and showed only moderate cytotoxicity against human CEM-TART T-cells[16] (IC_{50} = 53.0 μM).[17] The *syn*-diastereomer of compound *syn*-**4d** was also active with an IC_{50} = 8.6 μM but was slightly more cytotoxic toward T-cells (IC_{50} = 32.1 μM). Interestingly, the diastereomeric compound, *anti*-**4d**, showed no activity suggesting a specific molecular interaction might be responsible for its activity. Compound **4d** was active against a broader range of organisms including Gram-negative bacteria (*Escherichia coli*; MIC_{100} = 25.0 μM and *Acinetobacter baumanii*; MIC_{100} = 12.5 μM) as well as the Gram-positive bacterium *Bacillus subtilus* (MIC_{100} = 6.25 μM) and opportunistic fungi *Candida albicans* (MIC_{100} = 12.5 μM). Current studies are aimed at penetrating the mechanism of action of these new bicyclic guanidines antimicrobial agents.

In summary, we have developed a method for the synthesis of highly substituted bicyclic guanidines in good to excellent yields from readily accessible propargylguanidines. This cascade hydroamination−Michael addition sequence gives rise to products as a single regioisomer and with a constitutionally and geometrically stable ene−guanidine functional group. Substituent variations can deliver products with high diastereoselectivity despite the newly formed stereocenter being five atoms removed and spanned by an almost planar heterocyclic core. These interesting scaffolds have already garnered our interest as antitubercular agents. The modularity of this approach should expedite follow-up investigations to identify candidates with increased potency and selectivity against *M. tuberculosis*.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) See Supporting Information for Dose repsonse curves of Mtb to compounds **6d** and *syn*-**4d**.