JOC The Journal of Organic Chemistry

Article

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Halocyclization of Unsaturated Guanidines Mediated by Koser's Reagent and Lithium Halides

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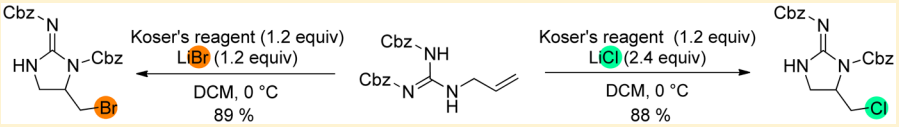
Supporting Information



ABSTRACT: The synthesis of halogenated cyclic guanidines through iodine(III)-mediated *umpolung* of halide salts is described. Cyclic guanidines of various sizes can be obtained with generally excellent regioselectivities through either a chloro- or a bromocyclization, using Koser's reagent and the corresponding lithium salt.

INTRODUCTION

Among nitrogen-containing heterocycles, cyclic guanidines hold a special place because of their particular properties such as strong basicity and rigidity. Guanidines in general possess interesting features from the organic chemist's point of view,[1] which has thus led to the development of many strategies for their synthesis.[2] Additionally, the guanidine motif can be found in a myriad of natural products.[3] Specifically, many of them incorporate the synthetically challenging cyclic guanidine moiety, toward which a considerable number of studies have been devoted in the field of total synthesis.[4]

Our own interest has been directed toward the synthesis of cyclic guanidine-containing amino acids such as enduracididine **1**[5] and tetrahydrolathyrine **2** (Figure 1).[6] These nonproteinogenic amino acids, as well as related congeners such as *β*-hydroxy-enduracididine[7] and capreomycidine,[8] can be considered as rigid analogues of arginine, and most of these have been found to be constituents of antibiotic cyclopeptides such as enduracidin,[9] capreomycin, or the very recently discovered teixobactin **3**, highly promising for treating resistant bacteria.[10]

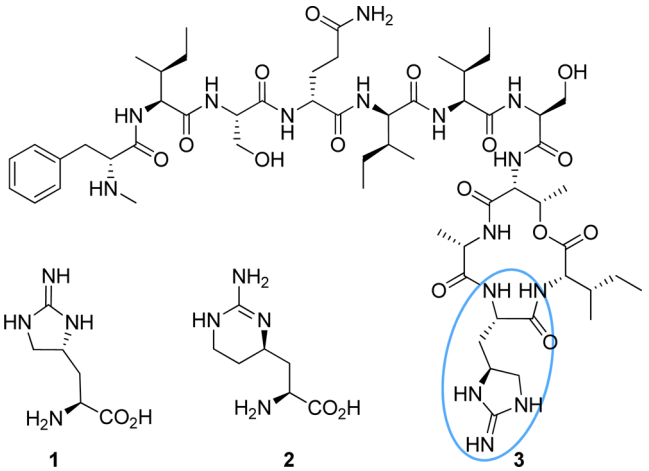
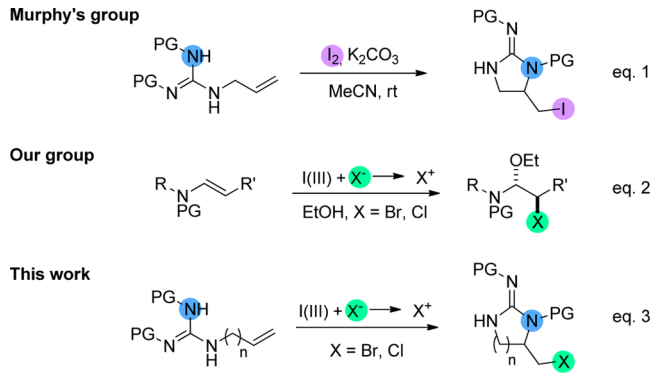


Figure 1. Structures of enduracididine **1**, tetrahydrolathyrine **2**, and teixobactin **3**.

While construction of cyclic guanidines is often tedious, as we previously experienced,[5,6] the synthesis of acyclic guanidines can be readily achieved from the corresponding amines using a variety of guanidylating reagents.[11] Thus, devising a modular cyclization strategy from these available starting materials seemed rather appealing. Following this strategy, several methods have been described relying on the Rh-,[12] Pd-,[13] or Ag-catalyzed[14] amination of propargylic derivatives and on the iodine-[15] or NBS-triggered[16] aminohalogenation of allylic compounds (Scheme 1, eq 1). In particular, the halocyclization of guanidines has been performed as the key step for the total synthesis of saxitoxin[17] and axinellamines.[18] In order to broaden the scope of this strategy, we anticipated that the hypervalent iodine(III)-mediated *umpolung* of halide salts that

Scheme 1. Previous Studies and Envisioned Strategy



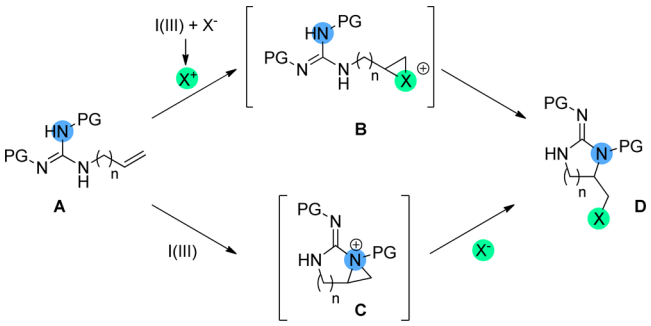
Received: July 28, 2015
Published: October 22, 2015

DOI: 10.1021/acs.joc.5b01750
J. Org. Chem. 2015, 80, 10624−10633

we recently employed for the ethoxyhalogenation of various enamides (eq 2)[19] should be amenable to initiating such a halocyclization (eq 3).

Hypervalent iodine derivatives have drawn much attention in the past few years because of their versatile reactivity, their accessibility, and their low toxicity.[20] Several cyclizations of guanidines[21] or amidines[22] have previously been reported relying on the oxidative properties of (diacetoxyiodo)benzene (PIDA). For our part, we wished to use the I(III) reagent to trigger the *umpolung* of a halide salt through a series of ligand exchanges around the central iodine atom,[19b] thereby generating an electrophilic species X^+ (Scheme 2, **A** → **B**)

Scheme 2. Plausible Mechanistic Pathways



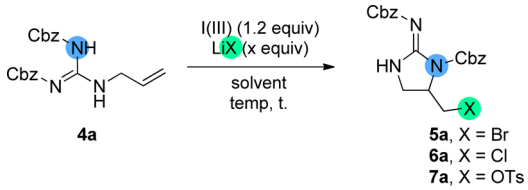
that could activate the double bond of an olefinic guanidine and enable the cyclization. While only the *exo* mode is represented, both *exo* and *endo* modes can be operative depending on the substitution pattern. An alternative scenario, whereby the starting material would be oxidized first to give an aziridinium, can also be envisaged (**A** → **C**).[23] Subsequent trapping by the halide should lead to the same adduct **D**. In this latter case, the regiochemistry governing the opening of the aziridinium **C** would also depend on the substitution pattern. Overall, regardless of the pathway that is effectively operational, similar adducts would be obtained.

RESULTS AND DISCUSSION

We chose bis-Cbz-protected allyl guanidine **4a** as a model substrate and began our study by probing the feasibility of the bromocyclization. Remarkably, the combination of 1.2 equiv of PIDA and 2.5 equiv of LiBr in acetonitrile at room temperature provided cyclic guanidine **5a** in 78% yield (Table 1, entry 1). The reaction was equally efficient in more (EtOH) or less (DCM) polar solvents, and an excellent 82% yield was obtained in both cases (entries 2−3). While a 2-fold amount of Br vs OAc is optimal for the ligand exchange process, only one halide is transferred to the substrate. The amount of LiBr was thus decreased to 1.2 equiv, and the desired product was isolated with an improved 85% yield (Table 1, entry 4). However, under the same reaction conditions using 2.5 equiv of LiCl (instead of LiBr) in ethanol, only a 20% yield of the chlorinated product **6a** was obtained (Table 1, entry 5). A slightly higher yield of **6a** was obtained in acetonitrile (Table 1, entry 6), but changing the chloride sources to $FeCl_3$,[19b] $ZnCl_2$, or TBACl did not lead to further improvement. $PhICl_2$[24] also provided **6a** but with only a moderately improved yield (entry 7). Finally, [hydroxy(tosyloxy)iodo]benzene (Koser's reagent)[25,26] was examined, and although the reaction time was extended, it allowed the formation of the desired adduct **6a** in a much better 75% yield (entry 8). The latter could be further increased to 88% by running the reaction in dichloromethane at 0 °C (entry 9). Interestingly, when a lower amount of LiCl (1.2 equiv) was used, a competitive tosyloxycyclization took place (entries 10, 11).

In the absence of lithium halide, this tosyloxycyclization remained the only effective process, providing cyclic guanidine **7a** and the corresponding mono-deprotected adduct **7a′** in a 40% overall yield (entry 12). Finally, the optimal chlorocyclization conditions were applied to the bromocyclization reaction

Table 1. Optimization of Reaction Conditions for the Bromo- and Chlorocyclization of 4a



4a

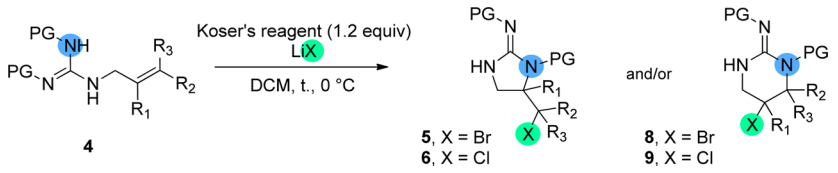
5a, X = Br
6a, X = Cl
7a, X = OTs

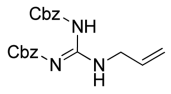
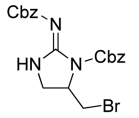
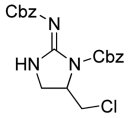
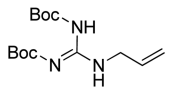
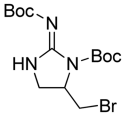
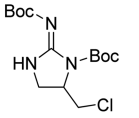
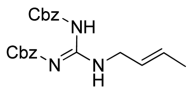
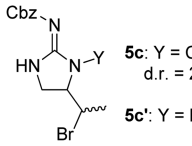
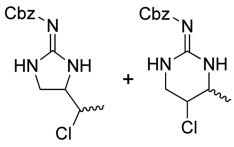
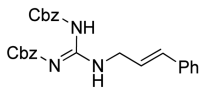
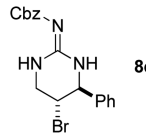
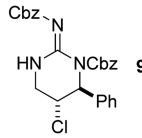
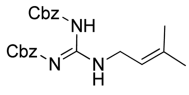
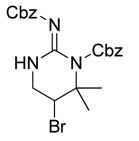
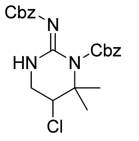
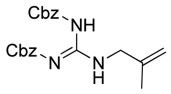
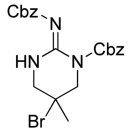
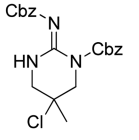
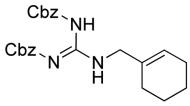
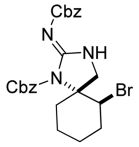
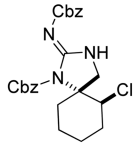
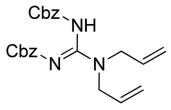
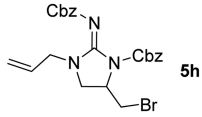
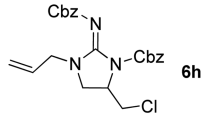
entry	I(III)	LiX (*x* equiv)	solvent	temp.	*t* (h)	yield (%)[a]
1	PIDA	LiBr (2.5)	MeCN	RT	1	**5a**, 78
2	PIDA	LiBr (2.5)	EtOH	RT	1	**5a**, 82
3	PIDA	LiBr (2.5)	DCM	RT	2	**5a**, 82
4	PIDA	LiBr (1.2)	EtOH	RT	1	**5a**, 85
5	PIDA	LiCl (2.5)	EtOH	RT	2	**6a**, 20
6	PIDA	LiCl (2.5)	MeCN	RT	1	**6a**, 31
7	$PhICl_2$		MeCN	RT	1	**6a**, 38
8	Koser's reagent	LiCl (2.4)	MeCN	RT	24	**6a**, 75
9	**Koser's reagent**	**LiCl (2.4)**	**DCM**	**0 °C**	**18**	**6a, 88**
10	Koser's reagent	LiCl (1.2)	MeCN	RT	24	**6a**, 33[b]
11	Koser's reagent	LiCl (1.2)	DCM	RT	24	**6a**, 73[c]
12	Koser's reagent		DCM	0 °C to RT	24	**7a**, 20[d]
13	**Koser's reagent**	**LiBr (1.2)**	**DCM**	**0 °C**	**1**	**5a, 89**

[a]Isolated yields. [b]The desired product was obtained in a mixture with **7a** (31%). [c]The desired product was obtained in a mixture with **7a** (15%). [d]Along with 20% of mono-Cbz adduct **7a′**.

DOI: 10.1021/acs.joc.5b01750
J. Org. Chem. 2015, 80, 10624−10633

Table 2. Substrate Scope for the Bromo- and Chlorocyclization of Allylic Guanidines



Entry	4	Substrate	Product	t. (h)	yield (%)[a]	Product	t.	yield (%)[a]
1	**4a**		 **5a**	1	89	 **6a**	18	88
2	**4b**		 **5b**	1	47	 **6b**	16	58
3	**4c**		 **5c**: Y = Cbz, d.r. = 2:1; **5c'**: Y = H	1	**5c**: 47[b]; **5c'**: 15	 **6c'** 1 : 0.5 **9c'**	17	quant.
4	**4d**		 **8d'**	2	51[c]	 **9d**	15	65[d]
5	**4e**		 **8e**	1	57	 **9e**	17	81
6	**4f**		 **8f**	1	76	 **9f**	24	76
7	**4g**		 **5g**	1	66[e]	 **6g**	16	61
8	**4h**		 **5h**	4	95	 **6h**	18	73

[a]Isolated yields; quant.: quantitative yield. [b]X-ray analysis confirmed the structure of both diastereomers. [c]X-ray analysis confirmed the relative configuration and the position of the remaining Cbz group. [d]X-ray analysis of the mono-deprotected **9d′** confirmed the relative configuration. [e]X-ray analysis of the mono-deprotected **5g′** confirmed the relative configuration.

which proceeded smoothly to give 89% yield of the desired product **5a** (entry 13).

We then went on to explore the scope of both processes starting with diversely substituted allylic guanidines (Table 2). First, the Cbz protecting groups of **4a** (entry 1) were replaced by Boc groups (**4b**). The reaction still proceeded but with a decreased efficiency (entry 2) aggravated by the moderate stability of the *t*-butylcarbamate group on silica gel. The *N*-Cbz-protected *E*-crotyl derivative **4c** is the only substrate for which some strong discrepancies between the bromo- and chlorocyclization processes were observed (entry 3). On the one hand, the bromocyclization proceeded in an *exo* fashion to give a mixture of bis- and mono-protected diastereoisomers **5c** and **5c′**, respectively. On the other hand, the chlorocyclization of **4c** exclusively led to mono-protected guanidines, though as a mixture of *exo* and *endo* adducts, **6c′** and **9c′**, respectively. In the cases of cinnamyl, prenyl, and methallyl derivatives **4d**–**f**, the *endo* mode became exclusive for both halides, leading to six-

DOI: 10.1021/acs.joc.5b01750
J. Org. Chem. 2015, 80, 10624−10633

membered halo-guanidines (entries 4–6). Interestingly, starting from **4d**, the process yielded only single diastereoisomers of adducts **8d′** (mono-protected) and **9d**; for both compounds, the relative configuration was confirmed by X-ray analysis.[27] In this case, as well as that of the prenyl derivative **4e**, the divergence in cyclization mode (from *5-exo* to *6-endo*) may be due to the stabilization of a positive charge (whether a carbocation or a partial transient charge) at the 6-position. However, in the case of methallyl derivative **4f**, steric hindrance at the 5-position may rather be the determining factor. For cyclohexenyl compound **4g**, the *5-exo* cyclization mode was fully re-established to yield the corresponding halo spiro compounds **5g** and **6g** (entry 7). Easily accessing this chlorinated spiro-guanidine framework is particularly interesting when considering the tremendous synthetic efforts that have recently been devoted to generate this type of scaffold.[18] Finally, bis-allylic substrate **4h** was subjected to the reaction conditions and cleanly afforded monoallylated guanidines **5h** and **6h**, which were obtained in excellent yields (entry 8).

While the substrate scope was quite general for allylic derivatives, some limitations were evidenced (Figure 2). First,

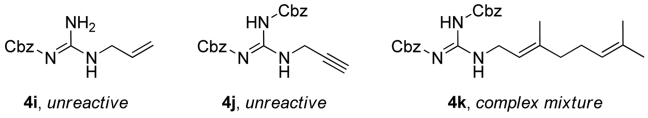


Figure 2. Substrate limitations.

mono-protected guanidine **4i** failed to react under the optimal reaction conditions (using either LiBr or LiCl). This was also true for the di-protected propargylic derivative **4j** that remained virtually untouched, which noticeably differs from metal-catalyzed strategies.[12−14] Finally, geranyl-derived substrate **4k** only led to complex mixtures due to a lack of selectivity of both brominating and chlorinating processes.

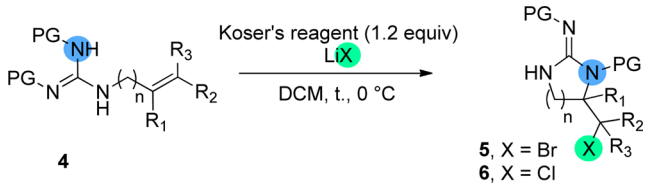
Regardless, the halo-cyclization reaction was still operative when longer unsaturated chains were appended to the guanidine moiety (Table 3). Homoallylic guanidine **4l** yielded the corresponding six-membered bromo- and chloro-adducts with good yields, concomitant with the partial (chloro) or total (bromo) loss of one Cbz group in the final product (entry 1).

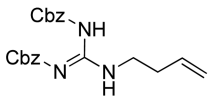
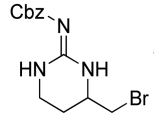
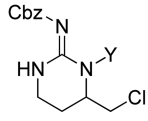
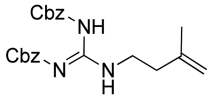
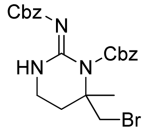
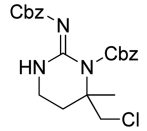
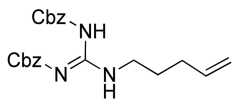
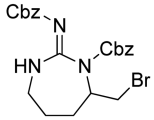
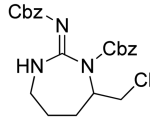
In both cases, the cyclization mode was exclusively *exo* as it was for the substrate having an additional methyl on the double bond **4m** (entry 2). Contrary to what was observed for the methallyl substrate **4f**, no product of endocyclization could be detected for substrate **4m**, presumably because the formation of a seven-membered ring is highly disfavored. Nevertheless, the seven-membered ring can be obtained, albeit in moderate yield, through the *exo* cyclization of pentenyl derivative **4n** (entry 3).

In order to appreciate the synthetic potential of the compounds prepared by our methodology, the five-membered bromo guanidine **5a** was subjected to several transformations. First, the bromide could be converted to nitrile **10** in a modest (unoptimized) 33% yield (Scheme 3). This homologation could serve as the basis for the synthesis of tiruchanduramine, an α-glucosidase inhibitor that has been isolated from *Synoicum macroglossum*.[28] Substitution by an azide to give **11**, which can thereafter be reduced to the corresponding primary amine **12**, was also possible. This simple synthon can be viewed as an easily accessible precursor for synthesizing analogues of anatoxin-a(s), a highly potent anticholinesterase isolated from the green alga *Anabaena flos-aquae*.[29]

In summary, either the bromo- or the chlorocyclization of unsaturated guanidines can be achieved through Koser's reagent-mediated *umpolung* of the corresponding lithium halide. This versatile and tunable transformation tolerates a wide substrate scope, and depending on the substitution

Table 3. Substrate Scope for the Bromo- and Chlorocyclization of Unsaturated Guanidines



Entry	4	Substrate	Product	t. (h)	yield (%)[a]	Product	t. (h)	yield (%)[a]
1	**4l**		 **5l'**	1	52[b]	 **6l**: Y = Cbz **6l'**: Y = H	17	**6l** : 19 **6l'**: 50[b]
2	**4m**		 **5m**	1.5	49	 **6m**	24	60
3	**4n**		 **5n**	1.5	23	 **6n**	24	21

[a]Isolated yields. [b]X-ray analysis confirmed the structure and the position of the remaining Cbz group.

DOI: 10.1021/acs.joc.5b01750
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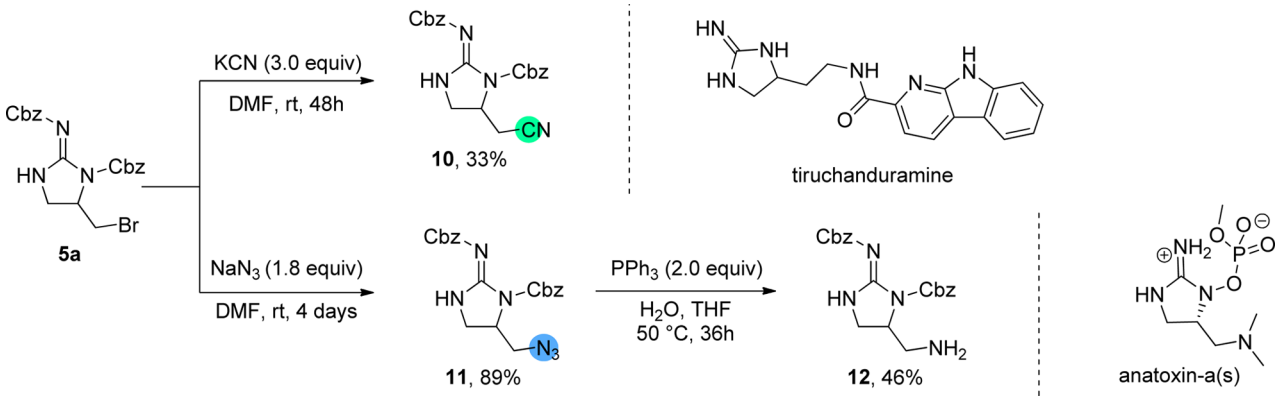
Scheme 3. Substrate Diversification



pattern of the starting olefin, various functionalized rings were obtained in moderate to high yields with overall good regio- and stereoselectivity. These compounds can serve as linchpins toward biologically relevant compounds, a line of research that is currently pursued in our group. Additionally, implementation of an asymmetric version of these transformations, using chiral hypervalent iodine reagents,[30] can be envisioned and will be investigated.

EXPERIMENTAL SECTION

General Methods. Melting points were measured in capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300 or 500 MHz NMR spectrometer. ^{13}C NMR spectra were recorded at 125 or 75 MHz using a broadband decoupled mode with the multiplicities obtained using a DEPT sequence. NMR experiments were carried out in $CDCl_3$, for which chemical shifts (δ) are reported in parts per million (ppm) with reference to $CDCl_3$ (^{1}H: 7.26; ^{13}C: 77.36) and MeOD, for which chemical shifts (δ) are reported in parts per million (ppm) with reference to MeOD (^{1}H: 3.34; ^{13}C: 49.86). Coupling constants (J) are reported in hertz (Hz). Mass spectra were obtained either with a LCT instrument using electrospray ionization (ES) or from a time-of-flight analyzer (ESI-MS) for the high-resolution mass spectra (HRMS). Flash chromatography was conducted on silica gel 60 (40-63 μm) at medium pressure (300 mbar). All reagents were obtained from commercial suppliers unless otherwise stated. Allylamine, geranylamine, and propargylamine were commercially available. 3-Methylbut-2-en-1-amine hydrochloride, 2-methylprop-2-en-1-amine hydrochloride, but-2-en-1-amine hydrochloride, but-3-en-1-amine hydrochloride, (*E*)-3-phenylprop-2-en-1-amine hydrochloride, and pent-4-en-1-amine hydrochloride were synthesized from the corresponding bromides by a previously reported two-step sequence (potassium phthalimide addition, followed by hydrazine-mediated deprotection).[15g] 3-Methylbut-3-en-1-amine was synthesized from the corresponding alcohol by a previously reported two-step sequence (phthalimide addition under Mitsunobu conditions, followed by hydrazine-mediated deprotection).[15g] Cyclohex-1-en-1-ylmethanamine hydrochloride was synthesized from the corresponding ester by a four-step sequence (reduction and bromination,[31] then potassium phthalimide addition, followed by hydrazine-mediated deprotection[15g]).

General Procedure 1: Guanidine Synthesis. To a solution of 1,3-bis(benzoxycarbonyl)-2-methyl-2-isothiourea (0.5 mmol, 179 mg, 1 equiv) in MeCN (15 mL) was added the amine (1 mmol, 2 equiv). The solution was stirred under argon for 20−48 h at room temperature. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (17:3 *n*Hept/EtOAc).

General Procedure 1′: Guanidine Synthesis. The procedure was identical to **GP1** except that triethylamine (1 mmol, 0.14 mL, 101 mg, 2 equiv) was added to the reaction mixture before addition of the amine hydrochloride (1 mmol, 2 equiv).

*N-Allyl-N′,N″-bis-Cbz-guanidine (**4a**).* Following **GP1** using 0.8 mL (0.57 g, 10 mmol, 2 equiv) of allylamine. 1.671 g, 91% yield, colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.80 (brs, 1H), 8.44 (brs, 1H), 7.44−7.31 (m, 10H), 5.91 (ddt, J = 17.4, 10.4, 5.5 Hz, 1H), 5.27 (d, J = 17.4 Hz, 1H), 5.21 (d, J = 10.4 Hz, 1H), 5.21 (s, 2H), 5.17 (s, 2H), 4.12−4.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 156.0, 154.0, 136.9, 134.8, 133.1, 128.9, 128.8, 128.6, 128.5, 128.3, 128.1, 117.0, 68.3, 67.3, 43.5; IR (neat) 3336, 1728, 1634, 1572, 1418, 1382, 1318, 1239, 1207, 1134, 1055, 742, 697 cm^{-1}; HRMS calcd for $C_{20}H_{21}N_3O_4$, $(M + H)^+$ 368.1610 found, 368.1604. Data in accordance with those described in the literature.[15g]

*N-Allyl-N′,N″-bis-Boc-guanidine (**4b**).* To a solution of *S*-methyl-*N*,*N*′-bis(*tert*-butoxycarbonyl)isothiourea (2.06 mmol, 595 mg, 1 equiv) in acetonitrile (60 mL) was added allylamine (0.30 mL, 228 mg, 4.0 mmol, 2 equiv). The solution was stirred under argon for 24 h at room temperature. The solvent was removed under reduced pressure to afford 597 mg, 97% yield, of the product as a light yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.45 (brs, 1H), 8.32 (brs, 1H), 5.83−5.78 (m, 1H), 5.17−5.07 (m, 2H), 4.00−3.97 (m, 2H), 1.41 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 155.8, 153.0, 133.1, 116.4, 82.8, 79.0, 43.0, 28.0, 27.8. Data in accordance with those described in the literature.[15g]

*N-But-2-enyl-N′,N″-bis-Cbz-guanidine (**4c**).* Following **GP1′** using 108 mg (1 mmol, 2 equiv) of but-2-en-1-amine hydrochloride. 91 mg, 48% yield, white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.64 (brs, 1H), 8.17 (brs, 1H), 7.31−7.15 (m, 10H), 5.60−5.53 (m, 1H), 5.44−5.36 (m, 1H), 5.06 (s, 2H), 5.02 (s, 2H), 3.90−3.85 (m, 2H), 1.60−1.55 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 155.9, 154.1, 137.1, 134.9, 134.1, 129.0, 128.9, 128.7, 128.6, 128.4, 128.2, 125.8, 68.4, 67.4, 43.3, 18.0; IR (neat) 3340, 3034, 2939, 1727, 1600, 1568, 1425, 1381, 1318, 1205, 1133, 1052 cm^{-1}; HRMS calcd for $C_{21}H_{23}N_3O_4$, $(M + H)^+$ 382.1767 found, 382.1758.

*N-(E)-3-Phenylprop-2-enyl-N′,N″-bis-Cbz-guanidine (**4d**).* Following **GP1′** using 170 mg (1 mmol, 2 equiv) of (*E*)-3-phenylprop-2-en-1-amine hydrochloride. 122 mg, 55% yield, white solid.(The product was contaminated with ca. 30% of *N*-3-phenylpropanyl-*N*′,*N*″-bis-Cbz-guanidine that was unreactive under the cyclization conditions); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.67 (brs, 1H), 8.34 (brs, 1H), 7.30−7.08 (m, 15H), 6.44 (d, J = 15.8 Hz, 1H), 6.10 (dt, J = 15.8, 6.3 Hz, 1H), 5.07 (s, 2H), 5.03 (s, 2H), 4.12 (dd, J = 6.0, 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 156.1, 154.1, 137.0, 136.6, 134.9, 133.0, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 128.1, 126.7, 124.4, 68.5, 67.5, 43.3; IR (neat) 3337, 3031, 2949, 1726, 1633, 1618, 1566, 1422, 1380, 1353, 1315, 1201, 1131, 1048 cm^{-1}; HRMS calcd for $C_{26}H_{25}N_3O_4$, $(M+H)^+$ 444.1923 found, 444.1918.

*N-3-Methylbut-2-enyl-N′,N″-bis-Cbz-guanidine (**4e**).* Following **GP1′** using 122 mg (1 mmol, 2 equiv) of 3-methylbut-2-en-1-amine hydrochloride. 83 mg, 42% yield, white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.62 (brs, 1H), 8.02 (brs, 1H), 7.31−7.15 (m, 10H), 5.15−5.11 (m, 1H), 5.06 (s, 2H), 5.03 (s, 2H), 3.90−3.86 (m, 2H), 1.62 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 155.5, 153.8, 137.6, 136.8, 134.6, 128.7, 128.6, 128.3, 128.1, 127.8, 118.7, 68.0, 67.1,

DOI: 10.1021/acs.joc.5b01750
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39.3, 25.6, 17.9; IR (neat) 3341, 3065, 2994, 1727, 1622, 1567, 1425, 1381, 1331, 1304, 1240, 1203, 1134, 1053 cm^{-1}; HRMS calcd for $C_{22}H_{25}N_3O_4$, $(M + H)^+$ 396.1923 found, 396.1916. Data in accordance with those described in the literature.[15g]

*N-2-Methylprop-2-enyl-N′,N″-bis-Cbz-guanidine (**4f**).* Following **GP1′** using 108 mg (1 mmol, 2 equiv) of 2-methylprop-2-en-1-amine hydrochloride. 117 mg, 61% yield, colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 11.67 (brs, 1H), 8.34 (brs, 1H), 7.14−7.29 (m, 10H), 5.07 (s, 2H), 5.01 (s, 2H), 4.78−4.77 (m, 2H), 3.90 (d, J = 5.5 Hz, 2H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 156.3, 154.1, 140.9, 137.0, 134.9, 129.0, 128.9, 128.7, 128.6, 128.4, 128.2, 111.5, 68.5, 67.5, 46.7, 20.8; IR (neat) 3338, 3034, 2924, 1717, 1633, 1619, 1571, 1422, 1381, 1314, 1232, 1135, 1093, 1043 cm^{-1}; HRMS calcd for $C_{21}H_{23}N_3O_4$, $(M + H)^+$ 382.1767 found, 382.1769.

*N-Methylcyclohex-1-enyl-N′,N″-bis-Cbz-guanidine (**4g**).* Following **GP1′** using 148 mg (1 mmol, 2 equiv) of cyclohex-1-en-1-ylmethanamine hydrochloride. 136 mg, 64% yield, yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 11.67 (brs, 1H), 8.22 (brs, 1H), 7.30−7.16 (m, 10H), 5.51−5.50 (m, 1H), 5.07 (s, 2H), 5.01 (s, 2H), 3.83 (d, J = 4.7 Hz, 2H), 1.91−1.84 (m, 4H), 1.54−1.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 155.9, 153.8, 136.7, 134.6, 133.0, 128.8, 128.7, 128.4, 128.4, 128.1, 127.9, 123.8, 68.1, 67.1, 47.0, 26.6, 25.0, 22.4, 22.2; IR (neat) 3341, 2931, 2606, 2499, 1727, 1640, 1571, 1437, 1383, 1319, 1230, 1206, 1127, 1052 cm^{-1}; HRMS calcd for $C_{24}H_{27}N_3O_4$, $(M + H)^+$ 422.2080 found, 422.2065.

*N-Diallyl-N′,N″-bis-Cbz-guanidine (**4h**).* To a solution of diallylamine (70 μL, 58 mg, 0.6 mmol, 1.2 equiv) in DCM (3 mL) was added 1,3-bis(benzoxycarbonyl)-2-methyl-2-thiopseudourea (179 mg, 0.5 mmol, 1 equiv) in DCM (2 mL). Then, silver triflate (180 mg, 0.7 mmol, 1.4 equiv) was added. The solution was stirred under argon for 62 h at room temperature. Water was added, and the solution was extracted with DCM (2 × 10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product. Flash column chromatography (17:3 *n*Hept/EtOAc) afforded 85 mg, 42% yield, of the product as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 10.27 (brs, 1H), 7.36−7.28 (m, 10H), 5.88−5.75 (m, 2H), 5.23 (s, 2H), 5.19 (d, J = 6.7 Hz, 1H), 5.187 (d, J = 6.7 Hz, 1H), 5.15 (d, J = 6.9 Hz, 4H), 4.06−4.03 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 156.0, 136.9, 135.5, 132.6, 128.9, 128.8, 128.7, 128.5, 128.2, 119.1, 68.4, 67.7, 51.2, 1CO not visible; IR (neat) 3150, 3033, 2949, 1752, 1641, 1600, 1483, 1442, 1411, 1378, 1276, 1251, 1212, 1173, 1108 cm^{-1}; HRMS calcd for $C_{23}H_{25}N_3O_4$, $(M + H)^+$ 408.1923 found, 408.1916.

*N-Allyl-N′-Cbz-guanidine (**4i**).* To a solution of (*N*)-benzyloxycarbonyl-1*H*-pyrazole-1-carboxamidine[32] (4.2 mmol, 1.026 g, 1 equiv) was added allylamine (40 mmol, 2.289 g, 3.0 mL, 9.5 equiv). The solution was stirred under argon for 2 h 30 min at 35 °C. The solution was cooled to room temperature, and the solvent was removed under reduced pressure to give the crude product. Flash column chromatography on silica gel (gradient from 15:5 to 0/20 *n*Hept/EtOAc) afforded 0.806 g, 82% yield, of the product as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (brs, 1H), 7.57−7.58 (m, 1H), 7.35−7.27 (m, 4H), 5.74−5.64 (m, 1H), 5.23 (d, J = 17.1 Hz, 1H), 5.16 (d, J = 10.3 Hz, 1H), 5.07 (s, 2H), 3.69 (d, J = 5.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 162.6, 137.5, 133.7, 128.6, 128.2, 128.0, 117.1, 66.4, 43.8. Data in accordance with those described in the literature.[15g]

*N-Propargyl-N′,N″-bis-Cbz-guanidine (**4j**).* Following **GP1** using 0.13 mL (110 mg, 2 mmol, 2 equiv) of propargylamine. Evaporation of the reaction mixture afforded 365 mg, quantitative yield, of the product as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 11.60 (brs, 1H), 8.35 (brs, 1H), 7.31−7.17 (m, 10H), 5.07 (s, 2H), 5.03 (s, 2H), 4.12 (dd, J = 5.1, 2.7 Hz, 2H), 2.18 (t, J = 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 155.6, 153.8, 136.7, 134.6, 129.0, 128.8, 128.6, 128.6, 128.3, 128.1, 78.6, 72.6, 68.5, 67.5, 31.0; IR (neat) 3336, 3289, 3034, 1728, 1617, 1563, 1424, 1380, 1346, 1310, 1288, 1237, 1201, 1133, 1085, 1050 cm^{-1}; HRMS calcd for $C_{20}H_{19}N_3O_4$, $(M + H)^+$ 366.1454 found, 366.1440.

*N-Geranyl-N′,N″-bis-Cbz-guanidine (**4k**).* Following **GP1** using 0.18 mL (153 mg, 1 mmol, 2 equiv) of geranylamine. 218 mg, 94% yield, yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 11.64 (brs, 1H), 8.05 (brs, 1H), 7.31−7.15 (m, 10H), 5.13 (t, J = 6.6 Hz, 1H), 5.06 (s, 2H), 5.03 (s, 2H), 4.97 (t, J = 7.0 Hz, 1H), 3.93−3.89 (m, 2H), 2.02−1.88 (m, 4H), 1.58 (s, 3H), 1.56 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 155.9, 154.1, 141.2, 136.9, 135.0, 131.9, 129.0, 128.9, 128.7, 128.6, 128.4, 128.1, 124.0, 118.9, 68.3, 67.4, 39.7, 39.5, 26.6, 25.9, 18.0, 16.7; IR (neat) 3340, 2924, 1727, 1635, 1619, 1565, 1423, 1380, 1301, 1236, 1201, 1129, 1050 cm^{-1}; HRMS calcd for $C_{27}H_{33}N_3O_4$, $(M + H)^+$ 464.2549 found, 464.2540.

*N-But-3-enyl-N′,N″-bis-Cbz-guanidine (**4l**).* Following **GP1′** using 108 mg (1 mmol, 2 equiv) of but-3-en-1-amine hydrochloride. 121 mg, 63% yield, white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 11.64 (brs, 1H), 8.23 (brs, 1H), 7.15−7.31 (m, 10H), 5.68 (ddt, J = 16.8, 10.2, 6.9 Hz, 1H), 5.07−5.01 (m, 2H), 5.07 (s, 2H), 5.03 (s, 2H), 3.42 (td, J = 6.8, 5.4 Hz, 2H), 2.23 (tdt, J = 6.8, 6.6, 1.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 156.2, 154.0, 137.0, 134.9, 129.0, 128.9, 128.6, 128.6, 128.4, 128.1, 118.0, 66.3, 67.4, 40.5, 33.3; IR (neat) 3338, 3128, 2952, 1729, 1640, 1572, 1426, 1382, 1322, 1263, 1213, 1138, 1054 cm^{-1}; HRMS calcd for $C_{21}H_{23}N_3O_4$, $(M + H)^+$ 382.1767 found, 382.1786.

*N-3-Methylbut-3-enyl-N′,N″-bis-Cbz-guanidine (**4m**).* Following **GP1** using 85 mg (1 mmol, 2 equiv) of 3-methylbut-3-en-1-amine. 151 mg, 76% yield, white solid; ^1H NMR (500 MHz, $CDCl_3$) δ 11.62 (brs, 1H), 8.19 (brs, 1H), 7.30−7.15 (m,10H), 5.08 (s, 2H), 5.02 (s, 2H), 4.77 (s, 1H), 4.69 (s, 1H), 3.47 (td, J = 6.8, 5.2 Hz, 2H), 2.19 (t, J = 6.8 Hz, 2H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 156.2, 154.1, 142.2, 136.9, 135.0, 129.0, 129.0, 128.7, 128.7, 128.4, 128.2, 113.2, 68.4, 67.4, 39.3, 37.0, 22.3; IR (neat) 3336, 3034, 2893, 1728, 1625, 1621, 1565, 1423, 1314, 1235, 1199, 1133, 1042 cm^{-1}; HRMS calcd for $C_{22}H_{25}N_3O_4$, $(M + H)^+$ 396.1923 found, 396.1911. Data in accordance with those described in the literature.[15g]

*N-Pent-4-enyl-N′,N″-bis-Cbz-guanidine (**4n**).* Following **GP1′** using 122 mg (1 mmol, 2 equiv) of pent-4-en-1-amine hydrochloride. 191 mg, 96% yield, white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 11.78 (brs, 1H), 8.35 (brs, 1H), 7.43−7.30 (m, 10H), 5.82 (ddt, J = 16.9, 9.9, 6.8 Hz, 1H), 5.20 (s, 2H), 5.15 (s, 2H), 5.05−5.00 (m, 2H), 3.47 (td, J = 7.0, 6.0 Hz, 2H), 2.14 (td, J = 7.2, 6.8 Hz, 2H), 1.71 (tt, J = 7.0, 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 156.2, 154.2, 137.6, 137.1, 134.9, 129.0, 128.9, 128.7, 128.6, 128.4, 128.1, 115.8, 68.4, 67.4, 40.8, 31.2, 28.4; IR (neat) 3319, 2928, 1720, 1637, 1621, 1578, 1431, 1256, 1209, 1137, 1050 cm^{-1}; HRMS calcd for $C_{22}H_{25}N_3O_4$, $(M + H)^+$ 396.1923 found, 396.1920. Data in accordance with those described in the literature.[21c]

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-5-((tosyloxy)methyl)-imidazolidine-1-carboxylate (**7a**) and (2-(((Benzyloxy)carbonyl)-imino)imidazolidin-4-yl)methyl 4-Methylbenzenesulfonate (**7a′**).* A solution of guanidine **4a** (37 mg, 0.1 mmol, 1 equiv) in DCM (2.5 mL) was cooled to 0 °C. Koser's reagent (0.12 mmol, 47 mg, 1.2 equiv) was added, and the solution was stirred for 24 h at 0 °C and then for 48 h at room temperature. The solvent was removed under reduced pressure to give the crude product. Flash column chromatography (DCM + 1.5% MeOH) afforded 11 mg (0.02 mmol, 20% yield) of the product **7a** as a white solid and 8 mg (0.02 mmol, 20% yield) of the product **7a′** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2H), 7.41−7.27 (m, 12H), 5.19 (s, 2H), 5.14 (s, 2H), 4.46−4.43 (m, 1H), 4.18−4.09 (m, 2H), 3.77−3.75 (m, 1H), 3.67−3.57 (m, 1H), 3.48−3.44 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 145.6, 135.5, 132.5, 130.3, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 69.0, 68.6, 67.8, 54.3, 44.2, 21.9, 3C not visible; IR (neat) 3345, 2893, 1760, 1712, 1653, 1598, 1306, 1237, 1163, 1025 cm^{-1}; HRMS calcd for $C_{27}H_{27}N_3O_7S$, $(M + Na)^+$ 560.1467 found, 560.1485.

^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.31−7.29 (m, 7H), 4.97 (s, 2H), 4.03−3.96 (m, 1H), 3.89−3.82 (m, 2H), 3.62 (dd, J = 9.5, 9.5 Hz, 1H), 3.34 (dd, J = 9.5, 5.8 Hz, 1H), 2.43 (s, 3H), 2 NH not visible; IR (neat) 3376, 3066, 2921, 2850, 1647, 1610, 1364, 1305, 1292, 1244, 1174, 1127, 1086, 956 cm^{-1}; HRMS calcd for $C_{19}H_{21}N_3O_5S$, $(M + H)^+$ 404.1280 found, 404.1286.

General Procedure for Bromocyclization. A solution of guanidine **4** (0.1 mmol, 1 equiv) and LiBr (0.12 mmol, 10 mg, 1.2

DOI: 10.1021/acs.joc.5b01750
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equiv) in DCM (2.5 mL) was cooled to 0 °C. Koser's reagent (0.12 mmol, 47 mg, 1.2 equiv) was added, and the solution was stirred for 1−4 h at 0 °C. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (DCM + 1−1.5% MeOH).

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-5-(bromomethyl)-imidazolidine-1-carboxylate (**5a**).* 40 mg, 89% yield, white solid; ^{1}H NMR (500 MHz, MeOD) δ 7.49−7.47 (m, 2H), 7.42−7.40 (m, 2H), 7.38−7.31 (m, 6H), 5.36 (d, J = 12.4 Hz, 1H), 5.27 (d, J = 12.4 Hz, 1H), 5.18−5.12 (m, 2H), 4.66−4.62 (m, 1H), 3.86−3.84 (m, 1H), 3.78−3.75 (m, 1H), 3.63−3.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 136.4, 134.9, 128.6, 128.4, 128.3, 128.0, 127.9, 68.5, 67.3, 55.6, 44.9, 32.9, 2C not visible; IR (neat) 3350, 1763, 1713, 1654, 1616, 1439, 1395, 1313, 1152, 740, 698 cm^{-1}; HRMS calcd for $C_{20}H_{20}{}^{79}BrN_3O_4$, $(M + H)^+$ 446.0715, found 446.0721.

*tert-butyl 5-(Bromomethyl)-2-((tert-butoxycarbonyl)imino)-imidazolidine-1-carboxylate (**5b**).* 18 mg, 47% yield, colorless oil; ^{1}H NMR (300 MHz, MeOD) δ 4.48−4.53 (m, 1H), 3.91 (dd, J = 13.0, 9.8 Hz, 1H), 3.80 (dd, J = 10.2, 5.9 Hz, 1H), 3.59−3.65 (m, 2H), 1.58 (s, 9H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.1, 82.8, 58.1, 36.6, 29.2, 29.1, 4C not visible; IR (neat) 3314, 2978, 2931, 1760, 1706, 1650, 1606, 1530, 1368, 1248, 1140 cm^{-1}; HRMS calcd for $C_{14}H_{24}{}^{79}BrN_3O_4$, $(M + H)^+$ 378.1028 found, 378.1022.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-5-(1-bromoethyl)-imidazolidine-1-carboxylate (**5c**).* 12 mg, 47% yield, mixture of two diastereoisomers (2:1), white solid, mp: 144−146 °C (CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) δ 7.48−7.47 (m, 2H), 7.41−7.32 (m, 8H), 5.39−5.34 (m, 1H), 5.28−5.25 (m, 1H), 5.19−5.09 (m, 2H), 4.77−4.70 (m, 1H), 4.61−4.42 (m, 1H), 4.26−4.27 (m, 1H), 3.95−3.60 (m, 2H), 1.62 (d, J = 7.2 Hz, 3H), 1.55 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.6, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.2, 123.9, 69.0, 67.8, 67.7, 66.9, 66.6, 60.2, 58.1, 52.5, 50.1, 50.0, 49.5, 45.0, 44.3, 40.7, 30.0, 21.7, 21.5, 20.5, 17.6, 6C not visible; IR (neat) 3347, 2955, 1762, 1712, 1651, 1615, 1436, 1396, 1380, 1310, 1265, 1235, 1144, 1026 cm^{-1}; HRMS calcd for $C_{21}H_{22}{}^{79}BrN_3O_4$, $(M + H)^+$ 460.0872, found 460.0870.

*Benzyl (4-(1-Bromoethyl)imidazolidin-2-ylidene)carbamate (**5c′**).* 3 mg, 15% yield, one diastereoisomer, white solid; ^{1}H NMR (300 MHz, MeOD) δ 7.30−7.42 (m, 5H), 5.02 (s, 2H), 4.26−4.31 (m, 1H), 3.86 (dd, J = 14.1, 3.8 Hz, 1H), 3.75−3.80 (m, 1H), 3.56 (dd, J = 14.1, 5.5 Hz, 1H), 1.37 (d, J = 7.1 Hz, 3H).

Benzyl ((4S,5R*)-5-Bromo-4-phenyltetrahydropyrimidin-2(1H)-ylidene)carbamate (**8d′**).* 20 mg, 51% yield, white solid; mp: 185−188 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (brs, 1H), 7.36−7.29 (m, 8H), 7.17−7.15 (m, 2H), 4.97 (d, J = 12.3 Hz, 1H), 4.93 (d, J = 12.3 Hz, 1H), 4.73 (m, 1H), 4.12 (ddd, J = 4.2, 4.2, 3.9 Hz, 1H), 3.43 (dd, J = 14.1, 3.9 Hz, 1H), 3.31 (dd, J = 14.1, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 158.3, 140.3, 137.4, 129.2, 128.8, 128.7, 128.5, 128.1, 126.7, 66.5, 60.4, 44.1, 43.1; IR (neat) 3242, 2989, 2855, 1628, 1558, 1454, 1387, 1336, 1245, 1204, 1160, 1052 cm^{-1}; HRMS calcd for $C_{18}H_{18}{}^{79}BrN_3O_2$, $(M + H)^+$ 388.0655, found 388.0638.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-5-bromo-6,6-dimethyl-tetrahydropyrimidine-1(2H)-carboxylate (**8e**).* 27 mg, 57% yield, colorless oil; ^{1}H NMR (300 MHz, MeOD) δ 7.45−7.48 (m, 2H), 7.35−7.40 (m, 4H), 7.30−7.33 (m, 4H), 5.28 (s, 2H), 5.07 (s, 2H), 4.50 (t, J = 4.5 Hz, 1H), 4.04 (dd, J = 14.6, 4.5 Hz, 1H), 3.73 (dd, J = 14.6, 4.5 Hz, 1H), 1.53 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 137.2, 131.0, 128.9, 128.7, 128.6, 128.6, 128.4, 128.3, 128.0, 69.7, 66.4, 49.9, 44.3, 28.6, 25.7, 2C not visible; IR (neat) 3234, 2977, 2875, 1727, 1640, 1553, 1455, 1387, 1345, 1281, 1263, 1144, 1037 cm^{-1}; HRMS calcd for $C_{22}H_{24}{}^{79}BrN_3O_4$, $(M + H)^+$ 474.1028, found 474.1032.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-5-bromo-5-methyltetra-hydropyrimidine-1(2H)-carboxylate (**8f**).* 35 mg, 76% yield, light yellow oil; the product is not stable in $CDCl_3$; ^{1}H NMR (300 MHz, MeOD) δ 7.48−7.51 (m, 2H), 7.32−7.43 (m, 8H), 5.32 (s, 2H), 5.16 (s, 2H), 4.06 (d, J = 10.7 Hz, 1H), 3.84 (d, J = 11.7 Hz, 1H), 3.64 (d, J = 10.7 Hz, 1H), 3.52 (d, J = 11.7 Hz, 1H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, MeOD) δ 139.5, 136.0, 130.4, 130.4, 130.3, 130.2, 130.2, 130.0, 129.9, 129.8, 129.6, 70.5, 62.2, 61.3, 53.9, 41.8, 24.5, 3C not visible; IR (neat) 3389, 2974, 1745, 1655, 1620, 1498, 1455, 1382, 1290, 1083 cm^{-1}; HRMS calcd for $C_{21}H_{22}{}^{79}BrN_3O_4$, $(M + H)^+$ 460.0872, found 460.0871.

(5R,6S*)-Benzyl 2-(((Benzyloxy)carbonyl)imino)-6-bromo-1,3-diazaspiro[4.5]decane-1-carboxylate (**5g**).* 33 mg, 66% yield, yellow oil; the product is not stable in $CDCl_3$. Attempts to recrystallize **5g** in CH_2Cl_2 led to the formation of crystals of mono-deprotected **5g′** that were suitable for X-ray analysis; ^{1}H NMR (300 MHz, MeOD) δ 7.51−7.49 (m, 2H), 7.41−7.29 (m, 8H), 5.32 (s, 2H), 5.19−5.10 (m, 2H), 3.90 (d, J = 11.8 Hz, 1H), 3.66 (d, J = 11.8 Hz, 1H), 2.42−2.33 (m, 1H), 2.24 (d, J = 13.3 Hz, 1H), 1.98 (d, J = 13.3 Hz, 1H), 1.81−1.64 (m, 4H), 1.47−1.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 157.7, 137.4, 128.8, 128.7, 128.6, 128.4, 128.2, 128.1, 68.8, 67.6, 55.4, 34.7, 34.2, 26.5, 22.3, 3C and 1CH not visible; IR (neat) 3335, 2941, 2865, 1713, 1649, 1620, 1436, 1382, 1326, 1294, 1264, 1162, 1138, 1118 cm^{-1}; HRMS calcd for $C_{24}H_{26}{}^{79}BrN_3O_4$, $(M + H)^+$ 500.1184, found 500.1183.

*Benzyl 3-Allyl-2-(((benzyloxy)carbonyl)imino)-5-(bromomethyl)-imidazolidine-1-carboxylate (**5h**).* 46 mg, 95% yield, colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.26 (m, 10H), 5.77 (ddt, J = 17.3, 9.6, 6.4 Hz, 1H), 5.29−5.28 (m, 1H), 5.25−5.23 (m, 1H), 5.18 (d, J = 12.3 Hz, 1H), 5.06 (d, J = 8.2 Hz, 1H), 5.02 (d, J = 8.2 Hz, 1H), 4.98 (d, J = 12.3 Hz, 1H), 4.53 (dddd, J = 8.7, 8.5, 2.8, 2.6 Hz, 1H), 4.0 (d, J = 6.4 Hz, 2H), 3.65−3.58 (m, 2H), 3.47 (dd, J = 10.3, 8.7 Hz, 1H), 3.36 (dd, J = 10.7, 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 151.4, 150.9, 137.1, 135.0, 131.3, 128.9, 128.8, 128.6, 128.5, 127.9, 120.0, 69.0, 67.5, 55.9, 47.8, 47.2, 32.9; IR (neat) 3033, 2952, 1753, 1712, 1615, 1487, 1455, 1389, 1260, 1190, 1109, 1026 cm^{-1}; HRMS calcd for $C_{23}H_{24}{}^{79}BrN_3O_4$, $(M + H)^+$ 486.1028, found 486.1052.

*Benzyl (4-(Bromomethyl)tetrahydropyrimidin-2(1H)-ylidene)-carbamate (**5l′**).* 17 mg, 52% yield, white solid; mp: 151−155 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, MeOD) δ 7.40−7.29 (m, 5H), 5.07 (s, 2H), 3.78−3.75 (m, 1H), 3.64−3.59 (m, 1H), 3.55−3.49 (m, 1H), 3.40−3.37 (m, 2H), 2.10−2.04 (m, 1H), 1.94−1.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 158.9, 137.7, 128.7, 128.4, 128.1, 66.5, 49.8, 36.2, 34.6, 30.0; IR (neat) 3250, 2922, 1630, 1561, 1455, 1387, 1341, 1245, 1158, 1052 cm^{-1}; HRMS calcd for $C_{13}H_{16}{}^{79}BrN_3O_2$, $(M + H)^+$ 326.0504, found 326.0510.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-6-(bromomethyl)-6-methyltetrahydropyrimidine-1(2H)-carboxylate (**5m**).* 23 mg, 49% yield, colorless oil; the product is not stable in $CDCl_3$; ^{1}H NMR (300 MHz, MeOD) δ 7.44−7.27 (m, 10H), 5.23 (s, 2H), 5.12 (d, J = 12.2 Hz, 1H), 5.06 (d, J = 12.2 Hz, 1H), 4.05 (d, J = 10.6 Hz, 1H), 3.77 (d, J = 10.6 Hz, 1H), 3.41−3.37 (m, 2H), 2.41−2.32 (m, 1H), 1.96−1.87 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 134.9, 129.0, 128.9, 128.8, 128.6, 128.6, 128.4, 128.3, 128.1, 128.0, 70.3, 67.2, 51.8, 40.7, 36.1, 30.1, 23.6, 3C not visible; IR (neat) 3256, 2927, 1742, 1631, 1608, 1497, 1455, 1384, 1348, 1262, 1228, 1160, 1083 cm^{-1}; HRMS calcd for $C_{22}H_{24}{}^{79}BrN_3O_4$, $(M + H)^+$ 474.1028, found 474.1034.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-7-(bromomethyl)-1,3-diazepane-1-carboxylate (**5n**).* 11 mg, 23% yield, colorless oil; the product is not stable in $CDCl_3$; ^{1}H NMR (300 MHz, MeOD) δ 7.41−7.29 (m, 10H), 5.19 (s, 2H), 5.18 (d, J = 12.5 Hz, 1H), 5.12 (d, J = 12.5 Hz, 1H), 4.43−4.35 (m, 1H), 3.76−3.71 (m, 1H), 3.51−3.40 (m, 2H), 3.31−3.29 (m, 1H), 2.07−2.02 (m, 1H), 1.97−1.92 (m, 1H), 1.77−1.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 130.2, 128.8, 128.7, 128.4, 128.3, 128.1, 68.6, 67.8, 56.1, 42.4, 31.4, 27.3, 22.9, 3C not visible; IR (neat) 3266, 2942, 1721, 1615, 1455, 1428, 1384, 1280, 1256, 1213, 1137 cm^{-1}; HRMS calcd for $C_{22}H_{24}{}^{79}BrN_3O_4$, $(M + H)^+$ 474.1023, found 474.1024.

General Procedure for Chlorocyclization. A solution of guanidine **4** (0.1 mmol, 1 equiv) and LiCl (0.24 mmol, 10 mg, 2.4 equiv) in DCM (2.5 mL) was cooled to 0 °C. Koser's reagent (0.12 mmol, 47 mg, 1.2 equiv) was added, and the solution was stirred for 15−24 h at 0 °C. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (DCM + 1−1.5% MeOH).

DOI: 10.1021/acs.joc.5b01750
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*Benzyl 2-(((Benzyloxy)carbonyl)imino)-5-(chloromethyl)-imidazolidine-1-carboxylate (**6a**).* 35 mg, 88% yield, white solid; ^{1}H NMR (500 MHz, MeOD) δ 7.48−7.32 (m, 10H), 5.36 (d, J = 12.4 Hz, 1H), 5.26 (d, J = 12.4 Hz, 1H), 5.18−5.12 (m, 2H), 4.66−4.65 (m, 1H), 3.91−3.83 (m, 2H), 3.74 (dd, J = 11.5, 2.3 Hz, 1H), 3.63 (dd, J = 11.5, 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 137.0, 135.0, 128.9, 128.8, 128.8, 128.6, 128.4, 128.3, 69.9, 69.0, 67.8, 56.4, 44.2, 2C not visible; IR (neat) 3346, 3033, 1762, 1713, 1653, 1614, 1497, 1438, 1395, 1380, 1238, 1157, 1015, 740, 697 cm^{-1}; HRMS calcd for $C_{20}H_{20}{}^{35}ClN_3O_4$, (M + H)$^+$ 402.1221, found 402.1223.

*tert-Butyl 2-((tert-Butoxycarbonyl)imino)-5-(chloromethyl)-imidazolidine-1-carboxylate (**6b**).* 19 mg, 58% yield, white solid; ^{1}H NMR (300 MHz, MeOD) δ 4.55−4.50 (m, 1H), 3.94−3.87 (m, 2H), 3.74 (dd, J = 11.5, 2.6 Hz, 1H), 3.67 (dd, J = 13.0, 3.9 Hz, 1H), 1.58 (s, 9H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, MeOD) δ 86.1, 82.7, 58.5, 52.2, 47.4, 29.2, 29.1, 3C not visible; IR (neat) 3321, 2978, 2933, 1760, 1706, 1650, 1607, 1531, 1368, 1319, 1248, 1140 cm^{-1}; HRMS calcd for $C_{14}H_{24}{}^{35}ClN_3O_4$, (M + H)$^+$ 334.1534, found 334.1537.

*Benzyl (4-(1-Chloroethyl)imidazolidin-2-ylidene)carbamate (**6c′**) and Benzyl (5-Chloro-4-methyltetrahydropyrimidin-2(1H)-ylidene)-carbamate (**9c′**).* 28 mg, quantitative yield, white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (brs, 1H), 9.16 (brs, 1H), 7.42−7.27 (m, 10H), 5.30−5.28 (m, 2H), 5.17−5.15 (m, 2H), 5.01 (s, 2H), 4.60−4.38 (m, 3H), 3.79−3.77 (m, 1H), 3.68−3.63 (m, 1H), 3.48−3.42 (m, 2H), 3.19−3.12 (m, 1H), 1.43 (d, J = 6.9 Hz, 3H), 1.38 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 158.1, 137.4, 134.6, 128.7, 128.6, 128.2, 68.9, 67.7, 66.6, 57.3, 54.8, 53.6, 52.1, 44.2, 20.9, 17.1; IR (neat) 3252, 2978, 2876, 1761, 1715, 1630, 1563, 1438, 1387, 1315, 1242, 1165, 1155, 1098, 1053, 1027 cm^{-1}; HRMS calcd for $C_{13}H_{16}{}^{35}ClN_3O_2$, (M + H)$^+$ 282.1009, found 282.1010.

(5R,6S*)-Benzyl 2-(((Benzyloxy)carbonyl)imino)-5-chloro-6-phenyltetrahydropyrimidine-1(2H)-carboxylate (**9d**).* 31 mg, 65% yield, one diastereoisomer, white solid; attempts to recrystallize **9d** in CH_2Cl_2 led to the formation of crystals of mono-deprotected **9d′** that were suitable for X-ray analysis; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (brs, 1H), 7.41−7.25 (m, 13H), 7.17−7.15 (m, 2H), 5.19−5.18 (m, 2H), 4.97 (d, J = 12.1 Hz, 1H), 4.92 (d, J = 12.1 Hz, 1H), 4.65 (d, J = 4.0 Hz, 1H), 4.05 (dt, J = 4.0, 4.0 Hz, 1H), 3.34 (dd, J = 13.9, 3.3 Hz, 1H), 3.24 (dd, J = 13.9, 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 158.4, 139.9, 137.5, 135.5, 129.2, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 128.1, 126.7, 69.9, 66.5, 60.1, 53.5, 42.6, 1C not visible; IR (neat) 3253, 2864, 1744, 1630, 1561, 1455, 1387, 1338, 1281, 1246, 1152, 1081, 1053, 1027 cm^{-1}; HRMS calcd for $C_{26}H_{24}{}^{35}ClN_3O_4$, (M + H)$^+$ 478.1533, found 478.1541.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-5-chloro-6,6-dimethyl-tetrahydropyrimidine-1(2H)-carboxylate (**9e**).* 35 mg, 81% yield, colorless oil; ^{1}H NMR (300 MHz, MeOD) δ 7.48−7.45 (m, 2H), 7.37−7.29 (m, 8H), 5.27 (s, 2H), 5.07 (s, 2H), 4.34 (t, J = 4.0 Hz, 1H), 3.91 (dd, J = 14.6, 4.0 Hz, 1H), 3.59 (dd, J = 14.6, 4.0 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 156.8, 154.1, 137.5, 134.9, 129.0, 128.8, 128.6, 128.2, 128.0, 70.4, 67.3, 58.8, 58.2, 44.3, 25.4, 22.2; IR (neat) 3259, 2928, 1746, 1633, 1600, 1497, 1455, 1387, 1348, 1270, 1257, 1220, 1150, 1094, 1026 cm^{-1}; HRMS calcd for $C_{22}H_{24}{}^{35}ClN_3O_4$, (M + H)$^+$ 430.1534, found 430.1514.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-5-chloro-5-methyltetrahydropyrimidine-1(2H)-carboxylate (**9f**).* 22 mg, 76% yield, colorless oil; ^{1}H NMR (500 MHz, MeOD) δ 7.50−7.48 (m, 2H), 7.42−7.31 (m, 8H), 5.32 (s, 2H), 5.15 (s, 2H), 4.15 (d, J = 11.7 Hz, 1H), 3.86 (d, J = 11.7 Hz, 1H), 3.71 (d, J = 11.7 Hz, 1H), 3.51 (d, J = 11.7 Hz, 1H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 134.6, 129.0, 128.7, 128.7, 128.6, 128.5, 128.3, 69.0, 67.7, 52.0, 50.4, 48.7, 24.1, 3C not visible; IR (neat) 3341, 2957, 1755, 1715, 1651, 1610, 1437, 1380, 1295, 1255, 1218, 1151, 1118, 1077 cm^{-1}; HRMS calcd for $C_{21}H_{22}{}^{35}ClN_3O_4$, (M + H)$^+$ 416.1377, found 416.1358.

(5R,6S*)-Benzyl 2-(((Benzyloxy)carbonyl)imino)-6-chloro-1,3-diazaspiro[4.5]decane-1-carboxylate (**6g**).* 28 mg, 61% yield, yellow oil; the product is not stable in $CDCl_3$; ^{1}H NMR (300 MHz, MeOD) δ 7.51−7.49 (m, 2H), 7.42−7.27 (m, 8H), 5.33 (s, 2H), 5.15 (s, 2H), 3.90 (d, J = 11.6 Hz, 1H), 3.62 (d, J = 11.6 Hz, 1H), 2.39−2.31 (m, 1H), 2.20−2.11 (m, 1H), 2.07−1.90 (m, 1H), 1.73−1.28 (m, 5H), CH not visible; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 157.7, 137.4, 135.2, 128.8, 128.7, 128.6, 128.5, 128.2, 127.9, 68.8, 67.6, 56.0, 48.7, 34.3, 33.8, 25.4, 22.3, 2C not visible; IR (neat) 3331, 2941, 2865, 1713, 1616, 1454, 1457, 1382, 1327, 1291, 1260, 1165, 1120, 1039 cm^{-1}; HRMS calcd for $C_{24}H_{26}{}^{35}ClN_3O_4$, (M + H)$^+$ 456.1690, found 456.1685.

*Benzyl 3-Allyl-2-(((benzyloxy)carbonyl)imino)-5-(chloromethyl)-imidazolidine-1-carboxylate (**6h**).* 32 mg, 73% yield, colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.26 (m, 10 H), 5.76 (ddt, J = 17.2, 9.8, 6.4 Hz, 1H), 5.30−5.28 (m, 1H), 5.25−5.23 (m, 1H), 5.17 (d, J = 12.4 Hz, 1H), 5.06 (d, J = 8.8 Hz, 1H), 5.01 (d, J = 8.8 Hz, 1H), 4.98 (d, J = 12.4 Hz, 1H), 4.51 (dddd, J = 8.5, 8.5, 3.3, 2.4 Hz, 1H), 4.02−3.97 (m, 2H), 3.76 (dd, J = 11.1, 3.3 Hz, 1H), 3.65−3.58 (m, 2H), 3.38 (dd, J = 10.6, 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 151.4, 151.0, 137.1, 135.0, 131.4, 128.9, 128.8, 128.5, 128.0, 120.0, 69.0, 67.5, 56.1, 47.8, 46.3, 44.0; IR (neat) 3033, 2923, 1751, 1712, 1613, 1487, 1455, 1388, 1251, 1191, 1107, 1009 cm^{-1}; HRMS calcd for $C_{23}H_{24}{}^{35}ClN_3O_4$, (M + H)$^+$ 442.1528, found 442.1526.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-6-(chloromethyl)tetrahydropyrimidine-1(2H)-carboxylate (**6l**).* 8 mg, 19% yield, white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (brs, 1H), 7.39−7.26 (m, 10H), 5.17 (d, J = 2.3 Hz, 2H), 5.06 (d, J = 1.3 Hz, 2H), 3.65 (tt, J = 6.2, 6.0 Hz, 1H), 3.50−3.46 (m, 2H), 3.24 (t, J = 6.0 Hz, 2H), 1.89−1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 135.6, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 69.9, 66.5, 50.2, 46.3, 36.4, 23.5; IR (neat) 3265, 2923, 1744, 1630, 1565, 1455, 1388, 1340, 1313, 1263, 1161, 1053 cm^{-1}; HRMS calcd for $C_{21}H_{22}{}^{35}ClN_3O_4$, (M + H)$^+$ 416.1377, found 416.1363.

*Benzyl (4-(Chloromethyl)tetrahydropyrimidin-2(1H)-ylidene)-carbamate (**6l′**).* 14 mg, 50% yield, white solid; mp: 141−145 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (brs, 1H), 7.29−7.18 (m, 5H), 4.98 (d, J = 1.4 Hz, 2H), 3.58−3.53 (m, 1H), 3.46−3.31 (m, 2H), 3.11 (t, J = 6.0 Hz, 2H), 1.77 (dt, J = 6.1, 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 158.9, 137.7, 128.7, 128.4, 128.1, 66.4, 50.0, 46.1, 36.1, 23.1; IR (neat) 3242, 2921, 1620, 1562, 1455, 1441, 1386, 1339, 1312, 1243, 1158, 1052 cm^{-1}; HRMS calcd for $C_{13}H_{16}{}^{35}ClN_3O_2$, (M + H)$^+$ 282.1009, found 282.1002.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-6-(chloromethyl)-6-methyltetrahydropyrimidine-1(2H)-carboxylate (**6m**).* 26 mg, 60% yield, colorless oil; the product is not stable in $CDCl_3$; ^{1}H NMR (300 MHz, MeOD) δ 7.44−7.25 (m, 10H), 5.22 (s, 2H), 5.12 (d, J = 12.5 Hz, 1H), 5.06 (d, J = 12.5 Hz, 1H), 4.15 (d, J = 11.4 Hz, 1H), 3.81 (d, J = 11.4 Hz, 1H), 3.46−3.37 (m, 2H), 2.33 (ddd, J = 14.0, 8.1, 5.2 Hz, 1H), 1.88 (ddd, J = 14.0, 6.7, 4.7 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 158.6, 137.6, 135.5, 129.0, 128.9, 128.8, 128.6, 128.4, 128.2, 69.9, 66.4, 58.4, 51.3, 35.6, 29.4, 25.5, 1C not visible; IR (neat) 3242, 2947, 1743, 1630, 1552, 1455, 1385, 1349, 1280, 1268, 1242, 1153, 1082 cm^{-1}; HRMS calcd for $C_{22}H_{24}{}^{35}ClN_3O_4$, (M + H)$^+$ 430.1534, found 430.1547.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-7-(chloromethyl)-1,3-diazepane-1-carboxylate (**6n**).* 9 mg, 21% yield, colorless oil; the product is not stable in $CDCl_3$; ^{1}H NMR (300 MHz, MeOD) δ 7.43−7.31 (m, 10H), 5.26 (s, 2H), 5.14 (s, 2H), 3.65−3.60 (m, 1H), 3.56−3.54 (m, 1H), 3.46−3.41 (m, 3H), 1.70−1.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 156.3, 154.2, 137.1, 134.9, 129.1, 129.0, 128.7, 128.7, 128.4, 128.2, 68.5, 67.4, 60.0, 45.4, 41.1, 29.5, 25.0; IR (neat) 3339, 2953, 1727, 1623, 1573, 1426, 1382, 1322, 1259, 1206, 1137, 1049 cm^{-1}; HRMS calcd for $C_{22}H_{24}{}^{35}ClN_3O_4$, (M + H)$^+$ 430.1534, found 430.1546.

*Benzyl 2-(((Benzyloxy)carbonyl)imino)-5-(cyanomethyl)-imidazolidine-1-carboxylate (**10**).* A round-bottom flask under argon was charged with guanidine **5a** (0.1 mmol, 45 mg, 1 equiv) and DMF (1.0 mL). KCN (0.3 mmol, 20 mg, 3 equiv) was added, and the solution was stirred for 48 h at room temperature. 1 M NaOH (10 mL) was added, and the solution was extracted with MTBE (3 × 10 mL). The combined organic phases were washed with water, dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography (DCM + 1.5% MeOH) afforded 13 mg

DOI: 10.1021/acs.joc.5b01750
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(0.033 mmol, 33% yield) of the product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (brs, 1H), 7.37−7.33 (m, 10 H), 5.22 (d, J = 3.2 Hz, 2H), 5.19 (d, J = 3.7 Hz, 2H), 4.35 (m, 1H), 4.02 (dd, J = 10.1, 9.7 Hz, 1H), 3.70 (dd, J = 10.1, 6.2 Hz, 1H), 2.79 (dd, J = 16.9, 5.3 Hz, 1H), 2.63 (dd, J = 16.9, 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 139.1, 129.2, 129.1, 129.0, 128.8, 128.7, 128.6, 117.2, 69.1, 68.2, 58.8, 49.4, 24.9, 3C not visible; IR (neat) 3333, 2960, 1759, 1715, 1655, 1601, 1442, 1381, 1308, 1254, 1170, 1022 cm^{-1}; HRMS calcd for $C_{21}H_{21}N_4O_4$, $(M + H)^+$ 393.1563, found 393.1558.

*Benzyl 5-(Azidomethyl)-2-(((benzyloxy)carbonyl)imino)-imidazolidine-1-carboxylate (**11**).* A round-bottom flask under argon was charged with guanidine **5a** (0.11 mmol, 50 mg, 1 equiv) and DMF (1.0 mL). NaN_3 (0.2 mmol, 13 mg, 1.8 equiv) was added, and the solution was stirred for 96 h at room temperature. Water (10 mL) was added, and the solution was extracted with MTBE (1 × 10 mL). The organic phase was washed with 5% Na_2CO_3 (1 × 10 mL) and then brine (1 × 10 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure, affording 40 mg (0.098 mmol, 89% yield) of the product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (brs, 1H), 7.45−7.29 (m, 10 H), 5.33 (d, J = 12.0 Hz, 1H), 5.26 (d, J = 12.0 Hz, 1H), 5.15 (m, 2H), 4.37−4.36 (m, 1H), 3.87−3.70 (m, 1H), 3.61−3.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 165.4, 163.6, 136.7, 135.0, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 68.9, 67.7, 54.9, 53.1, 52.4; IR (neat) 3345, 3033, 2920, 2104, 1759, 1712, 1651, 1606, 1439, 1395, 1379, 1304, 1240, 1141, 1022 cm^{-1}; HRMS calcd for $C_{20}H_{20}N_6O_4$, $(M + H)^+$ 409.1624, found 409.1611.

*Benzyl 5-(Aminomethyl)-2-(((benzyloxy)carbonyl)imino)-imidazolidine-1-carboxylate (**12**).* A round-bottom flask under argon was charged with guanidine **11** (0.29 mmol, 117 mg, 1 equiv) and dry THF (2.6 mL). PPh_3 (0.57 mmol, 150 mg, 2.0 equiv) and water (10 μL) were added, and the solution was stirred for 36 h at 50 °C.[33] The solution was warmed to room temperature, and the solvent was evaporated under reduced pressure. MTBE was added, and the pH of the solution was lowered to 1 with 2 M HCl with vigorous stirring. The aqueous layer was washed with MTBE (2 × 20 mL). Then, the pH was adjusted to 13 with 1 M NaOH. The solution was extracted with DCM (6 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered, and evaporated under reduced pressure, affording 51 mg (0.13 mmol, 46% yield) of the product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (brs, 1H), 7.36−7.27 (m, 10 H), 5.18 (brs, 2H), 5.06 (s, 2H), 5.01 (s, 2H), 3.87−3.83 (m, 1H), 3.59 (dd, J = 9.6, 9.6 Hz, 1H), 3.30 (dd, J = 9.6, 7.0 Hz, 1H), 3.16−3.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 163.5, 156.9, 137.3, 136.6, 128.8, 128.7, 128.5, 128.4, 128.3, 67.2, 66.9, 53.8, 45.5, 44.2; IR (neat) 3316, 2947, 2471, 2225, 1686, 1630, 1598, 1502, 1452, 1372, 1297, 1276, 1217, 1160, 1056 cm^{-1}; HRMS calcd for $C_{20}H_{22}N_4O_4$, $(M + H)^+$ 383.1719, found 383.1716.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01750.

Copies of ^{1}H NMR and ^{13}C NMR spectra (PDF)
Crystallographic data for compound **5c** (CIF)
Crystallographic data for compound **5g′** (CIF)
Crystallographic data for compound **5l′** (CIF)
Crystallographic data for compound **6l′** (CIF)
Crystallographic data for compound **8d′** (CIF)
Crystallographic data for compound **9d′** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the ANR (ANR-12-BSV1-0031-01) and the Institut de Chimie des Substances Naturelles for financial support and for fellowships (M.D. and S.N.-T., respectively).

■ REFERENCES

(1) For reviews on the use of guanidines as reagents or catalysts, see: (a) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, *2006*, 737. (b) Coles, M. P. *Chem. Commun.* **2009**, 3659. (c) Ishikawa, T. *Chem. Pharm. Bull.* **2010**, *58*, 1555. (d) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109. (e) Selig, P. *Synthesis* **2013**, *45*, 703. For reviews on the use of guanidines in coordination chemistry, see: (f) Bailey, P. J.; Pace, S. *Coord. Chem. Rev.* **2001**, *214*, 91. (g) Coles, M. P. *Dalton Trans.* **2006**, 985. (h) Edelmann, F. T. *Adv. Organomet. Chem.* **2008**, *57*, 183.

(2) (a) Rauws, T. R. M.; Maes, B. U. W. *Chem. Soc. Rev.* **2012**, *41*, 2463. (b) Alonso-Moreno, C.; Antiñolo, A.; Carrillo-Hermosilla, F.; Otero, A. *Chem. Soc. Rev.* **2014**, *43*, 3406. (c) Zhang, W.-X.; Xu, L.; Xi, Z. *Chem. Commun.* **2015**, *51*, 254.

(3) (a) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 377. (b) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep.* **2008**, *25*, 919. (c) Berlinck, R. G. S.; Burtoloso, A. C. B.; Trindade-Silva, A. E.; Romminger, S.; Morais, R. P.; Bandeira, K.; Mizuno, C. M. *Nat. Prod. Rep.* **2010**, *27*, 1871. (d) Castagnolo, D.; Schenone, S.; Botta, M. *Chem. Rev.* **2011**, *111*, 5247. (e) Berlinck, R. G. S.; Trindade-Silva, A. E.; Santos, M. F. C. *Nat. Prod. Rep.* **2012**, *29*, 1382.

(4) Ma, Y.; De, S.; Chen, C. *Tetrahedron* **2015**, *71*, 1145.

(5) Sanière, L.; Leman, L.; Bourguignon, J.-J.; Dauban, P.; Dodd, R. H. *Tetrahedron* **2004**, *60*, 5889.

(6) (a) Fellows, L. E.; Bell, E. A.; Leet, T. S.; Janzen, D. H. *Phytochemistry* **1979**, *18*, 1333. (b) Benohoud, M.; Leman, L.; Cardoso, S. H.; Retailleau, P.; Dauban, P.; Thierry, J.; Dodd, R. H. *J. Org. Chem.* **2009**, *74*, 5331.

(7) He, H.; Williamson, R. T.; Shen, B.; Graziani, E. I.; Yang, H. Y.; Sakya, S. M.; Petersen, P. J.; Carter, G. T. *J. Am. Chem. Soc.* **2002**, *124*, 9729.

(8) Herr, E. B.; Haney, M. E.; Pittenger, G. E.; Higgins, C. E. *Proc. Ind. Acad. Sci.* **1960**, *69*, 134.

(9) (a) Horii, S.; Kameda, Y. *J. Antibiot.* **1968**, *21*, 665. (b) Higashide, E.; Hatano, K.; Shibata, M.; Nakazawa, K. *J. Antibiot.* **1968**, *21*, 126. (c) Asai, M.; Muroi, M.; Sugita, N.; Kawashima, H.; Mizuno, K.; Miyake, A. *J. Antibiot.* **1968**, *21*, 138.

(10) Ling, L. L.; Schneider, T.; Peoples, A. J.; Spoering, A. L.; Engels, I.; Conlon, B. P.; Mueller, A.; Schäberle, T. F.; Hughes, D. E.; Epstein, S.; Jones, M.; Lazarides, L.; Steadman, V. A.; Cohen, D. R.; Felix, C. R.; Fetterman, K. A.; Millett, W. P.; Nitti, A. G.; Zullo, A. M.; Chen, C.; Lewis, K. *Nature* **2015**, *517*, 455.

(11) Katritzky, A. R.; Rogovoy, B. V. *ARKIVOC* **2005**, *iv*, 49.

(12) Gainer, M. J.; Bennett, N. R.; Takahashi, Y.; Looper, R. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 684.

(13) Zavesky, B. P.; Babij, N. R.; Wolfe, J. P. *Org. Lett.* **2014**, *16*, 4952.

(14) Kwon, K.-H.; Serrano, C. M.; Koch, M.; Barrows, L. R.; Looper, R. E. *Org. Lett.* **2014**, *16*, 6048.

(15) (a) Watanabe, M.; Okada, H.; Teshima, T.; Noguchi, M.; Kakehi, A. *Tetrahedron* **1996**, *52*, 2827. (b) Hirota, S.; Kato, R.; Suzuki, M.; Soneta, Y.; Otani, T.; Saito, T. *Eur. J. Org. Chem.* **2008**, *2008*, 2075. (c) Albrecht, C.; Barnes, S.; Böckemeier, H.; Davies, D.; Dennis, M.; Evans, D. M.; Fletcher, M. D.; Jones, I.; Leitmann, V.; Murphy, P. J.; Rowles, R.; Nash, R.; Stephenson, R. A.; Horton, P. N.; Hursthouse, M. B. *Tetrahedron Lett.* **2008**, *49*, 185. (d) Davies, D.; Fletcher, M. D.; Franken, H.; Hollinshead, J.; Kähm, K.; Murphy, P. J.; Nash, R.; Potter, D. M. *Tetrahedron Lett.* **2010**, *51*, 6825. (e) Bentya, A. V.; Vas'kevich, R. I.; Turov, A. V.; Rusanov, E. B.; Vovk, M. V.; Staninets, V. I. *Russ. J. Org. Chem.* **2011**, *47*, 1066. (f) Vas'kevich, R. I.; Bentya, A. V.; Turov, A. V.; Rusanov, E. B.; Staninets, V. I.; Vovk, M. V. *Russ. J. Org. Chem.* **2012**, *48*, 713. (g) Al Shuhaib, Z.; Davies, D. H.; Dennis, M.; Evans, D. M.; Fletcher, M. D.; Franken, H.; Hancock, P.;

DOI: 10.1021/acs.joc.5b01750
J. Org. Chem. 2015, 80, 10624−10633

Hollinshead, J.; Jones, I.; Kähm, K.; Murphy, P. J.; Nash, R.; Potter, D.; Rowles, R. *Tetrahedron* **2014**, *70*, 4412.
(16) (a) Chern, J.-W.; Tao, P.-L.; Wang, K.-C.; Gutcait, A.; Liu, S.-W.; Yen, M.-H.; Chien, S.-L.; Rong, J.-K. *J. Med. Chem.* **1998**, *41*, 3128. (b) Sawayama, Y.; Nishikawa, T. *Synlett* **2011**, *2011*, 651.
(17) Bhonde, V. R.; Looper, R. E. *J. Am. Chem. Soc.* **2011**, *133*, 20172.
(18) (a) Su, S.; Rodriguez, R. A.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 13922. (b) Rodriguez, R. A.; Barrios Steed, D.; Kawamata, Y.; Su, S.; Smith, P. A.; Steed, T. C.; Romesberg, F. E.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 15403.
(19) (a) Nocquet-Thibault, S.; Retailleau, P.; Cariou, K.; Dodd, R. H. *Org. Lett.* **2013**, *15*, 1842. (b) Nocquet-Thibault, S.; Minard, C.; Retailleau, P.; Cariou, K.; Dodd, R. H. *Tetrahedron* **2014**, *70*, 6769.
(20) (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (d) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (f) Brown, M.; Farid, U.; Wirth, T. *Synlett* **2013**, *24*, 424. (g) Singh, F. V.; Wirth, T. *Chem. - Asian J.* **2014**, *9*, 950.
(21) PIDA-mediated dehydrogenative cyclization on arenes: (a) Chi, Y.; Zhang, W.-X.; Xi, Z. *Org. Lett.* **2014**, *16*, 6274. PIDA-mediated dehydrogenative cyclization on an sp^3 CH bond: (b) Iwata, M.; Kanoh, K.; Imaoka, T.; Nagasawa, K. *Chem. Commun.* **2014**, *50*, 6991. (c) Enantioselective and intramolecular I(III)-mediated diamination, including guanidine substrates: Mizar, P.; Laverny, A.; El-Sherbini, M.; Farid, U.; Brown, M.; Malmedy, F.; Wirth, T. *Chem. - Eur. J.* **2014**, *20*, 9910.
(22) Cu(II)-catalyzed aminooxygenation: (a) Sanjaya, S.; Chiba, S. *Org. Lett.* **2012**, *14*, 5342. Cu(II)-catalyzed dehydrogenative cyclization on sp^3 CH bonds: (b) Chen, H.; Sanjaya, S.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2013**, *15*, 212. Transition-metal-free aminooxygenation and deamination: (c) Chen, H.; Kaga, A.; Chiba, S. *Org. Lett.* **2014**, *16*, 6136. NIS/PIDA-mediated diamination: (d) Zhang, J.; Wu, W.; Zhang, X.; Zhang, G.; Xu, S.; Shi, M. *Chem. - Asian J.* **2015**, *10*, 544.
(23) Aziridinium intermediates have been postulated in related transformations involving I(III) reagents; see: ref 22c and: Kong, W.; Feige, P.; de Haro, T.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 2469.
(24) While $PhICl_2$ can be an attractive chlorinating reagent, it is only moderately stable and has to be prepared beforehand as only few suppliers sell it.
(25) Koser, G. F. *Aldrichimica Acta* **2001**, *34*, 89.
(26) For the sake of generality and convenience, we chose to favor the use of widely available derivatives (PIDA or Koser's reagent for example) as the *umpolung* promotors. The option to use other common compounds such as iodosobenzene was discarded because they need to be synthesized beforehand.
(27) Though the bis-protected guanidine **9d** was obtained after the reaction, as confirmed by NMR and MS data, deprotection occurred during the crystallization process and the X-ray analysis was eventually performed on the mono-protected adduct **9d′**. This phenomenon was also observed for compound **5g**, for which X-ray analysis was performed on the mono-protected adduct **5g′**. CCDC 1422195−1422200 contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
(28) Ravinder, K.; Vijender Reddy, A.; Krishnaiah, P.; Ramesh, P.; Ramakrishna, S.; Laatsch, H.; Venkateswarlu, Y. *Tetrahedron Lett.* **2005**, *46*, 5475.
(29) Matsunaga, S.; Moore, R. E.; Niemczura, W. P.; Carmichael, W. W. *J. Am. Chem. Soc.* **1989**, *111*, 8021.
(30) Liang, H.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11849.
(31) Mori, M.; Kuzuba, Y.; Kitamura, T.; Sato, Y. *Org. Lett.* **2002**, *4*, 3855.
(32) Pluym, N.; Brennauer, A.; Keller, M.; Ziemek, R.; Pop, N.; Bernhardt, G.; Buschauer, A. *ChemMedChem* **2011**, *6*, 1727.
(33) This protocol was adapted from: Slaitas, A.; Yeheskiely, E. *Eur. J. Org. Chem.* **2002**, *2002*, 2391.

DOI: 10.1021/acs.joc.5b01750
J. Org. Chem. 2015, 80, 10624−10633