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

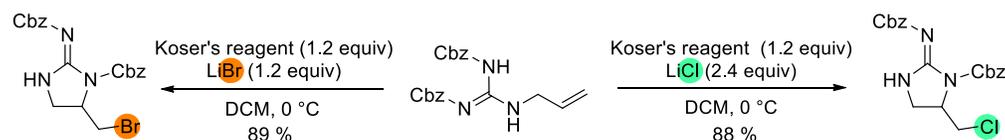
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**ABSTRACT:** The synthesis of halogenated cyclic guanidines through iodine(III)-mediated *umpolung* of halide salts is described. Cyclic guanidines of various sizes can be obtained with generally excellent regioselectivities through either a chloro-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

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## 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<sup>1</sup> which has thus led to the development of many strategies for their synthesis.<sup>2</sup> Additionally, the guanidine motif can be found in a myriad of natural products.<sup>3</sup> Specifically, many of them incorporate the synthetically challenging cyclic guanidine moiety, towards which a considerable number of studies has been devoted in the field of total synthesis.<sup>4</sup>

Our own interest has been directed towards the synthesis of cyclic guanidine-containing amino acids such as enduracididine **1**<sup>5</sup> and tetrahydrolathyrine **2** (Figure 1).<sup>6</sup> These non-proteinogenic amino acids, as well as related congeners such as  $\beta$ -hydroxy-enduracididine<sup>7</sup> and capreomycin,<sup>8</sup> can be considered as rigid analogs of arginine and most of these have been found to be constituents of antibiotic cyclopeptides such as enduracidin,<sup>9</sup> capreomycin or the very recently discovered teixobactin **3** highly promising for treating resistant bacteria.<sup>10</sup>

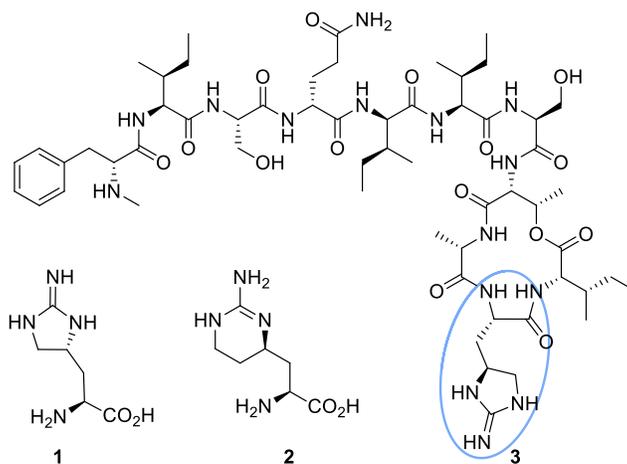
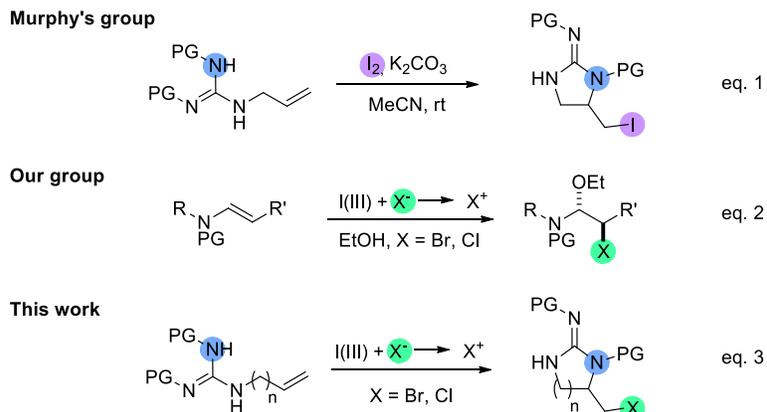


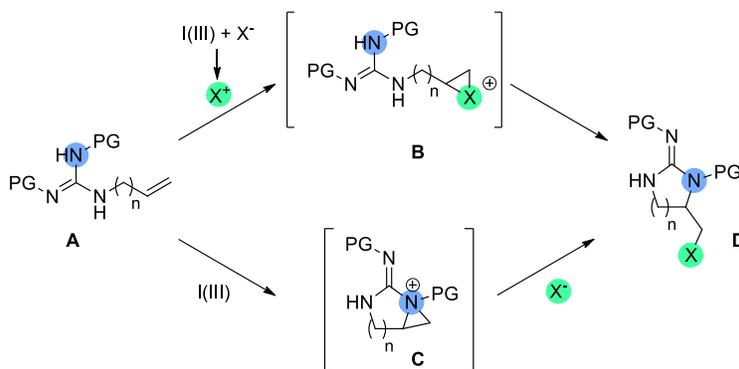
Figure 1. Structures of enduracididine **1**, tetrahydrolathyrine **2** and teixobactin **3**

While construction of cyclic guanidines is often tedious, as we previously experienced,<sup>5,6</sup> the synthesis of acyclic guanidines can be readily achieved from the corresponding amines using a variety of guanidylating reagents.<sup>11</sup> 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-,<sup>12</sup> Pd<sup>13</sup> or Ag-catalyzed<sup>14</sup> amination of propargylic derivatives and on the iodine-<sup>15</sup> or NBS-triggered<sup>16</sup> 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<sup>17</sup> and axinellamines.<sup>18</sup> In order to broaden the scope of this strategy, we anticipated that the hypervalent iodine(III)-mediated *umpolung* of halide salts that we recently employed for the ethoxyhalogenation of various enamides (eq. 2)<sup>19</sup> should be amenable to initiating such a halocyclization (eq. 3).



Scheme 1. Previous Studies and Envisioned Strategy

Hypervalent iodine derivatives have drawn much attention in the last few years because of their versatile reactivity, their accessibility and their low toxicity.<sup>20</sup> Several cyclizations of guanidines<sup>21</sup> or amidines<sup>22</sup> 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,<sup>19b</sup> thereby generating an electrophilic species  $X^+$  (Scheme 2, **A**  $\rightarrow$  **B**) 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**  $\rightarrow$  **C**).<sup>23</sup> 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.



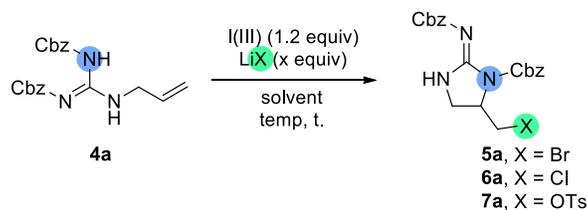
Scheme 2. Plausible Mechanistic Pathways

## 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 equivalents of PIDA and 2.5 equivalents 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 two-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 equivalents and the desired product was isolated with an improved 85% yield (Table 1, entry 4). However, under the same reaction conditions

using 2.5 equivalents 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<sub>3</sub>,<sup>19b</sup> ZnCl<sub>2</sub> or TBACl did not lead to further improvement. PhICl<sub>2</sub> also provided **6a** but with only a moderately improved yield (entry 7). Finally **hydroxy(tosyloxy)iodobenzene** (Koser's reagent)<sup>24</sup> 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).

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



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

<sup>a</sup> Isolated yields. <sup>b</sup> The desired product was obtained in a mixture with **7a** (31%). <sup>c</sup> The desired product was obtained in a mixture with **7a** (15%). <sup>d</sup> Along with 20% of mono-Cbz adduct **7a'**.

Finally, the optimal chlorocyclization conditions were applied to the bromocyclization reaction which proceeded smoothly to give 89% yield of the desired product **5a** (entry 13).

We 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 chloro-cyclization process 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 case of cinnamyl, prenyl and methallyl derivatives **4d-f** the *endo* mode became exclusive for both halides, leading to 6-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.<sup>25</sup> 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.<sup>18</sup> Finally, bis-allylic substrate **4h** was subjected to the reaction conditions and cleanly afforded mono-allylated guanidines **5h** and **6h** which were obtained in excellent yields (entry 8).



<sup>a</sup> Isolated yields; <sup>b</sup> X-Ray analysis confirmed the structure of both diastereomers. <sup>c</sup> X-Ray analysis confirmed the relative configuration and the position of the remaining Cbz group. <sup>d</sup> X-Ray analysis of the mono deprotected **9d'** confirmed the relative configuration. <sup>e</sup> X-Ray analysis of the mono deprotected **5g'** confirmed the relative configuration.

While the substrate scope was quite general for allylic derivatives, some limitations were evidenced (Figure 2). First, 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.<sup>12–14</sup> Finally, geranyl-derived substrate **4k** only led to complex mixtures due to a lack of selectivity of both brominating and chlorinating processes.

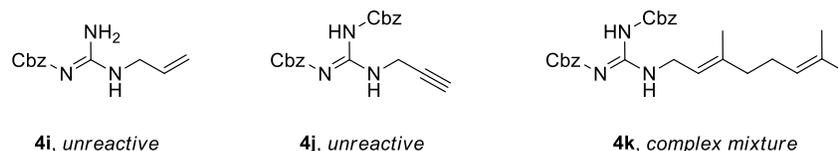


Figure 2. Substrate Limitations

Regardless, the halo-cyclization reaction was still operative when longer unsaturated chains were appended to the guanidine moiety (Table 3). Homo-allylic 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).

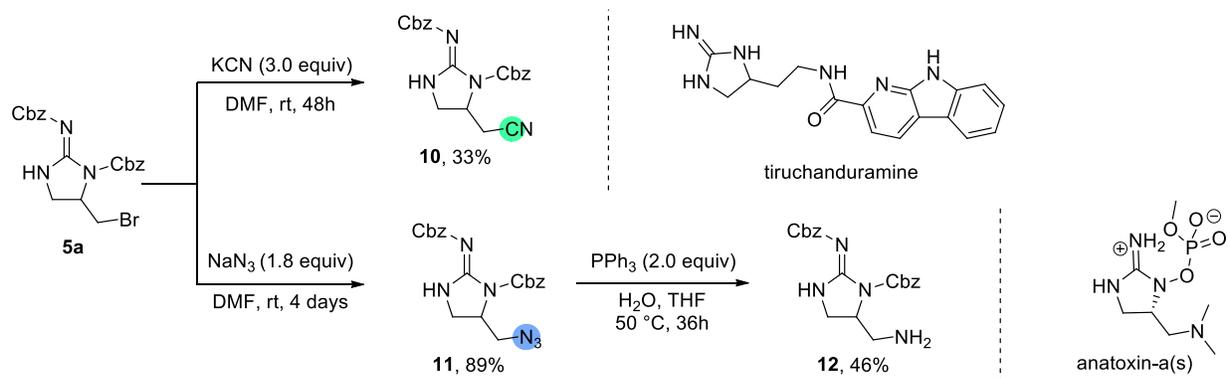
Table 3. Substrate Scope for the Bromo- and Chlorocyclization of Unsaturated Guanidines

Entry	4	Substrate	Product	t. (h)	yield (%) <sup>a</sup>	Product	t. (h)	yield (%) <sup>a</sup>
1	<b>4l</b>			1	52 <sup>b</sup>		17	<b>6l'</b> : 19 <b>6l'</b> : 50 <sup>b</sup>
2	<b>4m</b>			1.5	49		24	60
3	<b>4n</b>			1.5	23		24	21

<sup>a</sup> Isolated yields; <sup>b</sup> X-Ray analysis confirmed the structure and the position of the remaining Cbz group.

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 endo-cyclization could be detected for substrate **4m**, presumably because the formation of a 7-membered ring is highly disfavored. Nevertheless, the 7-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 5-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  $\alpha$ -glucosidase inhibitor that has been isolated from *Synoicum macroglossum*.<sup>26</sup> 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 analogs of anatoxin-a(s), a highly potent anticholinesterase isolated from the green alga *Anabaena flos aquae*.<sup>27</sup>



Scheme 3. Substrate Diversification

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 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 towards 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,<sup>28</sup> can be envisioned and will be investigated.

## EXPERIMENTAL SECTION

**General Methods.** Melting points were measured in capillary tubes and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a 300 or 500 MHz NMR spectrometers. <sup>13</sup>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<sub>3</sub>, for which chemical shifts ( $\delta$ ) are reported in parts per million (ppm) with reference to CDCl<sub>3</sub> (<sup>1</sup>H: 7.26; <sup>13</sup>C: 77.36) and MeOD, for which chemical shifts ( $\delta$ ) are reported in parts per million (ppm) with reference to MeOD (1H: 3.34; 13C: 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  $\mu$ m) 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 the Gabriel synthesis.<sup>15g</sup> 3-Methylbut-3-en-1-amine was synthesized from the alcohol by the Mitsunobu reaction.<sup>15g</sup> Cyclohex-1-en-1-ylmethanamine hydrochloride and cyclopent-1-en-1-ylmethanamine hydrochloride were synthesized from the corresponding ester by sequential reduction<sup>30</sup>, bromination<sup>30</sup> and a Gabriel synthesis.<sup>15g</sup>

**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 20h-48h 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; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 11.80 (brs, 1H, NH), 8.44 (brs, 1H, NH), 7.44-7.31 (m, 10H arom.), 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>, (M+H)<sup>+</sup> 368.1610 found, 368.1604. Data in accordance with those described in the literature.<sup>15g</sup>

*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; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 11.45 (brs, 1H, NH), 8.32 (brs, 1H, NH), 5.83-5.78 (m, 1H), 5.17-5.07 (m, 2H), 4.00-3.97 (m, 2H), 1.41 (s, 18H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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.<sup>15g</sup>

*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; mp: 32 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 11.64 (brs, 1H, NH), 8.17 (brs, 1H, NH), 7.31-7.15 (m, 10H arom.), 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>, (M+H)<sup>+</sup> 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 isolated with 38 % of an unidentified product; mp: 68 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 11.67 (brs, 1H, NH), 8.34 (brs, 1H, NH), 7.30-7.08 (m, 15H arom.), 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>, (M+H)<sup>+</sup> 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; mp: 68 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 11.62 (brs, 1H, NH), 8.02 (brs, 1H, NH), 7.31-7.15 (m, 10H arom.), 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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, 39.3, 25.6, 17.9; IR (neat) 3341, 3065, 2994, 1727, 1622, 1567, 1425, 1381, 1331, 1304, 1240, 1203, 1134, 1053 cm<sup>-1</sup>; HRMS calcd for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>, (M+H)<sup>+</sup> 396.1923 found, 396.1916. Data in accordance with those described in the literature.<sup>15g</sup>

*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; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 11.67 (brs, 1H, NH), 8.34 (brs, 1H, NH), 7.14-7.29 (m, 10H arom.), 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>, (M+H)<sup>+</sup> 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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 11.67 (brs, 1H, NH), 8.22 (brs, 1H, NH), 7.30-7.16 (m, 10H arom.), 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_4$ ,  $(\text{M}+\text{H})^+$  422.2080 found, 422.2065.

*N*-diallyl-*N'*,*N''*-bis-*Cbz*-guanidine (**4h**): To a solution of diallylamine (70  $\mu\text{L}$ , 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 x 10 mL). The combined organic phases were dried with  $\text{MgSO}_4$ , 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.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.27 (brs, 1H, NH), 7.36-7.28 (m, 10H arom.), 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_4$ ,  $(\text{M}+\text{H})^+$  408.1923 found, 408.1916.

*N*-allyl-*N'*-*Cbz*-guanidine (**4i**): To a solution of (*Z*)-benzyl-amino(1H-pyrazol-1-yl)methylene-carbamate<sup>31</sup> (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 2h30 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.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (brs, 1H, NH), 7.57-7.58 (m, 1H arom.), 7.35-7.27 (m, 4H arom.), 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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.<sup>Erreur ! Signet non défini.</sup>

*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.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  11.60 (brs, 1H, NH), 8.35 (brs, 1H, NH), 7.31-7.17 (m, 10H arom.), 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_4$ ,  $(\text{M}+\text{H})^+$  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;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  11.64 (brs, 1H, NH), 8.05 (brs, 1H, NH), 7.31-7.15 (m, 10H arom.), 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_4$ ,  $(\text{M}+\text{H})^+$  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; mp: 30  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  11.64 (brs, 1H, NH), 8.23 (brs, 1H, NH), 7.15-7.31 (m, 10H arom.), 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_4$ ,  $(\text{M}+\text{H})^+$  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; mp: 43  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  11.62 (brs, 1H, NH), 8.19 (brs, 1H, NH), 7.30-7.15 (m, 10H arom.), 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_4$ ,  $(\text{M}+\text{H})^+$  396.1923 found, 396.1911. Data in accordance with those described in the literature.<sup>15g</sup>

*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; mp: 43  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  11.78 (brs, 1H, NH), 8.35 (brs, 1H, NH), 7.43-7.30 (m, 10H arom.), 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);

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_4$ ,  $(\text{M}+\text{H})^+$  396.1923 found, 396.1920. Data in accordance with those described in the literature.<sup>21c</sup>

*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 then 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.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{27}\text{H}_{27}\text{N}_3\text{O}_7\text{S}$ ,  $(\text{M}+\text{Na})^+$  560.1467 found, 560.1485.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_5\text{S}$ ,  $(\text{M}+\text{H})^+$  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 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 1h-4h 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; mp: 108 °C;  $^1\text{H}$  NMR (500 MHz, MeOD)  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{20}\text{H}_{20}^{79}\text{BrN}_3\text{O}_4$ ,  $(\text{M} + \text{H})^+$  446.0715, found 446.0721.

*Tert-butyl 5-(bromomethyl)-2-((tert-butoxycarbonyl)imino)imidazolidine-1-carboxylate (5b)*: 18 mg, 47% yield, colorless oil;  $^1\text{H}$  NMR (300 MHz, MeOD)  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{14}\text{H}_{24}^{79}\text{BrN}_3\text{O}_4$ ,  $(\text{M} + \text{H})^+$  378.1028 found, 378.1022.

*Benzyl 2-(((benzyloxy)carbonyl)imino)-5-(1-bromoethyl)imidazolidine-1-carboxylate (5c)*: 12 mg, 47% yield, (2:1) mixture of two diastereoisomers, white solid;  $^1\text{H}$  NMR (500 MHz, MeOD)  $\delta$  7.47-7.48 (m,  $2\text{H}_\text{A}+2\text{H}_\text{B}$  arom.), 7.30-7.42 (m,  $8\text{H}_\text{A}+8\text{H}_\text{B}$  arom.), 5.34-5.39 (m,  $1\text{H}_\text{A}+1\text{H}_\text{B}$ ), 5.25-5.28 (m,  $1\text{H}_\text{A}+1\text{H}_\text{B}$ ), 5.14-5.19 (m,  $2\text{H}_\text{A}$ ), 5.08-5.09 (m,  $2\text{H}_\text{B}$ ), 4.74-4.77 (m,  $1\text{H}_\text{A}$ ), 4.55-4.58 (m,  $1\text{H}_\text{B}$ ), 4.42-4.51 (m,  $1\text{H}_\text{A}$ ), 4.26-4.27 (m,  $1\text{H}_\text{B}$ ), 3.76-3.85 (m,  $2\text{H}_\text{A}$ ), 3.68-3.70 (m,  $1\text{H}_\text{B}$ ), 3.51-3.60 (m,  $1\text{H}_\text{B}$ ), 1.63 (d,  $J = 7.2$  Hz,  $3\text{H}_\text{A}$ , dia1), 1.56 (d,  $J = 7.2$  Hz,  $3\text{H}_\text{A}$ , dia2), 1.40 (d,  $J = 7.2$  Hz,  $3\text{H}_\text{B}$ , dia1), 1.36 (d,  $J = 7.2$  Hz,  $3\text{H}_\text{B}$ , dia2);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{21}\text{H}_{22}^{79}\text{BrN}_3\text{O}_4$ ,  $(\text{M} + \text{H})^+$  460.0872, found 460.0870.

*Benzyl (4-(1-bromoethyl)imidazolidin-2-ylidene)carbamate (5c')*: 3 mg, 15% yield, one diastereoisomer, white solid; mp: 161  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz, MeOD)  $\delta$  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: 187  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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<sup>-1</sup>; HRMS calcd for C<sub>18</sub>H<sub>18</sub><sup>79</sup>BrN<sub>3</sub>O<sub>2</sub>, (M + H)<sup>+</sup> 388.0655, found 388.0638.

*Benzyl 2-(((benzyloxy)carbonyl)imino)-5-bromo-6,6-dimethyltetrahydropyrimidine-1(2H)-carboxylate (8e)*: 27 mg, 57% yield, colorless oil; <sup>1</sup>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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>22</sub>H<sub>24</sub><sup>79</sup>BrN<sub>3</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 474.1028, found 474.1032.

*Benzyl 2-(((benzyloxy)carbonyl)imino)-5-bromo-5-methyltetrahydropyrimidine-1(2H)-carboxylate (8f)*: 35 mg, 76% yield, light yellow oil; the product is not stable in CDCl<sub>3</sub>; <sup>1</sup>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); <sup>13</sup>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<sup>-1</sup>; HRMS calcd for C<sub>21</sub>H<sub>22</sub><sup>79</sup>BrN<sub>3</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 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<sub>3</sub>; <sup>1</sup>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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>24</sub>H<sub>26</sub><sup>79</sup>BrN<sub>3</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 500.1184, found 500.1183.

*Benzyl 3-allyl-2-(((benzyloxy)carbonyl)imino)-5-(bromomethyl)imidazolidine-1-carboxylate (5h)*: 46 mg, 95% yield, colorless oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{23}\text{H}_{24}^{79}\text{BrN}_3\text{O}_4$ , ( $\text{M} + \text{H}$ ) $^+$  486.1028, found 486.1052.

*Benzyl (4-(bromomethyl)tetrahydropyrimidin-2(1H)-ylidene)carbamate (5l)*: 17 mg, 52% yield, white solid;  $^1\text{H}$  NMR (300 MHz, MeOD)  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{13}\text{H}_{16}^{79}\text{BrN}_3\text{O}_2$ , ( $\text{M} + \text{H}$ ) $^+$  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  $\text{CDCl}_3$ ;  $^1\text{H}$  NMR (300 MHz, MeOD)  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{22}\text{H}_{24}^{79}\text{BrN}_3\text{O}_4$ , ( $\text{M} + \text{H}$ ) $^+$  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  $\text{CDCl}_3$ ;  $^1\text{H}$  NMR (300 MHz, MeOD)  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{22}\text{H}_{24}^{79}\text{BrN}_3\text{O}_4$ , ( $\text{M} + \text{H}$ ) $^+$  474.1028, 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 15h-24h 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-(chloromethyl)imidazolidine-1-carboxylate (6a)*: 35 mg, 88% yield, white solid; mp: 99 °C; <sup>1</sup>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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>20</sub>H<sub>20</sub><sup>35</sup>ClN<sub>3</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 402.1221, found 402.1223.

*Tert-butyl 2-((tert-butoxycarbonyl)imino)-5-(chloromethyl)imidazolidine-1-carboxylate (6b)*: 19 mg, 58% yield, white solid; mp: 129 °C; <sup>1</sup>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); <sup>13</sup>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<sup>-1</sup>; HRMS calcd for C<sub>14</sub>H<sub>24</sub><sup>35</sup>ClN<sub>3</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 334.1534, found 334.1537.

*Benzyl (4-(1-chloroethyl)imidazolidin-2-ylidene)carbamate (6c')* and *(E)-benzyl (5-chloro-4-methyltetrahydropyrimidin-2(1H)-ylidene)carbamate (9c')*: 28 mg, quantitative yield, white solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.70 (brs, 1H), 9.16 (brs, 1H), 7.42-7.27 (m, 5H<sub>A</sub> + 5H<sub>B</sub>), 5.30-5.28 (m, 2H<sub>A</sub>, dia 1), 5.17-5.15 (m, 2H<sub>A</sub>, dia 2), 5.01 (s, 2H<sub>B</sub>), 4.60-4.38 (m, 3H<sub>A</sub>), 3.79-3.77 (m, 1H<sub>A</sub>), 3.68-3.63 (m, 1H<sub>B</sub>), 3.48-3.42 (m, 2H<sub>B</sub>), 3.19-3.12 (m, 1H<sub>B</sub>), 1.43 (d, *J* = 6.9 Hz, 3H<sub>A</sub>, dia 1), 1.38 (d, *J* = 6.5 Hz, 3H<sub>A</sub>, dia 2), 1.21 (d, *J* = 6.5 Hz, 3H<sub>B</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>13</sub>H<sub>16</sub><sup>35</sup>ClN<sub>3</sub>O<sub>2</sub>, (M + H)<sup>+</sup> 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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>26</sub>H<sub>24</sub><sup>35</sup>ClN<sub>3</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 478.1533, found 478.1541.

*Benzyl 2-(((benzyloxy)carbonyl)imino)-5-chloro-6,6-dimethyltetrahydropyrimidine-1(2H)-carboxylate (9e)*: 35 mg, 81% yield, colorless oil; <sup>1</sup>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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>22</sub>H<sub>24</sub><sup>35</sup>ClN<sub>3</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 430.1534, found 430.1514.

*Benzyl 2-(((benzyloxy)carbonyl)imino)-5-chloro-5-methyltetrahydropyrimidine-1(2H)-carboxylate (9f)*: 22 mg, 76% yield, colorless oil; <sup>1</sup>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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>21</sub>H<sub>22</sub><sup>35</sup>ClN<sub>3</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 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<sub>3</sub>; <sup>1</sup>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; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS calcd for C<sub>24</sub>H<sub>26</sub><sup>35</sup>ClN<sub>3</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 456.1690, found 456.1685.

*Benzyl 3-allyl-2-(((benzyloxy)carbonyl)imino)-5-(chloromethyl)imidazolidine-1-carboxylate (6h)*: 32 mg, 73% yield, colorless oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{23}\text{H}_{24}^{35}\text{ClN}_3\text{O}_4$ , (M + H) $^+$  442.1534, found 442.1526.

*Benzyl 2-(((benzyloxy)carbonyl)imino)-6-(chloromethyl)tetrahydropyrimidine-1(2H)-carboxylate (6l)*: 8 mg, 19% yield, white solid;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{21}\text{H}_{22}^{35}\text{ClN}_3\text{O}_4$ , (M + H) $^+$  416.1377, found 416.1363.

*Benzyl (4-(chloromethyl)tetrahydropyrimidin-2(1H)-ylidene)carbamate (6l')*: 14 mg, 50% yield, white solid; mp: 143  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{13}\text{H}_{16}^{35}\text{ClN}_3\text{O}_2$ , (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  $\text{CDCl}_3$ ;  $^1\text{H}$  NMR (300 MHz, MeOD)  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{22}\text{H}_{24}^{35}\text{ClN}_3\text{O}_4$ , (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  $\text{CDCl}_3$ ;  $^1\text{H}$  NMR (300 MHz, MeOD)  $\delta$  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);  $^{13}\text{C}$  NMR (75 MHz,

CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>; HRMS calcd for C<sub>22</sub>H<sub>24</sub><sup>35</sup>ClN<sub>3</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 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 48h at room temperature. NaOH 1M (10 mL) was added and the solution was extracted with MTBE (3x10 mL). The combined organic phases were washed with water, dried with MgSO<sub>4</sub>, filtered and evaporated under reduce pressure. Flash column chromatography (DCM + 1.5 % MeOH) afforded 13 mg (0.033 mmol, 33 % yield) of the product as a colorless oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>; HRMS calcd for C<sub>21</sub>H<sub>21</sub>N<sub>4</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 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<sub>3</sub> (0.2 mmol, 13 mg, 1.8 equiv.) was added and the solution was stirred for 96h at room temperature. Water (10 mL) was added and the solution was extracted with MTBE (1x10 mL). The organic phase was washed with Na<sub>2</sub>CO<sub>3</sub> 5% (1x10 mL), then brine (1x10 mL), dried with MgSO<sub>4</sub>, filtered and evaporated under reduce pressure affording 40 mg (0.098 mmol, 89 % yield) of the product as a colorless oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>; HRMS calcd for C<sub>20</sub>H<sub>20</sub>N<sub>6</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 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<sub>3</sub>

(0.57 mmol, 150 mg, 2.0 equiv.) and water (10  $\mu$ L) were added and the solution was stirred for 36h at 50 °C.<sup>29</sup> The solution was warmed up to room temperature and the solvent was evaporated under reduce pressure. MTBE was added and the pH of the solution was lowered to 1 with HCl 2M with vigorous stirring. The aqueous layer was washed with MTBE (2x20 mL). Then the pH was adjusted to 13 with NaOH 1M. The solution was extracted with DCM (6x20 mL). The combined organic phases were dried with MgSO<sub>4</sub>, filtered and evaporated under reduce pressure affording 51 mg (0.13 mmol, 46 % yield) of the product as a colorless oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.90 (brs, 1H), 7.36-7.27 (m, 10 H), 5.18 (brs, 2H, NH<sub>2</sub>), 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>; HRMS calcd for C<sub>20</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>, (M + H)<sup>+</sup> 383.1719, found 383.1716.

### Supporting Information Available

Copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra. Crystallographic data for compounds **5c**, **5g'**, **5l'**, **6l'**, **8d'**, and **9d'**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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