

# Generation and Reactivity of 2-Amido-1,3-diaminoallyl Cations: Cyclic Guanidine Annulations via Net (3+2) and (4+3) Cycloadditions

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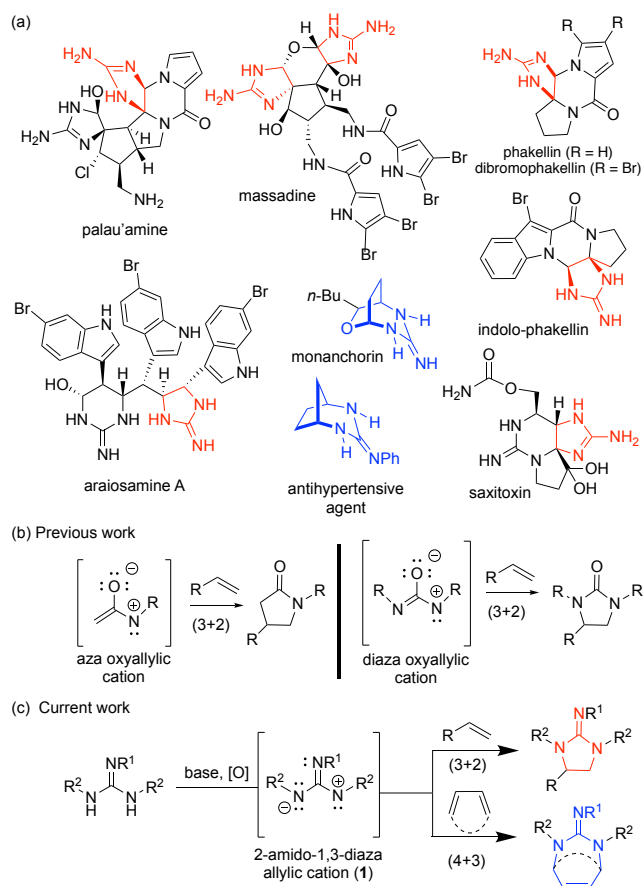
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Supporting Information Placeholder

**ABSTRACT:** Toward a method for direct conversion of alkenes to cyclic guanidines, we report that 1,3-dipolar cycloadditions of 2-amido-1,3-diamino allylic cations with electron rich alkenes provides a new method for direct cyclic guanidine annulation. Generated under oxidative conditions, the 2-amido-1,3-diaminoallyl cations, react as 1,3-dipoles providing rapid access to 2-amino imidazolines through net (3+2) cycloadditions. The utility is demonstrated through a concise synthesis of the oroidin alkaloid, phakellin. The described 1,3-dipole also participates in net (4+3) cycloadditions with dienes. Several observations suggest a stepwise, ionic, net cycloaddition leading to initial carbocation formation as evidenced by initial formation of constitutional isomers and intervening eliminations. Complex aziridines are formed with dienes suggestive of nitrene intermediates and results in net tetra-functionalization of dienes.

Cyclic guanidines (2-amino imidazolines) play an important role in medicinal chemistry and biochemistry and are found in numerous natural products.<sup>1</sup> The hydrogen bonding capability of this polar, basic moiety is useful in the design of small molecule drugs in particular for interactions with RNA and DNA.<sup>2</sup> Numerous natural products including saxitoxin<sup>3</sup> and members of the pyrrolo-2-aminoimidazole alkaloid family possess cyclic guanidines (Figure 1a).<sup>4</sup> Reported methods for the synthesis of cyclic guanidines include functionalization of diamines<sup>5</sup> and metal-promoted hydroaminations of propargyl guanidines.<sup>6</sup> In terms of direct functionalization of alkenes, Tepe and co-workers reported a *N*-bromosuccinimide initiated, one-pot annulation of a Boc-guanidine to an alkene in their synthesis of dibromophakellin, indolophakellin,<sup>7</sup> and a proteasome inhibitor derivative, bromoindolo-phakellin.<sup>8</sup> Previous methods for cyclic guanidine annulation of alkenes include intramolecular Pd-mediated oxidative diaminations,<sup>9</sup> intramolecular Pd- and Ag-catalyzed aminations,<sup>10</sup> and radical-mediated net cycloadditions with diaziridinimines.<sup>11</sup> Our interest in the synthesis and biosynthesis of various pyrrole aminoimidazole alkaloid family members<sup>12</sup> led us to consider alternative direct routes for cyclic guanidine annulation of alkenes.

Aza-oxyallylic cations were previously developed for 1,3-dipolar cycloadditions with alkenes (Fig. 1b)<sup>13</sup> following proposals of this intermediate by Sheehan dating back to the 1960s.<sup>14</sup> The Jeffrey group was the first to demonstrate the utility of aza-oxyallyl cations generated under oxidative conditions for (4+3)<sup>15</sup> cycloadditions with alkenes. Subsequently, the Jeffrey<sup>16</sup> and Wu<sup>17</sup> groups extended the use of these 1,3-dipoles to (3+2) dearomative cycloadditions with indoles. Liao employed the aza-oxyallyl cation in their



**Figure 1.** (a) Natural products and other bioactive compounds bearing a cyclic guanidine (2-aminoimidazolidine) or bicyclic guanidines accessible from (3+2) or (4+3) dipolar cycloadditions (b) previously developed aza-oxyallylic and diaza-oxyallylic cations for (3+2) cycloadditions leading to pyrrolidines and imidazolones (c) current studies describing novel 2-amido-1,3-diaza allylic cations for (3+2) and (4+3) dipolar cycloadditions.

formal synthesis of minifiensine<sup>18</sup> and Xing reported its use for conversion of alkynes to pyrrolidinone derivatives.<sup>19</sup> These cycloadditions all employed chemical oxidants to generate these 1,3-dipoles, however, Luo recently described the use of electrochemical oxidation for the generation of di-aza-oxyallylic cations for (3+2) cycloadditions with indoles.<sup>20</sup> Jeffrey also reported the use of di-aza-oxyallylic cations for (4+3) cycloadditions leading to bicyclic ureas (Fig. 1b).<sup>16b, 16d</sup>

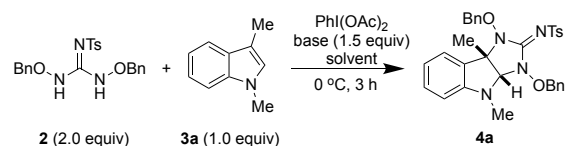
Building on these precedents, we envisioned generation of a 2-amido-1,3-diaza allylic cation **1** that might undergo a formal cycloaddition with alkenes (Fig. 1c). Herein, we report the generation and application of this intermediate for direct functionalization of alkenes through net (3+2) cycloadditions and also (4+3) cycloadditions with dienes. Mechanistic details of this reaction and competing pathways were uncovered through isolation of several interesting by-products.

We anticipated that an appropriately substituted guanidine, on treatment with a base and an oxidant, could generate a 2-amido 1,3-diaza-allylic cation (**1**) that could undergo both (3+2) and (4+3) cycloadditions. Previous studies by Kikugawa<sup>21</sup> and Jeffrey<sup>15</sup> suggested that an *N*-alkoxy group stabilizes and likely promotes generation of oxy-substituted aza-allylic cations likely through increasing NH acidity but also through electron donation stabilization of the incipient allylic cation. Thus, two *N*-alkoxy groups and also a *N*-tosyl group on guanidine **2** were studied initially to further increase the NH acidity and enable a facile deprotonation and subsequent oxidation of the resulting anion to deliver the targeted 2-amido-1,3-diaza-allylic cation **1**.<sup>16d</sup>

Our studies of the proposed cycloaddition began with 1,3-dimethyl indole as a substrate, building on conditions developed by Jeffrey for a similar transformation with aza-oxyallylic cations.<sup>16f</sup> We initiated our studies employing sodium tetrafluoropropoxide (NaTFP) as base and PhI(OAc)<sub>2</sub> (PIDA, added as a CH<sub>3</sub>CN solution) as oxidant in CH<sub>2</sub>Cl<sub>2</sub>, a solvent required to solubilize guanidine **2**. Addition of guanidine **2** followed by indole **3a** indeed provided the expected (3+2) cycloadduct **4a** in 64% yield after 3 h (Table 1, entry 1; structure confirmed by X-ray crystallography, see SI for details). A solvent screen (entries 2-4) revealed that the solvent mixture of 2,2,3,3-tetrafluoro-1-propanol<sup>22</sup>, dichloromethane, and acetonitrile (1:4:8) led to the highest yield of cycloadduct **4a** (90% yield, entry 5). In efforts to expand the solvents useful for this transformation, CH<sub>3</sub>CN was also studied and when combined with dropwise addition of PIDA in CH<sub>3</sub>CN, this condition provided cycloadduct **4a** in 80% yield (entry 6). Reversing the addition order, by adding guanidine **2** as a solution in CH<sub>3</sub>CN to a mixture of indole **3a**, oxidant, and base produced the cycloadduct **4a** in significantly reduced yield (20%, entry 8) likely due to competitive oxidation of the electron rich indole. Importantly, solid Na<sub>2</sub>CO<sub>3</sub> (Table 1, entry 9) led to **4a** in 86% yield (entry 9) while no base led to cycloadduct, albeit in

reduced yield (52%, entry 10). However, as expected, no reaction was observed in the absence of oxidant PhI(OAc)<sub>2</sub> (entry 11) and the use of PhI(OCOCF<sub>3</sub>)<sub>2</sub> did not lead to improvement (entry 12). Additionally, use of only CH<sub>3</sub>CN as solvent and solid Na<sub>2</sub>CO<sub>3</sub> provided 70% yield of cycloadduct **4a** (entry 13).

**Table 1. Optimization of (3+2) cycloaddition with indole 2a**



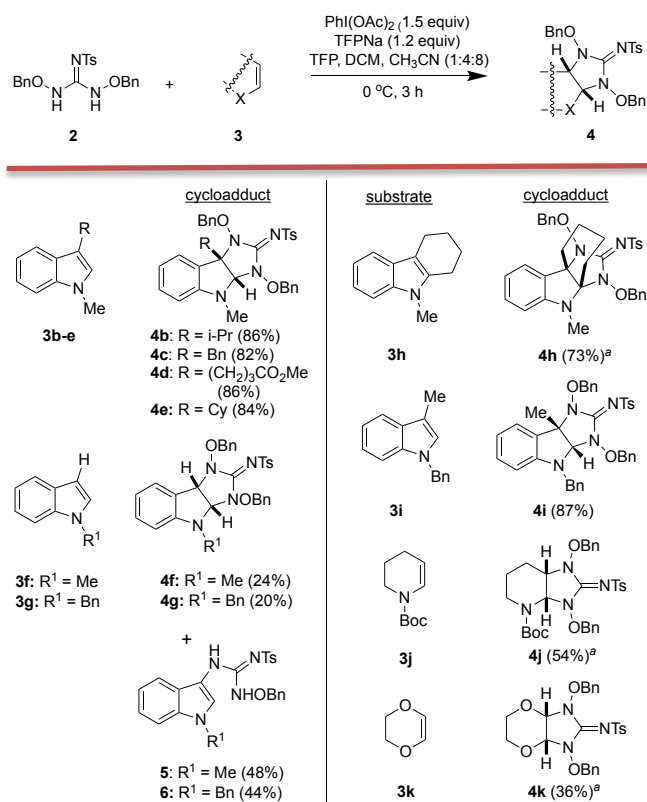
entry	oxidant (equiv)	solvent	% yield <sup>b</sup>
1	1.5	CH <sub>2</sub> Cl <sub>2</sub>	64
2	1.5	TFP	42
3	1.5	CH <sub>2</sub> Cl <sub>2</sub> / CH <sub>3</sub> CN (1:2)	66
4	1.5	TFP/ CH <sub>3</sub> CN (1:8)	73
5	1.5	TFP/CH <sub>2</sub> Cl <sub>2</sub> / CH <sub>3</sub> CN (1:4:8)	90
6	1.5	CH <sub>3</sub> CN	80
7	1.0	TFP/CH <sub>2</sub> Cl <sub>2</sub> /CH <sub>3</sub> CN (1:4:8)	52 <sup>c</sup>
8	2.0	“	20 <sup>d</sup>
9	1.5	“	86 <sup>e</sup>
10	1.5	“	52 <sup>f</sup>
11	-	“	0
12	1.5	“	50 <sup>g</sup>
13	1.5	CH <sub>3</sub> CN	70 <sup>h</sup>

<sup>a</sup>General procedure: Indole **3a** (0.275 mmol, 1.0 equiv), was added as a CH<sub>2</sub>Cl<sub>2</sub> (3.2 mL) solution (slowly, over ~1 min) to guanidine **2** (0.552 mmol, 2.0 equiv) and NaTFP (0.331 mmol, 1.2 equiv) in solvent indicated under nitrogen at 0 °C. PhI(OAc)<sub>2</sub> (82.5 mM in CH<sub>2</sub>Cl<sub>2</sub>, TFP, or CH<sub>3</sub>CN, 5.0 mL) was then added slowly (over ~1 min) and stirred at 0 °C for 3 h. <sup>b</sup>Isolated, purified yields. <sup>c</sup>Employed 1.0 equiv each of indole **3a** and NaTFP. <sup>d</sup>Guanidine **2** (1.2 equiv) as an CH<sub>3</sub>CN solution was added to a mixture of NaTFP (2.0 equiv), oxidant, and indole. <sup>e</sup>Solid Na<sub>2</sub>CO<sub>3</sub> (1.2 equiv) was employed as base. <sup>f</sup>No base was added. <sup>g</sup>PhI(OCOCF<sub>3</sub>)<sub>2</sub> (1.5 equiv) used as oxidant. <sup>h</sup>Solid Na<sub>2</sub>CO<sub>3</sub> (1.2 equiv) employed as base. TFP = 2,2,3,3-tetrafluoro-1-propanol; NaTFP = sodium 2,2,3,3-tetrafluoro-1-propoxide.

Employing the optimized conditions, we investigated several 1,3-disubstituted indoles and these substrates underwent cycloaddition efficiently to provide tricyclic adducts **4b-e** in 82-86% yields (Table 2). Bulky substituents at C-3, *e.g.* *i*-propyl and cyclohexyl, were tolerated providing the corresponding cycloadducts **4b** and **4e**, along with a pendant ester producing cycloadduct **4d** (86%). The use of C3-unsubstituted substrates **3f,g** led to extensive production of non-cyclized indolo guanidines **5,6** in addition to the expected (3+2) adducts **4f,g**. 2,3-Disubstituted indoles had diminished rates of cycloaddition but still led to good mass recovery providing cycloadduct **4h** (73%; confirmed by X-ray crystallography,

see SI for details) along with recovered starting material (21%). Use of a removable substituent on the indole nitrogen, *e.g.* *N*-benzyl group, was also tolerated providing the *N*-benzyl adduct **4i** (87%).

**Table 2. Guanidine annulations via net (3+2) cycloadditions of guanidine **2** and electron-rich alkenes **3****



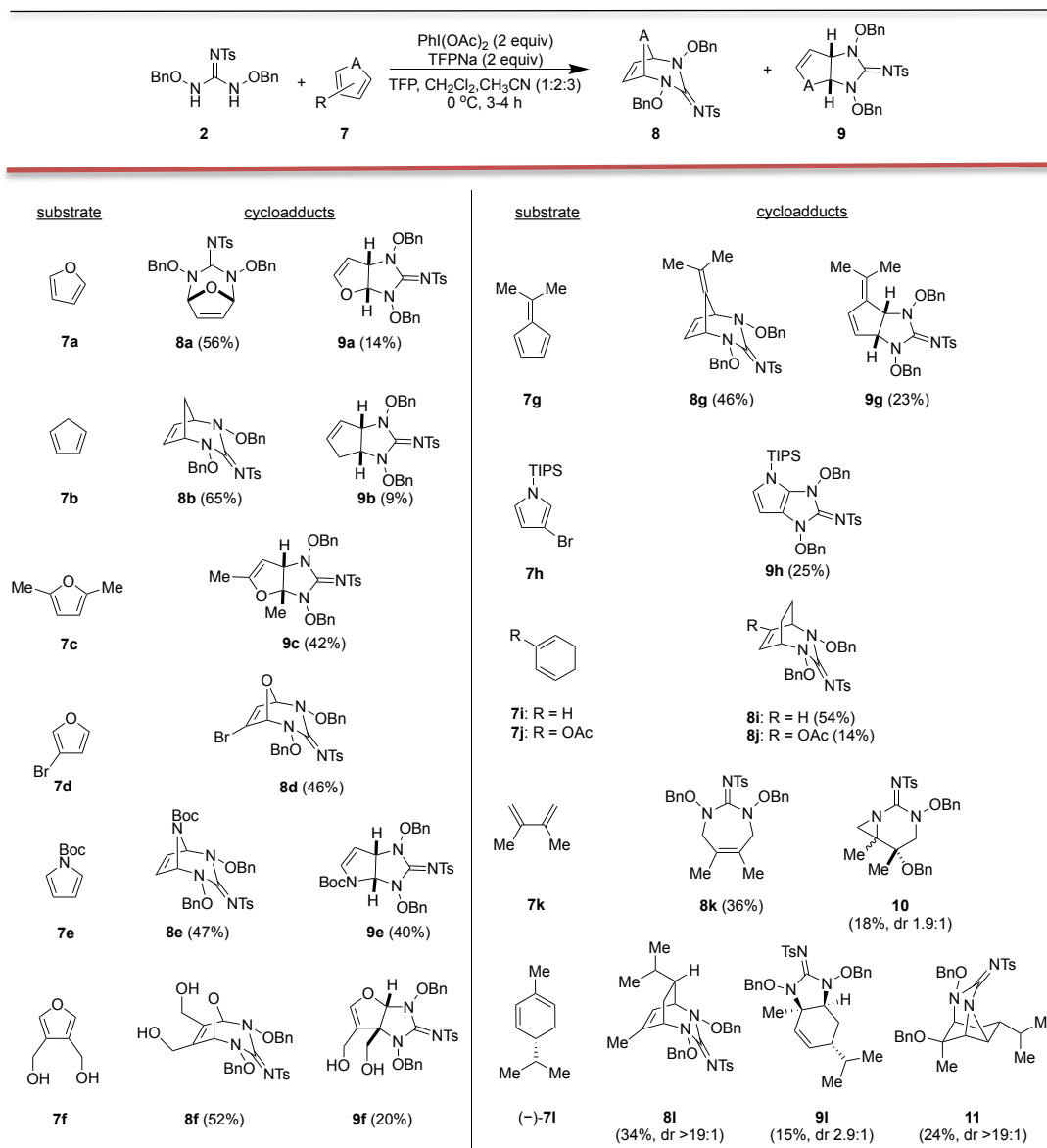
<sup>a</sup> ~10-20% starting material was recovered

Several 6-membered oxygen and nitrogen containing heterocycles were also studied, and generally only electron rich alkenes participated, providing the corresponding *N*-Boc piperidine-fused guanidine **4j** (54%) and the 1,4-dioxane fused-guanidine **4k** (36%) accompanied by ~20%

starting material in both cases. However, *N*-H and *N*-Me pyrrole substrates were oxidized under the reaction conditions. A number of less electron-rich alkenes did not participate in this cycloaddition including dihydropyran, cyclohexene, pinene, styrenes, dihydropyran, and also alkynes (see SI for details).

We also studied the potential for (4+3) cycloadditions of the 2-amido diaminoallylic cation **1** with dienes. Following extensive optimization with furan (**7a**, see SI for optimization details), which previously demonstrated good reactivity in related cycloadditions,<sup>16b, 16d</sup> application to various dienes led to several novel bridged guanidines **8**, in some cases accompanied by intervening (3+2) cycloadducts **9**, and a few unanticipated aziridines **10**, **11** (Table 3). Cyclopentadiene (**7b**) and 6,6-dimethyl fulvene (**7g**) provided both bridged and fused cyclic guanidines through net (4+3) and (3+2) cycloadditions, respectively. Several furans and pyrroles **7c-g**, **h** also participate. 3-Bromofuran (**7d**) provided the bridged ether **8d** (46%) equipped with a vinyl bromide for further functionalization. Similarly, dihydroxy furan (**7f**) participates providing both cycloadducts **8f** (52%) and **9f** (20%) showing tolerance to unprotected alcohols. The *N*-silyl bromopyrrole **7h** led to regeneration of the pyrrole ring following (3+2) cycloaddition due to HBr elimination. Cyclohexadiene (**7i**) gave only the (4+3) cycloadduct **8i** in 54% yield while 2-acetoxy cyclohexadiene led to poor yields of the bridged cycloadduct **8j** (14%) likely due to acetate hydrolysis under the basic reaction conditions. The acyclic diene, 2,3-dimethylbutadiene (**7k**), led to an interesting and informative by-product (*vide infra*), aziridine **10**, in 18% yield as a mixture of diastereomers (dr, 1.9:1) accompanied by the expected (4+3) cycloadduct **8k** (36%). Similarly, (–)- $\alpha$ -phellandrene also gave cycloadducts **8l** (34%) and **9l** (15%, dr 2.9:1, major diastereomer shown) accompanied by 24% of aziridine **11** accomplishing an overall *syn*-tetra-functionalization of the diene.

**Table 3. (4+3)/(3+2) Cycloaddition reactions of dienes **7** with the 1,3-dipole derived from guanidine **2****



<sup>a</sup>Cycloadduct **9g** was found to be unstable and one isolated decomposition product (**9g'**, not shown; see SI for further details) presumably derives from a retroene process (see Scheme 1, intermediate **16**) leading to loss of benzaldehyde (*cf.* formation of indoles **5,6** (Table 2)).

Several lines of evidence gathered during this study suggest a stepwise, ionic mechanism for the described net cycloadditions (Scheme 1A). With indole substrate **3**, nucleophilic addition of the C-3 olefinic carbon to the allylic cation **1** provides a stabilized carbocation, iminium **12**. Cycloadditions with C3-unsubstituted indoles **12** ( $R^2 = H$ ) enables deprotonation of the iminium, driven by rearomatization, to give indole **5** which suggests a competitive elimination of intermediate **12** and a stepwise mechanism. Interestingly, indole **5** had lost one benzyloxy group which we propose derives from a retro-ene process from anionic intermediate **16**. However, with C3-substituted indoles **12** ( $R^2 \neq H$ ), rearomatization through elimination is not possible and thus these substrates provide higher yields of (3+2)

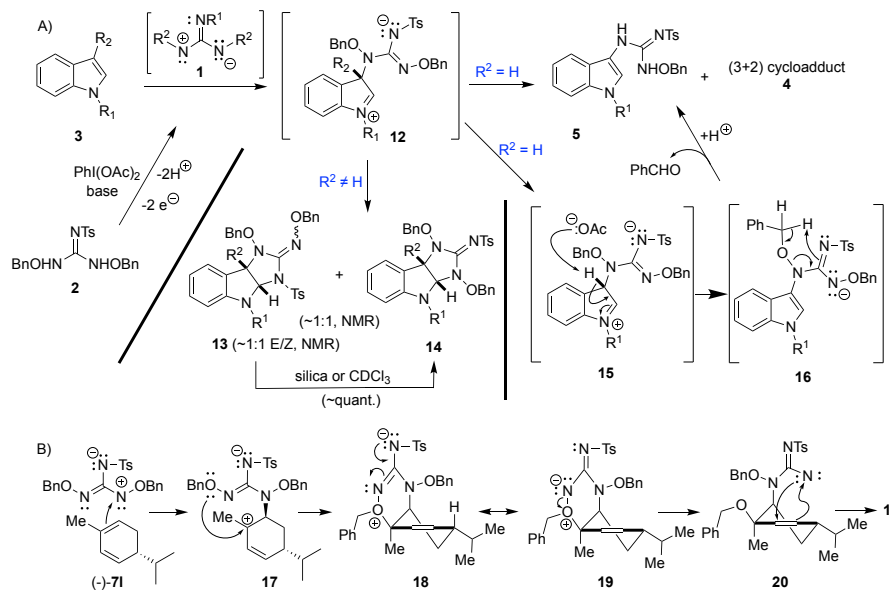
cycloadducts **4**. In this case, initial adducts were determined to be a ~1:1 mixture of oxime **13** (~1:1, *E/Z*) and cycloadduct **14**. This would be anticipated for a stepwise mechanism proceeding through iminium **12** followed by ring closure by either the pendant *N*-Ts or *N*-OBn substituted amines. In early studies, the crude reaction mixture was directly loaded on SiO<sub>2</sub> prior to NMR analysis and under these conditions, oxime **13** is converted to the more stable tosylimine **14**. This was verified by isolation of oximes **13** (~1:1, *E/Z*) and exposure to mild acid leading to quantitative conversion to cycloadduct **14**.

The formation of bicyclic aziridines **10** and **11** from diene **7k** and  $\alpha$ -phellandrene **7l**, respectively, provide further

support for a stepwise, net cycloaddition. A proposed mechanism for formation of aziridine **11** invokes initial formation of a stabilized tertiary, allylic carbocation **17**, followed by cyclization of the pendant oxygen atom of the *N*-OBn group leading to the zwitterion **18/19** (Scheme

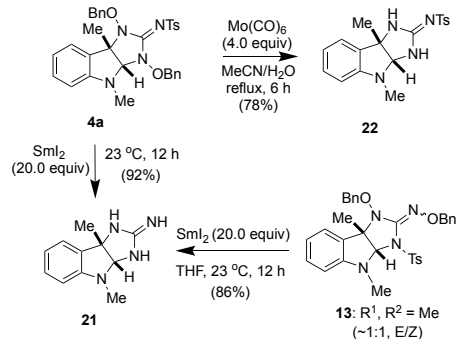
1B). This process further weakens the N-O bond facilitating heterolytic bond cleavage to give nitrene **20** enabling a highly diastereoselective, intramolecular aziridination leading to tricyclic aziridine **11** (and similarly **10**).

**Scheme 1. Proposed mechanisms for by-products suggestive of stepwise guanidine annulations**



The N-O bonds of indolo-guanidine **4a** could be selectively cleaved by  $\text{Mo}(\text{CO})_6$  to furnish tosyl indolo-guanidine **22** in 78% yield (Scheme 2).<sup>17</sup> Global deprotection of indolo-guanidine **4a** was achieved with excess  $\text{SmI}_2$  to provide guanidine **21** in 92% yield. To provide further structural confirmation for oximes **13** (~1:1 *E/Z*), treatment with excess  $\text{SmI}_2$  also led to the same cyclic guanidine **21**. However, we cannot at this time exclude the possibility that rearrangement to adduct **4a** precedes deprotection under these conditions.

**Scheme 2. Methods for partial and complete deprotection of indole **4a** and correlation to oximes **13****

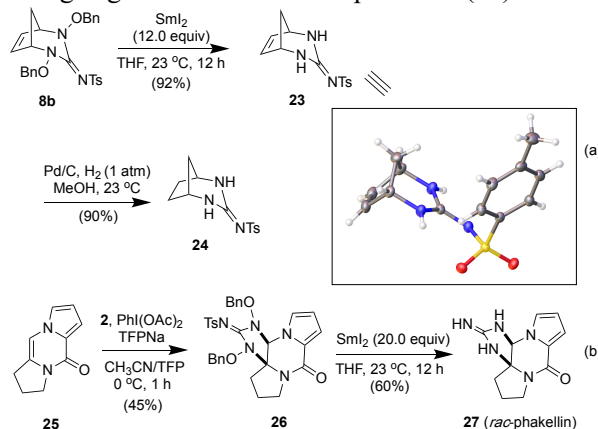


We targeted the synthesis of the *N*-tosyl variant **24** of the [2.3.0] *N*-phenyl bicyclic guanidine (see Fig. 1) previously developed as an antihypertensive agent (Scheme 3a).<sup>23</sup> Selective removal of the benzyloxy groups in this case was achieved with  $\text{SmI}_2$  (12.0 equiv) to obtain alkene

**23** (ORTEP, inset Scheme 3a). Subsequent hydrogenation produced the *N*-Ts bicyclic guanidine **24** (82%, 2 steps).

As a model study for the projected ring annulation to palau'amine, we applied this method to the pyrrolo-imidazole alkaloid, phakellin (**27**, Scheme 3b). Indeed, the electron rich tricyclic alkene **25**,<sup>24</sup> delivered the desired (3+2) cycloadduct **26** (45%) along with elimination product **29** (21%, not shown; *cf.* **5**, see SI for details). Global deprotection of guanidine **26** with  $\text{SmI}_2$  provided *rac*-phakellin (**27**) in 60% yield.

**Scheme 3. Applications of the 1,3-dipolar cycloaddition to bridged guanidine **24** and *rac*-phakellin (**27**)**





In conclusion, we developed a new method for direct guanidine annulation of alkenes leading to tricyclic and bridged bicyclic guanidines through both (3+2) and (4+3) net cycloadditions. The aziridines and other by-products isolated in addition to the observed reactivity of primarily electron rich alkenes, supports a stepwise, net cycloaddition. Further studies of this novel 1,3-dipole, the 2-amido diaminoallylic cation **1**, including computational studies of this intermediate and reaction pathways, along with further applications are underway.

## ASSOCIATED CONTENT

The supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures, X-ray diffraction, spectroscopic data for all new compounds including <sup>1</sup>H and <sup>13</sup>C NMR spectra (PDF).

Crystallographic data for **4a** (CIF)

Crystallographic data for **4h** (CIF)

Crystallographic data for **23** (CIF)

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## Notes

The authors declare no competing financial interest.

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