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Synthesis of Cyclic Guanidines via Silver-Catalyzed Intramolecular Alkene Hydroamination Reactions of *N*-Allylguanidines

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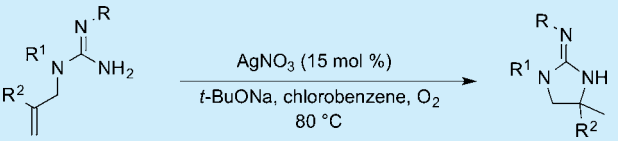
Supporting Information

ABSTRACT: The silver-catalyzed hydroamination of tosyl-protected *N*-allylguanidines is described. These reactions provide substituted cyclic guanidines in high yields. The reactions are amenable to the construction of quaternary stereocenters as well as both monocyclic and bicyclic guanidine products.



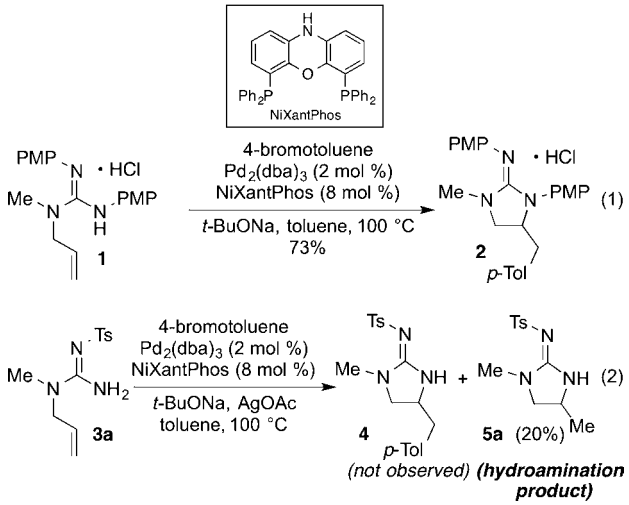
Cyclic guanidines are an important class of compounds that exhibit highly interesting biological activities,[1] and they have also found applications as synthetically useful organocatalysts.[2] The preparation of cyclic guanidines has often been accomplished via ring-closing S_N2 reactions,[3] haloamination of alkenes,[4] or through guanylation of 1,2-diamine derivatives.[5,6] More recent approaches have involved metal-catalyzed transformations that typically allow for generation of cyclic guanidines in an efficient manner from simple precursors.[7,8]

One powerful method for the metal-catalyzed synthesis of nitrogen heterocycles that has attracted considerable attention over the past 25 years is the intramolecular hydroamination of amines bearing pendant alkenes.[9] However, despite the high level of activity in this field and the many advances that have resulted, intramolecular alkene hydroamination reactions of guanidine nucleophiles have not previously been described. Looper, Gin, and van der Eycken have independently conducted elegant work on metal-catalyzed alkyne hydroamination reactions of guanidines,[10] but extension of these methods to analogous alkene hydroaminations has remained elusive.

We recently described a new approach to the synthesis of cyclic guanidines **2** via Pd-catalyzed alkene carboamination reactions between aryl bromides and *N*-allylguanidines bearing *N*-PMP protecting groups (**1**) (Scheme 1, eq 1).[11−13] These transformations provided the desired products in good chemical yield for a variety of different substrate combinations. However, removal of the PMP protecting groups proved to be quite challenging, and efforts to cleave both PMP groups from the product were not successful.

To overcome this limitation, we began to explore alternative *N*-protecting groups for the carboamination reactions, and initial studies on the use of substrates bearing a single *N*-tosyl protecting groups (e.g., **3a**) provided promising preliminary results.[12] During efforts to optimize these reactions we examined the influence of silver salts on reactions of **3a**, as other studies conducted in our lab suggested that formation of cationic intermediate palladium complexes may facilitate reactions of relatively electron-poor substrates.[12,14] Although

Scheme 1. Unexpected Hydroamination



these conditions failed to provide the desired alkene carboamination product **4** (Scheme 1, eq 2), we were intrigued to discover that the cyclic guanidine **5a** derived from the hydroamination of the alkene was produced in 20% yield. A series of control reactions demonstrated that the palladium was not necessary for the transformation to occur, but the presence of silver acetate (1 equiv), and base was required for the reaction to occur.[15]

Given the significance of the guanidine products and the novelty of the hydroamination reaction, we set out to optimize the Ag-catalyzed conversion of **3a** to **5a** (Table 1). Since our preliminary result employed a stoichiometric amount of AgOAc, we began our optimization studies by modifying the conditions shown in Scheme 1, eq 2 by simply omitting the aryl bromide and the palladium catalyst, and decreasing the loading of silver acetate to 10 mol % (Table 1, entry 1). Unfortunately,

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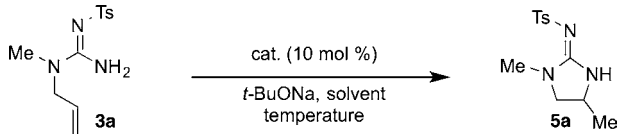
Table 1. Optimization Studies[a]



entry	catalyst	solvent	T (°C)	atmosphere	yield[b] (%)
1	AgOAc	$PhCH_3$	100	N_2	<2[c]
2	AgOTf	$PhCH_3$	100	N_2	14[c]
3	AgOTf	$Ph(CH_3)_2$	138	N_2	40[c]
4	AgOTf	$Ph(CH_3)_2$	138	N_2	45
5	Ag_2O	$Ph(CH_3)_2$	138	N_2	15
6	$Cu(OTf)_2$	$Ph(CH_3)_2$	138	N_2	25
7	CuI	$Ph(CH_3)_2$	138	N_2	18
8	$AuPPh_3OTf$	$Ph(CH_3)_2$	138	N_2	<2
9	AgOTf	$Ph(CH_3)_2$	138	O_2	70
10	$AgNO_3$	$Ph(CH_3)_2$	138	O_2	99[d]
11	$AgNO_3$	$PhCH_3$	40	O_2	<2[d]
12	$AgNO_3$	$PhCH_3$	80	O_2	99[d]
13	$AgNO_3$	$PhCH_3$	80	air	85[d]
14	$AgNO_3$	PhCl	80	air	99
15	$AgNO_3$	PhCl	80	O_2	99
16	$AgNO_3$	PhCl	80	N_2	60[e,f]
17	$AgNO_3$	PhCl	80	N_2	99[e,g]

[a]Conditions: 1.0 equiv of **3a**, 1.0 equiv of *t*-BuONa, 10 mol % of catalyst, solvent (0.1 M), 40−138 °C, 17−21 h. Reactions were conducted on a 0.075−0.25 mmol scale. [b]Yields were determined by ^{1}H NMR analysis using phenanthrene as an internal standard. [c]The reaction was conducted in the presence of the ligand NiXantPhos (10 mol %). [d]The reactions were conducted at 0.033 M concentration. [e]The reaction was conducted in distilled and degassed chlorobenzene. [f]Reaction progress was stopped at 60% conversion (40% unreacted starting material). [g]The reaction was conducted using 1 equiv of $AgNO_3$.

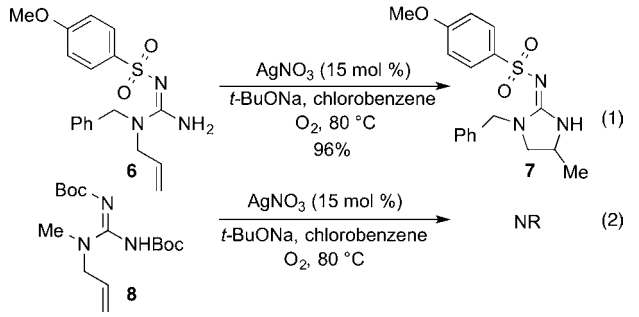
these conditions failed to produce the desired product. However, use of AgOTf as catalyst and a higher reaction temperature (138 °C) did result in catalyst turnover, and provided the desired product in 40% yield (Table 1, entry 3). Omission of the phosphine ligand from the reaction mixture led to a slight improvement in yield (45%) (Table 1, entry 4). A brief survey of copper and gold catalysts did not provide satisfactory results.

During the course of these optimization studies, we noticed that chemical yields were not satisfactorily reproducible, and we began to suspect that adventitious oxygen may play a role in these reactions. As such, we carried out the AgOTf-catalyzed hydroamination of **3a** under an atmosphere of oxygen and were pleased to discover the desired product was formed in 70% yield (Table 1, entry 9). When silver nitrate was employed as catalyst and the concentration was decreased to 0.033 M, the reaction provided 99% yield of **5a** (Table 1, entry 10). Finally, the use of chlorobenzene as solvent allowed the reactions to be conducted at a higher, more synthetically useful concentration (0.1 M) at lower temperature (80 °C).

Further experimentation indicated the reaction could be conducted under an atmosphere of air rather than O_2 (Table 1, entries 13 and 14). However, reactions carried out under air proved to give inconsistent results that appeared to depend on the level of atmospheric humidity present on any given day. Control experiments were carried out under a nitrogen atmosphere to further examine the role of O_2 in these reactions. Treatment of **3a** with 10 mol % of $AgNO_3$ under N_2 in degassed chlorobenzene led to only 60% conversion of starting material to product (Table 1, entry 16). However, use of a full equivalent of $AgNO_3$ under these oxygen-free conditions gave results comparable to the use of 10 mol % $AgNO_3$ under an oxygen atmosphere (Table 1, entry 17).

Before further exploring the scope of these reactions, we quickly surveyed the influence of two other nitrogen protecting groups on reactivity. As shown in Scheme 2, eq 1, use of substrate **6** bearing an *N*-*p*-methoxyphenylsulfonyl group led to the formation of the desired product **7** in 96% yield. Unfortunately efforts to prepare the analogous *p*-nitrophenyl derivative have thus far been unsuccessful. In addition, the reaction of diboc protected substrate **8** failed to produce the desired hydroamination product (Scheme 2, eq 2).

Scheme 2. *N*-Substituent Effects



In order to examine the scope of the silver-catalyzed guanidine hydroamination reactions, several substrates with different substitution patterns were synthesized and subjected to the optimized reaction conditions. As shown in Table 2, substrates **3a−d** and **3g−j** bearing a variety of substituents on the noncyclizing nitrogen atom were converted to the desired products in excellent yields (Table 2, entries 1−4 and 7−10). In addition, substitution on the internal alkene carbon was tolerated as substrates **3e** and **3f** were converted to cyclic guanidines **5e** and **5f** in high yield (Table 2, entries 5 and 6), although slightly higher reaction temperatures (100 °C) were required in these cases. Several functional groups including a cyclic acetal (Table 2, entry 8), an aryl ether (Table 2, entry 10), and a TBS-protected alcohol (Table 2, entry 9) were also tolerated, although approximately 20% of desilylated product was generated in this latter reaction. Although transformations of 1,1-disubstituted alkene substrates proceeded smoothly, efforts to carry out the Ag-catalyzed hydroamination of 1,2-disubstituted alkene substrates **9** or **10** (Scheme 3) were unsuccessful. No desired products were obtained in these reactions even with increased catalyst loadings (40 mol % Ag) and temperatures (138 °C). In addition, preliminary studies on 6-membered ring formation from substrate **11** failed to produce the desired cyclic guanidine product.

To explore the diastereoselectivity of these reactions, we sought to prepare substrates analogous to **3** but bearing a substituent (methyl or phenyl) at the allylic position. Unfortunately, the use of standard methods to generate these compounds has thus far been unsuccessful. Nonetheless, we were gratified to find the intramolecular alkene hydroamination reactions are amenable to the stereoselective construction of bicyclic guanidine derivatives. As shown in Scheme 4, eq 1, treatment of **12** with a $AgNO_3$ catalyst and *t*-BuONa under an oxygen atmosphere afforded bicyclic product **13** in 89% yield

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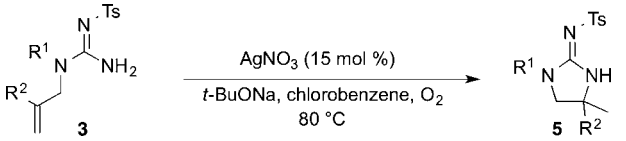
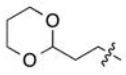
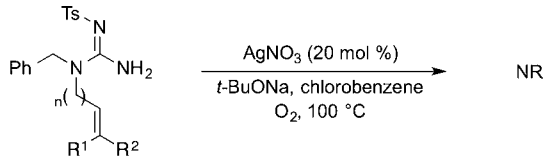
Table 2. Ag-Catalyzed Intramolecular Hydroamination Reactions[a]



entry	Substrate 3	R^1	R^2	Product 5	yield (%)[b]
1	**3a**	Me	H	**5a**	95
2	**3b**	Bn	H	**5b**	98
3	**3c**	Allyl	H	**5c**	97
4	**3d**	PMP	H	**5d**	99
5[c]	**3e**	Bn	Me	**5e**	94
6[c]	**3f**	Et	Me	**5f**	96
7	**3g**	$(CH_2)_2Ph$	H	**5g**	97
8	**3h**		H	**5h**	89
9[d]	**3i**	$(CH_2)_3OTBS$	H	**5i**	72
10	**3j**	$(CH_2)_2OPh$	H	**5j**	88

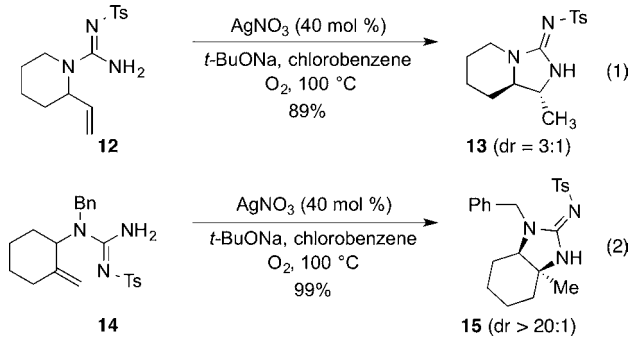
[a]Conditions: 1.0 equiv substrate **3**, 1.0 equiv *t*-BuONa, 15 mol % $AgNO_3$, chlorobenzene (0.1 M), O_2 balloon, 80 °C, 16−18 h. Reactions were conducted on a 0.25 mmol scale. [b]Isolated yield (average of two or more experiments). [c]The reaction was conducted using 20 mol % $AgNO_3$ catalyst at 100 °C for 18 h. [d]Approximately 20% of the desilylated alcohol was also generated.

Scheme 3. Unsuccessful Hydroaminations



9, R^1 = cyclopropyl, R^2 = H, n = 1
10, R^1 = H, R^2 = Me, n = 1
11, R^1, R^2 = H, n = 2

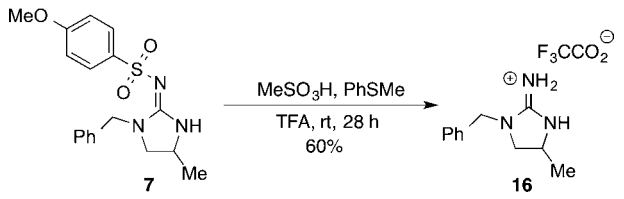
Scheme 4. Synthesis of Bicyclic Guanidines



and 3:1 dr. The analogous hydroamination of **14** afforded bicycle **15** in 99% yield and >20:1 dr (Scheme 4, eq 2).

We briefly examined deprotection of the *N*-arylsulfonyl group to afford the corresponding NH guanidine product. We have previously illustrated that *N*-tosyl groups can be cleaved from 2-aminoimidazoles (aromatic guanidine derivatives) via reduction with Li/naphthalene.[12] Unfortunately, our preliminary efforts to apply those conditions to the cyclic guanidine **5b** gave unsatisfactory results. Analysis of the reaction mixture by NMR and ESI-MS indicated the *N*-tosyl group was cleaved, but competing cleavage of the *N*-benzyl group was also observed. In addition, it proved to be very difficult to recover the deprotected material after aqueous workup due to water solubility. However, deprotection of the corresponding *N*-4-methoxyphenylsulfonyl derivative **7** under acidic conditions afforded the desired guanidinium salt **16** in 60% yield (Scheme 5).

Scheme 5. Deprotection



Currently, the mechanism of the Ag-catalyzed alkene hydroamination reactions remains unclear. We have no evidence to suggest these transformations do not proceed in a manner analogous to other hydroamination reactions that employ electrophilic late-metal catalysts (alkene activation by the catalyst, attack of the pendant nucleophile, and proto-demetalation).[9] However, in contrast to typical late-metal catalyzed alkene hydroamination reactions, which are typically conducted under neutral or slightly acidic conditions, the strong base *t*-BuONa is essential for our transformations. Thus, it is possible that these reactions proceed via an atypical pathway. The role of oxygen is also not entirely clear at this point. However, the observation that the hydroamination of **3a** in degassed chlorobenzene solvent under a N_2 atmosphere proceeded to 60% conversion (Table 1, entry 16) with 10 mol % catalyst and full conversion (99% yield) with a full equivalent of $AgNO_3$ (Table 1, entry 17) indicates oxygen is not essential for reactivity or catalyst turnover. As such, it appears likely that oxygen plays a role in stabilizing (or preventing reduction of) the silver catalyst.

In conclusion, we have developed the first metal-catalyzed intramolecular alkene hydroamination reactions of guanidine nucleophiles. These transformations provide access to five-membered cyclic guanidines bearing methyl substituents adjacent to a ring nitrogen atom in excellent yield. Future studies will be directed toward expanding the scope of these transformations and developing enantioselective variants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00598.

Experimental procedures, characterization data for all new compounds, and ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Berlinck, R. G. S.; Romminger, S. *Nat. Prod. Rep.* **2016**, *33*, 456. (b) Berlinck, R. G. S.; Trindade-Silva, A. E.; Santos, M. F. C. *Nat. Prod. Rep.* **2012**, *29*, 1382.
(2) Selig, P. *Synthesis* **2013**, *45*, 703.
(3) For representative examples, see: (a) O'Donovan, D. H.; Rozas, I. *Tetrahedron Lett.* **2012**, *53*, 4532. (b) Kim, H. − O.; Mathew, F.; Ogbu, C. *Synlett* **1999**, *1999*, 193.
(4) Daniel, M.; Blanchard, F.; Nocquet-Thibault, S.; Cariou, K.; Dodd, R. H. *J. Org. Chem.* **2015**, *80*, 10624 and references cited therein.
(5) For representative examples, see: (a) Nalli, S. M.; Clarkson, G. J.; Franklin, A. S.; Bellone, G.; Shipman, M. *Synlett* **2008**, *2008*, 2339. (b) Huber, D.; Leclerc, G.; Ehrhardt, J. D.; Andermann, G. *Tetrahedron Lett.* **1987**, *28*, 6453.
(6) For a recent review on the synthesis of cyclic guanidines, see: Lemrova, B.; Soural, M. *Eur. J. Org. Chem.* **2015**, *2015*, 1869.
(7) For a recent review, see: Zhang, W. − X.; Xu, L.; Xi, Z. *Chem. Commun.* **2015**, *51*, 254.
(8) (a) Hövelmann, C. H.; Streuff, J.; Brelot, L.; Muñiz, K. *Chem. Commun.* **2008**, 2334. (b) Zhao, B.; Du, H.; Shi, Y. *Org. Lett.* **2008**, *10*, 1087. (c) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073. (d) Büchi, G.; Rodriguez, A. D.; Yakushijin, K. *J. Org. Chem.* **1989**, *54*, 4494. (e) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887. (f) Mulcahy, J. V.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 12630.
(9) For recent reviews, see: (a) Julian, L. D. *Top. Heterocycl. Chem.* **2013**, *32*, 109. (b) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596. (c) Schafer, L. L.; Yim, J. C. H.; Yonson, N. In *Metal-Catalyzed Cross Coupling Reactions and More*; De Meijere, A., Brase, S., Oestreich, M., Eds.; Wiley VCH: Weinheim, 2014; p 1135. (d) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (e) Liu, C.; Bender, C. F.; Han, X.; Widenhoefer, R. A. *Chem. Commun.* **2007**, 3607.
(10) (a) Giles, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3116. (b) Gainer, M. J.; Bennett, N. R.; Takahashi, Y.; Looper, R. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 684. (c) Gibbons, J. B.; Gligorich, K. M.; Welm, B. E.; Looper, R. E. *Org. Lett.* **2012**, *14*, 4734. (d) Perl, N. R.; Ide, N. D.; Prajapati, S.; Perfect, H. H.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 1802. (e) Ermolat'ev, D. S.; Bariwal, J. B.; Steenackers, H. P. L.; DeKeersmaecker, S. C. J.; Van der Eycken, E. V. *Angew. Chem., Int. Ed.* **2010**, *49*, 9465. (f) Kwon, K.-H.; Serrano, C. M.; Koch, M.; Barrows, L. R.; Looper, R. E. *Org. Lett.* **2014**, *16*, 6048. (g) Gibbons, J. B.; Salvant, J. M.; Vaden, R. M.; Kwon, K. − H.; Welm, B. E.; Looper, R. E. *J. Org. Chem.* **2015**, *80*, 10076.
(11) Zavesky, B. P.; Babij, N. R.; Fritz, J. A.; Wolfe, J. P. *Org. Lett.* **2013**, *15*, 5420.
(12) For related Pd-catalyzed carboamination reactions between *N*-propargyl guanidines and aryl bromides that afford substituted 2-aminoimidazole products, see: Zavesky, B. P.; Babij, N. R.; Wolfe, J. P. *Org. Lett.* **2014**, *16*, 4952.
(13) For reviews on Pd-catalyzed alkene carboamination reactions, see: (a) Wolfe, J. P. *Top. Heterocycl. Chem.* **2013**, *32*, 1. (b) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351. (c) Wolfe, J. P. *Synlett* **2008**, *2008*, 2913. (d) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571.
(14) (a) Fornwald, R. M.; Fritz, J. A.; Wolfe, J. P. *Chem. - Eur. J.* **2014**, *20*, 8782. (b) Peterson, L. J.; Wolfe, J. P. *Adv. Synth. Catal.* **2015**, *357*, 2339.
(15) For reviews on Ag-catalyzed syntheses of heterocycles, see: (a) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodriguez-Garcia, I. *Chem. Rev.* **2008**, *108*, 3174. (b) Weibel, J. − M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149.

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Org. Lett. 2016, 18, 2331−2334