Catalytic Synthesis of Cyclic Guanidines via Hydrogen Atom Transfer and Radical-Polar Crossover

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ABSTRACT: Cyclic guanidines are found in many biologically active compounds and natural products. Further, the formation of the atypical 7-membered ring of cyclic guanidine remains challenging due to a lack of efficient preparation strategies and low yield. Herein, a catalytic synthetic method for cyclic guanidines was developed via transition-metal hydrogen atom transfer and radical-polar crossover. This mild and functional-group tolerant process enabled the cyclization of an alkenyl guanidines bearing common protective groups, such as Cbz and Boc groups. This powerful method not only provided typical 5- and 6-membered rings but also the atypical 7-membered ring. The derivatization of the products afforded various heterocycles. We also investigated the selective cyclization of mono-protected or hetero-protected (TFA and Boc) alkenyl guanidines and their further derivatizations.

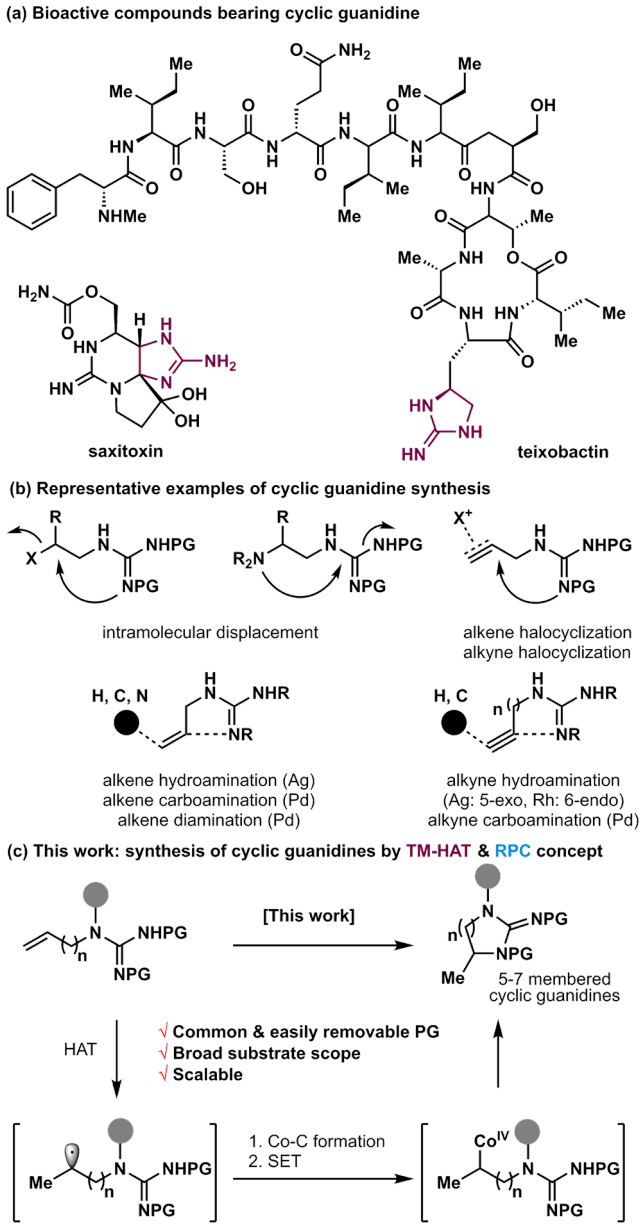
Guanidine is an inherently effective basic motif. For instance, arginine, a series of amino acids, contains the guanidine motif and contributes to the expression of biological functions.[1] Moreover, its cyclic form is present in potent bioactive compounds and natural products,[2] such as saxioxin[3] (blocker of voltage-gated sodium channels) and teixobactin[4] (an antibiotics for resistant bacteria) (Scheme 1). Because of these chemical and medicinal properties of cyclic guanidines, the development of a useful method for their synthesis has been of long-standing interest in organic synthesis.[2,5] There are various methods for synthesizing cyclic guanidines, such as intramolecular displacement,[6] halocyclization,[7] and others.[8] Metal-catalyzed processes were developed, including alkene hydroamination (Ag),[9] alkene carboamination (Pd),[10] alkene diamination (Pd),[11] alkyne hydroamination (Ag, Rh),[12] alkyne carboamination (Pd),[13] C–H amination (Rh),[14] cyclization via (π-allyl) palladium intermediate,[15] carbenylative amination (Pd).[16] Both, traditional and metal-catalyzed methods have been used in the synthesis of complex natural products.[17] Despite numerous examples of cyclic guanidine formation, the atypical and more challenging 7-membered ring, which is an undeveloped chemical space, has not been prepared efficiently. It is also noteworthy that potent drug candidates containing 7-membered ring have been reported in recent years.[18] Dodd and co-workers reported two examples of 7-membered ring guanidines synthesized via halocyclization, however, to the best of our knowledge, there is significant potential to improve the yields (23% and 21%).[7e] Herein, we demonstrate a powerful, catalytic, Markovnikov-selective, and scalable hydroamination that affords cyclic guanidines via the transition-metal hydrogen atom transfer (TM-HAT) and radical-polar crossover (RPC).

Recently, TM-HAT catalytic systems have been used by many groups to facilitate various transformations of alkenes with excellent functional group tolerance.[19] We have previously reported the unique effect of *N*-fluorocollidinium salt on the TM-HAT system that enables the ionic process via the RPC mechanism, which led to further transformations developed by us[20] and other groups.[21] Encouraged by these reports, we envisioned that an alkenyl guanidine bearing a common and easily removable protective groups (carboxybenzyl (Cbz) and or *tert*-butoxycarbonyl (Boc) could be cyclized via the TM-HAT and RPC approach. The use of these common protective groups was not successful for hydroaminations nor similar transformations with different catalysis.[9-10,11c] Moreover, we assumed that the high reactivity based on the TM-HAT/RPC mechanism could efficiently form an unusual ring size of cyclic guanidines.

We initially chose to examine the 5-exo cyclization of alkenyl guanidine **1a** bearing two Cbz groups and obtained the desired cyclic guanidine **2a** in 88% yield using previously developed reaction conditions: cobalt catalyst **C1**, *N*-fluoro-2,4,6-collidinium trifluoromethanesulfonate (Me_3NFPY·OTf), and 1,1,3,3-tetramethyldisiloxane (Scheme 2, entry 1). When phenylsilane was used, the yield of **2a** decreased due to the formation of cyclic urea **3a** (entry 2). Screening of various cobalt complexes (**C1** – **C3**) revealed that the four *tert*-butyl groups were essential for acceptable conversion (entries 1, 3, 4). We found that the previously developed complex **C4** provided slightly better conversion than that of **C1** (entry 5). Replacing the

counteranion of Me_3NFPY salt with tetrafluoroborate (BF_4) or hexafluorophosphate (PF_6) did not improve the efficiency of the reaction (entries 6 and 7). Moreover, 841 mg (2.30 mmol) of **2a** could be synthesized from 1.02 g of **1a** (82%).

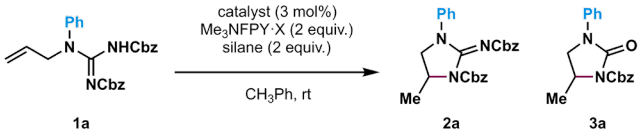
Scheme 1 (a) Representative Examples of Natural Products bearing Cyclic Guanidine, (b) Representative Methods affording Cyclic Guanidine, and (c) This Work: Synthesis of Cyclic Guanidine by the TM-HAT and RPC Concept



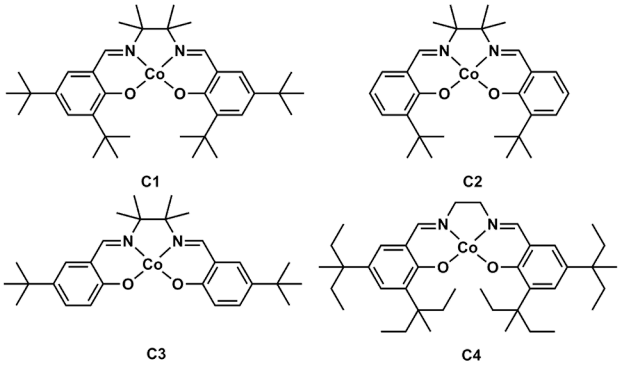
With the optimal conditions, we next briefly examined the scope of the substituted alkenyl guanidine forming 5-membered ring products (**1b** – **1g**) (Scheme 3). The substrates bearing the electron-withdrawing chloro (**1b**) or electron-donating methoxy (**1c**) in the *p*-position of the aniline unit gave **2b** and **2c** in good yields, respectively. The dimethylated product **2d** was also synthesized from the disubstituted alkenyl guanidine **1d** in 80% yield together with a hydroxylated compound (9%). The yields were also excellent for the substrates, including methylamine (**1e**), benzylamine (**1f**), and phenethylamine (**1g**).

Encouraged by this result, we next applied the same concept to form rings. Other than those with 5-members. We discovered that 6-exo and 7-exo cyclizations were possible under the same reaction conditions (**2h** and **2i**) (Scheme 4). The yields of **2h** using **C4** and **C1** were identical, but **C4** proved to be advantageous for producing **2i**. Although this method was ineffective for the formation of 8-membered guanidine **2j**, we focused on the preparation of various 7-membered guanidines.

Scheme 2. Optimization of Reaction Condition

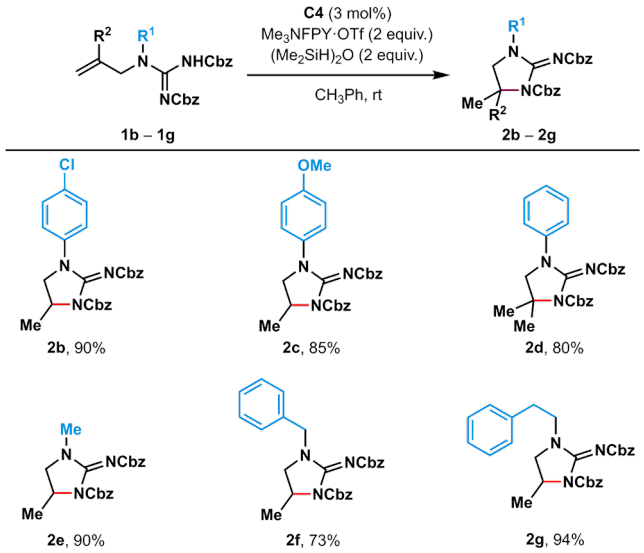


entry	cat.	X	silane	2a (%)[a]
1	C1	OTf	$(Me_2SiH)_2O$	88
2	C1	OTf	$PhSiH_3$	59 (+25% **3a**)
3	C2	OTf	$(Me_2SiH)_2O$	74
4	C3	OTf	$(Me_2SiH)_2O$	32
5	C4	OTf	$(Me_2SiH)_2O$	90, 84[b], 82[c]
6	C4	BF_4	$(Me_2SiH)_2O$	76
7	C4	PF_6	$(Me_2SiH)_2O$	83



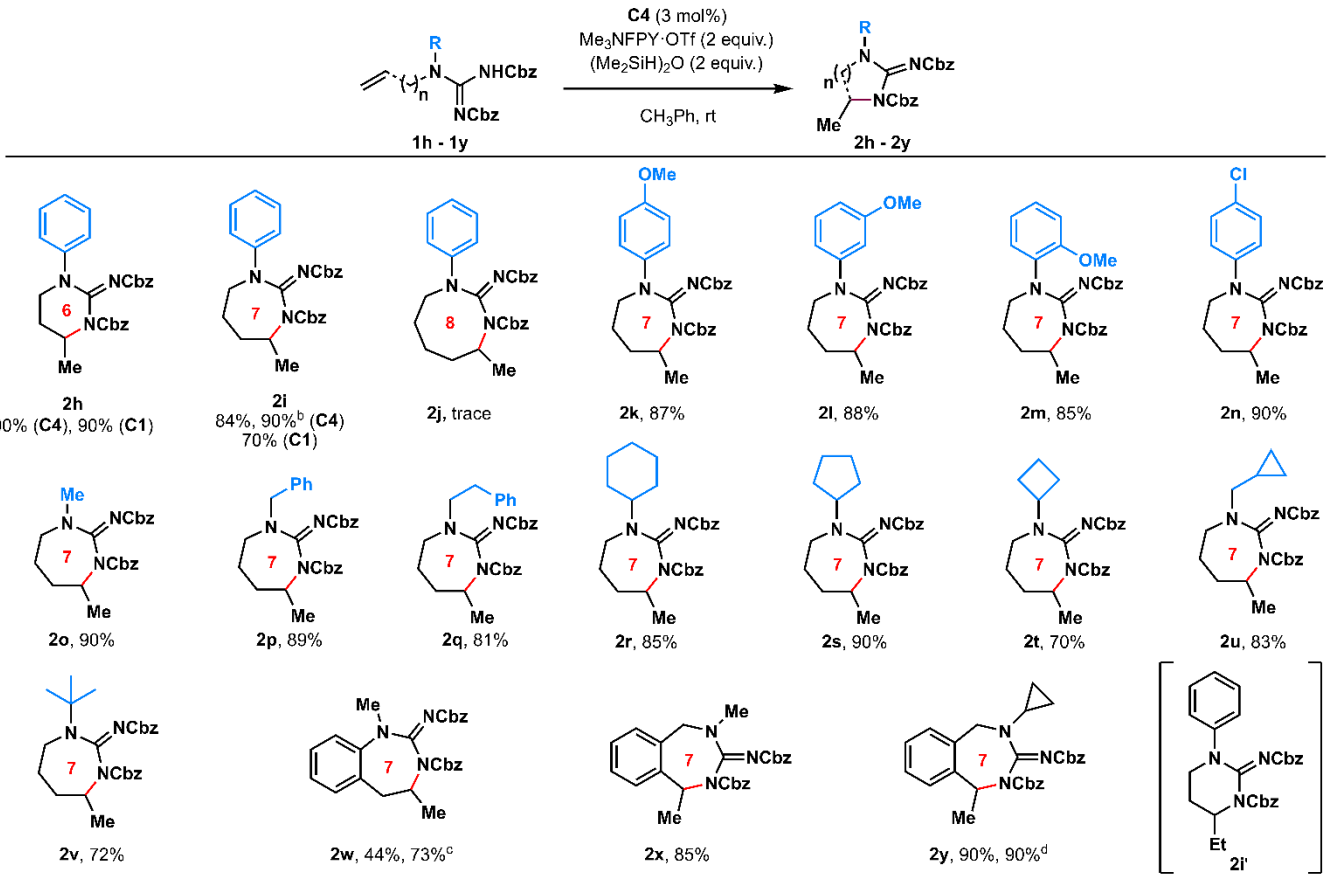
Conditions: alkenyl guanidine (0.1 mmol), catalyst (0.003 mmol), $Me_3NFPY{\cdot}X$ (0.2 mmol), silane (0.2 mmol), CH_3Ph (1.0 mL), room temperature, 20 h. [a]NMR yield using 1,4-bis(trifluoromethyl)benzene as the internal standard. [b]isolation yield [c]2.30 mmol scale

Scheme 3. Scope of Alkenyl Guanidines Affording 5-Membered Ring Products[a]



Conditions: alkenyl guanidine (0.1 mmol), catalyst (0.003 mmol), *N*-fluorocollidinium trifluoromethanesulfonate (0.2 mmol), 1,1,3,3-tetramethyldisiloxane (0.2 mmol), CH_3Ph (1.0 mL), room temperature, 20 h. [a]isolation yield

Scheme 4. Scope of Alkenyl Guanidines Affording Products of 6- and 7-Membered Rings[a]



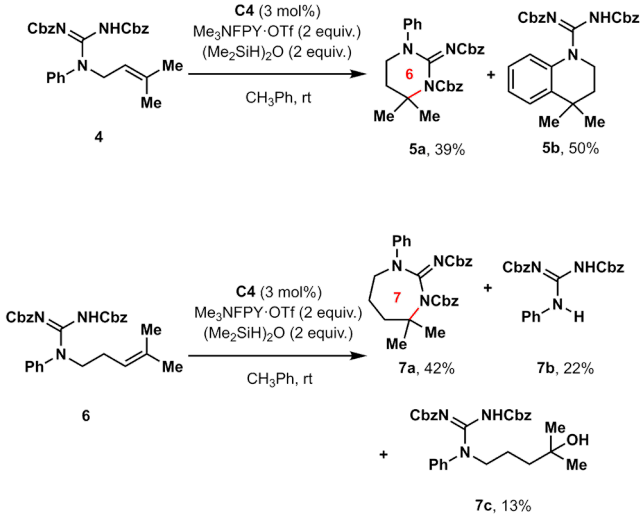
Conditions: alkenyl guanidine (0.1 mmol), **C4** (0.003 mmol), *N*-fluorocollidinium trifluoromethanesulfonate (0.2 mmol), 1,1,3,3-tetramethyldisiloxane (0.2 mmol), CH_3Ph (1.0 mL), room temperature, 20 h. [a]isolation yield [b]3.00 mmol scale [c]9 mol% of **C4** was used. [d]4.13 mmol scale

We next examined the electronic and steric effects using substrates with aniline units bearing electron-donating or electron-withdrawing groups in different positions on the aniline ring. We found no significant differences when using substrates **1k** – **1n** that gave the corresponding 4-methoxy (**2k**), 3-methoxy (**2l**),2-methoxy (**2m**), and 4-chloro (**2n**) products. Again, replacing the aniline unit with an aliphatic amine such as methylamine, benzyla-

mine, and phenethylamine, resulted in comparable yields (**2o** – **2q**). The products bearing more hindered amine such as cyclohexylamine (**2r**), cyclopentylamine (**2s**), and *tert*-butylamine (**2v**), were prepared in 72 – 90% yields. Strained carbocycles such as the cyclobutyl (**2s**) and cyclopropylmethyl groups (**2u**) were tolerated in this reaction condition. Moreover, we could prepare benzocyclic guanidines (**2w** – **2y**) in 73 – 90% yields using the same method. We reinvestigated the scalability of this reaction using 1.42 g (3.00 mmol) of **1i** and obtained **2i** in 90% isolation yield. This scale-up experiment enabled the isolation and structural determination of a small amount of byproduct **2i′** (6%), probably produced via the 1,2-H shift of the alkylCo(IV) intermediate. We also prepared 1.80 g of benzocyclic **2y** in 90% yield, together with a small amount of complex byproduct mixtures, from 2.00 g (4.13 mmol) of **1y**.

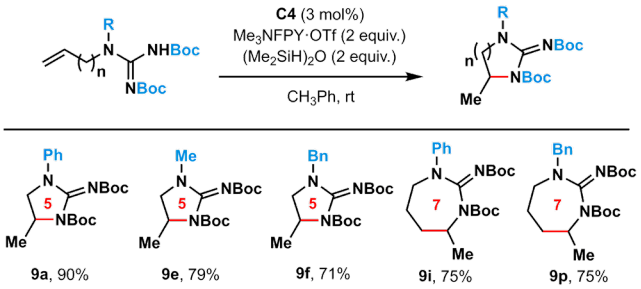
We also examined cyclizations using trisubstituted alkenyl guanidines (Scheme 5). Although the formation of the 6-membered cyclic guanidine **5a** was amenable, the yield was less than moderate due to a side reaction (hydroarylation) affording **5b**, which had also been reported by our group.[20d] The use of **C1** did not improve the yield of **5a** (14%). 7-membered cyclic guanidine **7a** was also obtained; however, the byproducts **7b** and **7c** were also formed in small amounts.

Scheme 5. Cyclization of Trisubstituted Alkenyl Guanidines



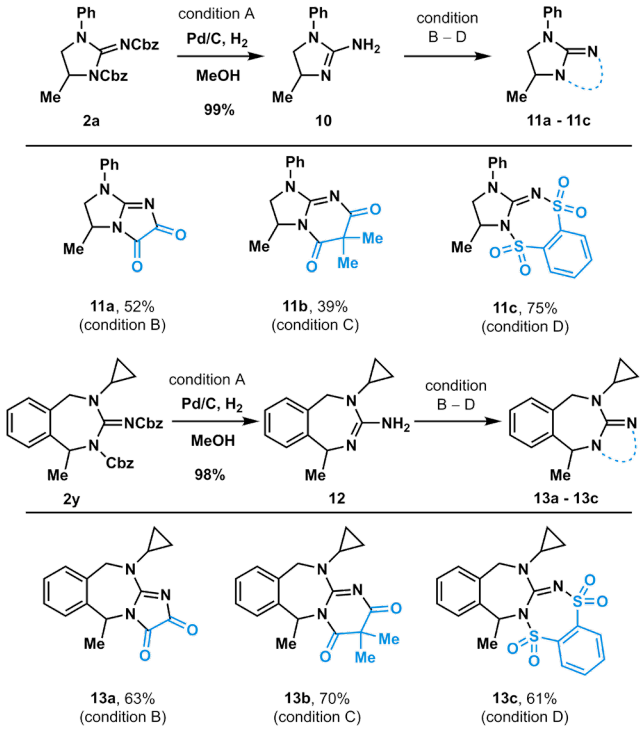
As expected, replacing the two Cbz groups of **1a** with the Boc groups, another common protective group, resulted in a 90% yield of the 5-membered cyclic guanidine **9a** (Scheme 6). The products containing methylamine **9e** and benzylamine **9f** were also synthesized in good yields. It should be noted that **9e** could not been synthesized by the previously reported hydroamination method.[9] 7-membered cyclic guanidine **9i** was obtained in 75% yield together with the alkene-isomerized byproduct and 6-membered cyclic guanidine similar to **2i′**. Moreover, the product **9p** bearing a benzylamine unit was obtained in comparable yield.

Scheme 6. Cyclization of Alkenyl Guanidines Bearing Boc group[a]



Conditions: alkenyl guanidine (0.5 mmol), catalyst (0.015 mmol), *N*-fluorocollidinium trifluoromethanesulfonate (1.0 mmol), 1,1,3,3-tetramethyldisiloxane (1.0 mmol), CH_3Ph (5.0 mL), room temperature, 20 h. [a]isolation yield

Scheme 7. Derivatization of Cyclic Guanidines[a]

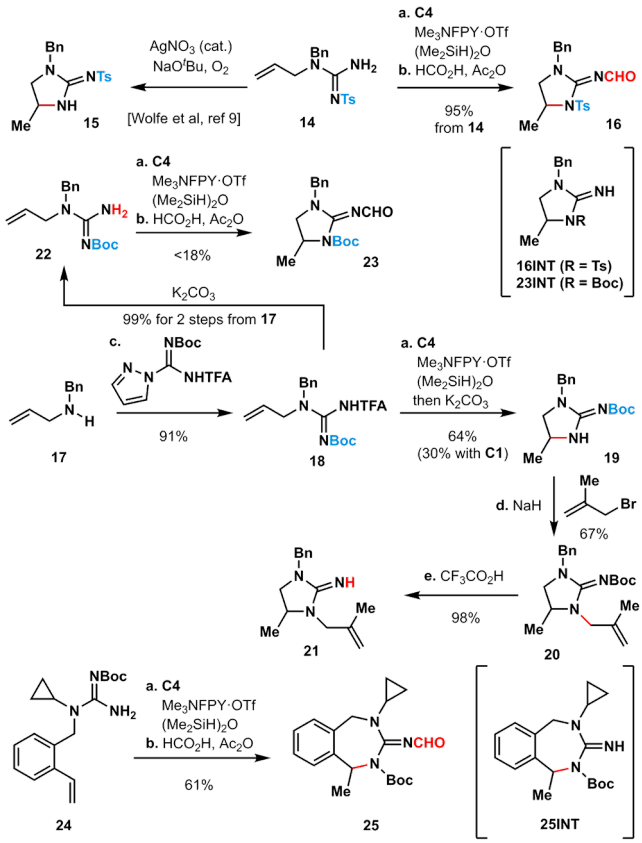


(A) Pd/C, H_2, MeOH, rt, 1 h (B) oxalyl chloride (2.0 equiv.), NEt_3 (5.0 equiv.), CH_2Cl_2 (0.03 M), rt, 12 h (C) dimethylmalonyl dichloride (2.0 equiv.), NEt_3 (5.0 equiv.), CH_2Cl_2 (0.03 M), rt, 12 h (D) 1,2-benzenedisulfonyl dichloride (2.0 equiv.), NEt_3 (5.0 equiv.), CH_2Cl_2 (0.03 M), rt, 12 h

In order to demonstrate the synthetic potential of the cyclic guanidines prepared by this method, 5-membered cyclic guanidine **2a** was subjected to deprotection and diversification (Scheme 7). The conventional palladium-catalyzed hydrogenation of **2a** produced free cyclic guanidine **10** almost quantitatively, which was further transformed into bicyclic guanidines **11a** and **11b**, and tricyclic guanidine **11c** in moderate yields. We also derivatized 7-membered guanidine **2y** in the same manner to produce tricyclic guanidines **13a** and **13b** and tetracyclic **13c** in moderate yields.

For comparison, we performed cobalt catalysis with mono-Ts guanidine **14**, which had been successfully used in hydroamination reactions (Scheme 8). To our surprise, we found that the product selectivity was clearly complementary. It was reported that **15** was selectively obtained under Wolfe's conditions,[9] whereas we observed a high-polar compound (assumed as **16INT**), which could not be purified by silica gel chromatography. The formylation of this crude mixture enabled the isolation and structural determination as **16**. Thus, this result indicates that our reactive nitrogen atom of the guanidine moiety is different that of Wolfe's.

Scheme 8. Selective Cyclization of Mono-protected or Hetero-protected (TFA (trifluoroacetyl) and Boc) Alkenyl Guanidine and Further Derivatizations.



(a) **C4**, $Me_3NFPY{\cdot}OTf$, $(Me_2SiH)_2O$, CH_3Ph, rt, 20 h (b) HCO_2H, Ac_2O, NEt_3, CH_2Cl_2, rt 3 h (c) *N*-Boc-*N'*-TFA-pyrazole-1-carboxamidine, THF, rt, 3 h (d) NaH, 3-bromo-2-methylpropene, DMF, rt, 1 h (e) trifluoroacetic acid, CH_2Cl_2, rt 3 h

Toward further examination of the scope of guanidine, we prepared alkenyl guanidines **18** and **22** by Baran's method.[7h] The cyclization of Boc-TFA (trifluoroacetyl) guanidine **18**, followed by treatment with potassium carbonate (to remove remaining TFA group), selectively produced **19** in 64% yield. This yield was not improved using **C1** instead of **C4**. The alkylation of cyclic guanidine **19** and its Boc deprotection affording **21** were both amenable by conventional methods. On the other hand, the cyclization of mono-Boc guanidine **22** yielded a high-polar compound (assumed as **23INT**). This structure was clearly elucidated by the formylation to be **23**. Unfortunately, the yield of Boc-guanidine **23** was much lower than that of Ts-guanidine **16**. This cyclization/formylation sequence also afforded **25** in 61% yield, although the cyclization of the corresponding Boc-TFA guanidine resulted in a complex product mixture.

In summary, we developed a catalytic, Markovnikov-selective, scalable method for synthesizing cyclic guanidines using a TM-HAT/RPC approach. We efficiently constructed 5, 6, and 7-membered cyclic guanidines bearing common and easily removable Cbz or Boc under mild conditions. This unique and powerful method enabled the expansion of the chemical space of atypical 7-membered cyclic guanidines. Further diversifications of the products through cobalt catalysis led to various heterocycles. The investigations using alkenyl guanidines bearing the mono-Boc or Boc-TFA protective groups revealed the selective product formation and expansion of accessible cyclic guanidines by further transformations. We are currently investigating enantioselective variants using a chiral cobalt catalyst.

ASSOCIATED CONTENT

Experimental procedures and analytical data (^1H and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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