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

Toshiya Ohuchi, Hiroki Koyama, and Hiroki Shigehisa*,

Faculty of Pharmacy, Musashino University
1-1-20 Shinmachi Nishitokyo-shi, Tokyo 202-8585, Japan

KEYWORDS. Hydrogen atom transfer, radical-polar crossover, cyclic guanidine, heterocycles

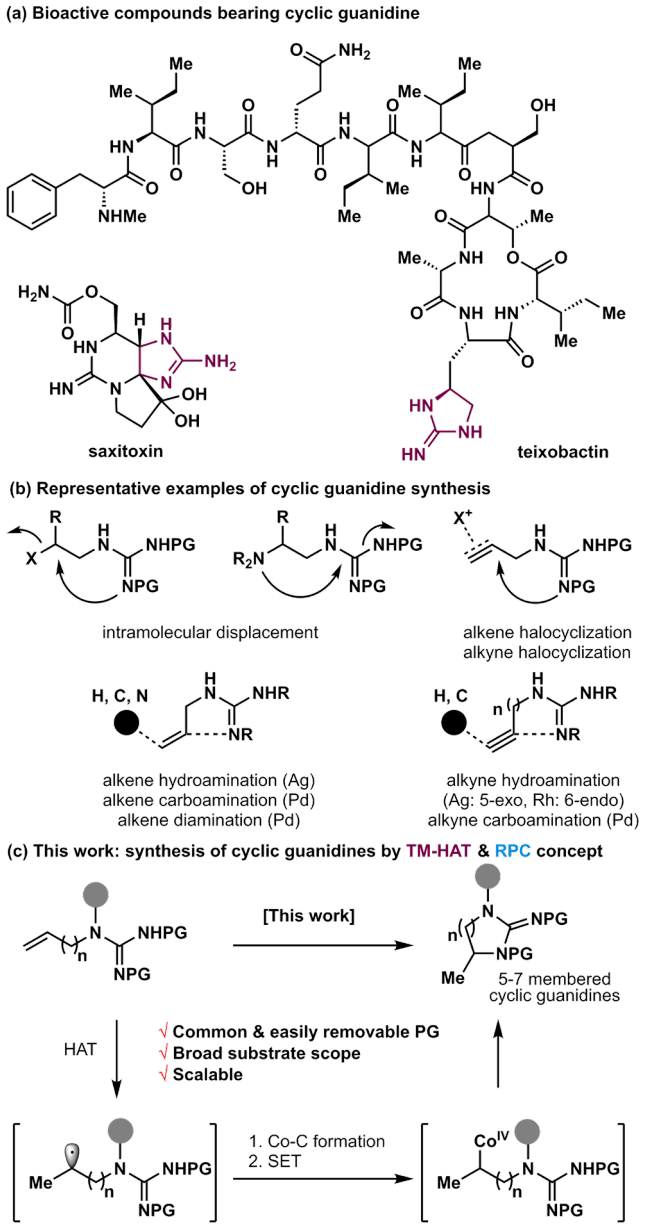
ABSTRACT: A catalytic synthesis of cyclic guanidines, which are found in many biologically active compounds and natural products, was developed, wherein transition-metal hydrogen atom transfer and radical-polar crossover were employed. This mild and functional-group tolerant process enabled the cyclization of alkenyl guanidines bearing common protective groups, such as Cbz and Boc. This powerful method not only provided the common 5- and 6-membered rings but also an unusual 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 a biologically and chemically pivotal basic motif. For instance, the amino acid arginine, contains a 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] (a blocker of voltage-gated sodium channels) and teixobactin[4] (an antibiotic for resistant bacteria) (Scheme 1). Because of the chemical and medicinal background of cyclic guanidines, the development of an useful method for their synthesis has been long-standing interest in organic synthesis.[2,5] Therefore, protocols have been developed, such as intramolecular displacement,[6] halocyclization,[7] and others.[8] Metal-catalyzed process have been 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, unusual and more challenging 7-membered rings formation has not been developed efficiently. To the best of our knowledge, Dodd and coworkers reported two examples of 7-membered ring guanidines synthesized via halocyclization, however, there is significant potential to further improve the yields (23% and 21%).[7e] Herein, we show a powerful, catalytic, Markovnikov selective, and scalable hydroamination that affords cyclic guanidines via transition-metal hydrogen atom transfer (TM-HAT) and radical-polar crossover (RPC).

Recently, TM-HAT catalytic systems have been used by many groups as a useful concept to develop various transformations of alkenes with excellent functional group tolerance.[18] We have previously reported the unique effect of *N*-fluorocollidinium salt on the TM-HAT system, which enable ionic process to occur RPC mechanism, leading to further transformations developed by us[19] and other groups.[20] Encouraged by these reports, we envisioned that an alkenyl guanidine bearing a common and easily removable protective group (carboxybenzyl (Cbz) and or *tert*-butoxycarbonyl (Boc) could be cyclized via TM-HAT and RPC approach. Employing 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 TM-HAT/RPC mechanism could efficiently form cyclic guanidines with unusual ring size.

We initially elected to examine the 5-exo cyclization of alkenyl guanidine **1a** bearing two Cbz groups and gratifyingly obtained the desired cyclic guanidine **2a** in 88% yield using the reaction conditions 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 previously developed complex **C4** provided slightly better conversion than that of **C1** (entry 5). Replacing the OTf counteranion of the 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%).

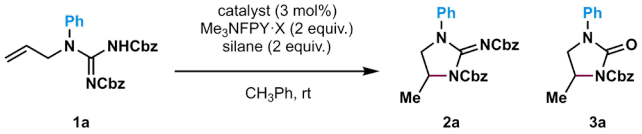
Scheme 1 (a) Representative Examples of Natural Products bearing Cyclic Guanidine, (b) Representative Methods affording Cyclic Guanidine, and (c) This Work: Synthesis of Cyclic Guanidine by TM-HAT & RPC Concept



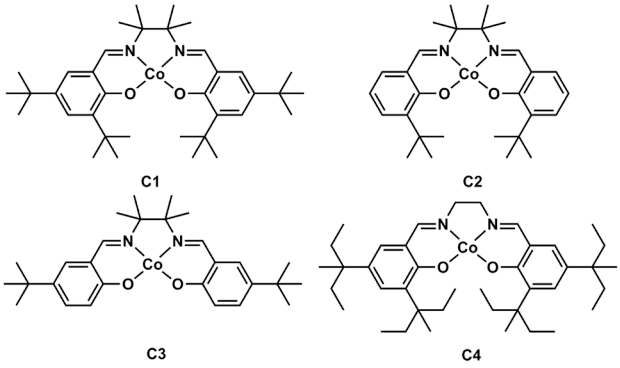
With the optimal conditions in hand, we next briefly examined the scope of substituted alkenyl guanidine forming five-membered ring products (**1b** – **1g**) (Scheme 3). The substrates bearing *p*-chloro (**1b**) or *p*-methoxy (**1c**) aniline unit gave **2b** and **2c**, respectively, in good yields.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

Encouraged by theses result, we next applied the same concept to form larger rings. To our great delight, 6-exo and 7-exo cyclizations were possible under the same reaction conditions gave **2h** and **2i**, respectively (Scheme 4). Although the yields of **2h** using **C4** and **C1** were identical, the superior efficiency of **C4** to that of **C1** was clarified when **C4** produced **2i** in a higher yield than that provided by **C1**. As 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

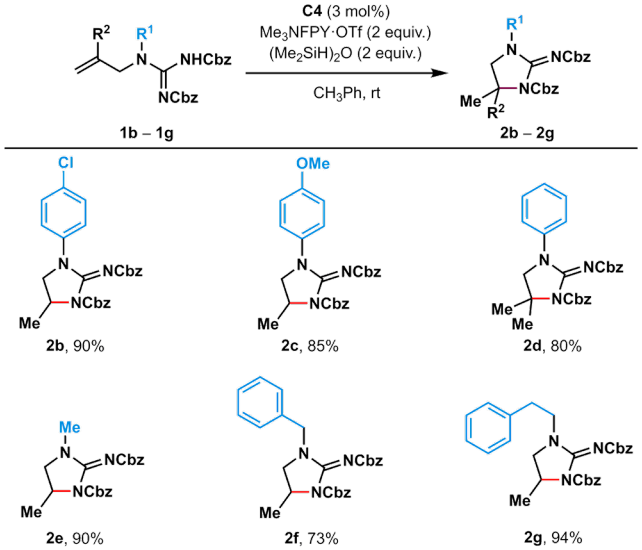


entry	cat.	X	silane	2a (%)[a]
1	C1	OTf	$(Me_2SiH)_2O$	88
2	C1	OTf	$PhSiH_3$	59 (+25% **3a**)
3	C2	OTf	$(Me_2SiH)_2O$	74
4	C3	OTf	$(Me_2SiH)_2O$	32
5	C4	OTf	$(Me_2SiH)_2O$	90, 84[b], 82[c]
6	C4	BF_4	$(Me_2SiH)_2O$	76
7	C4	PF_6	$(Me_2SiH)_2O$	83



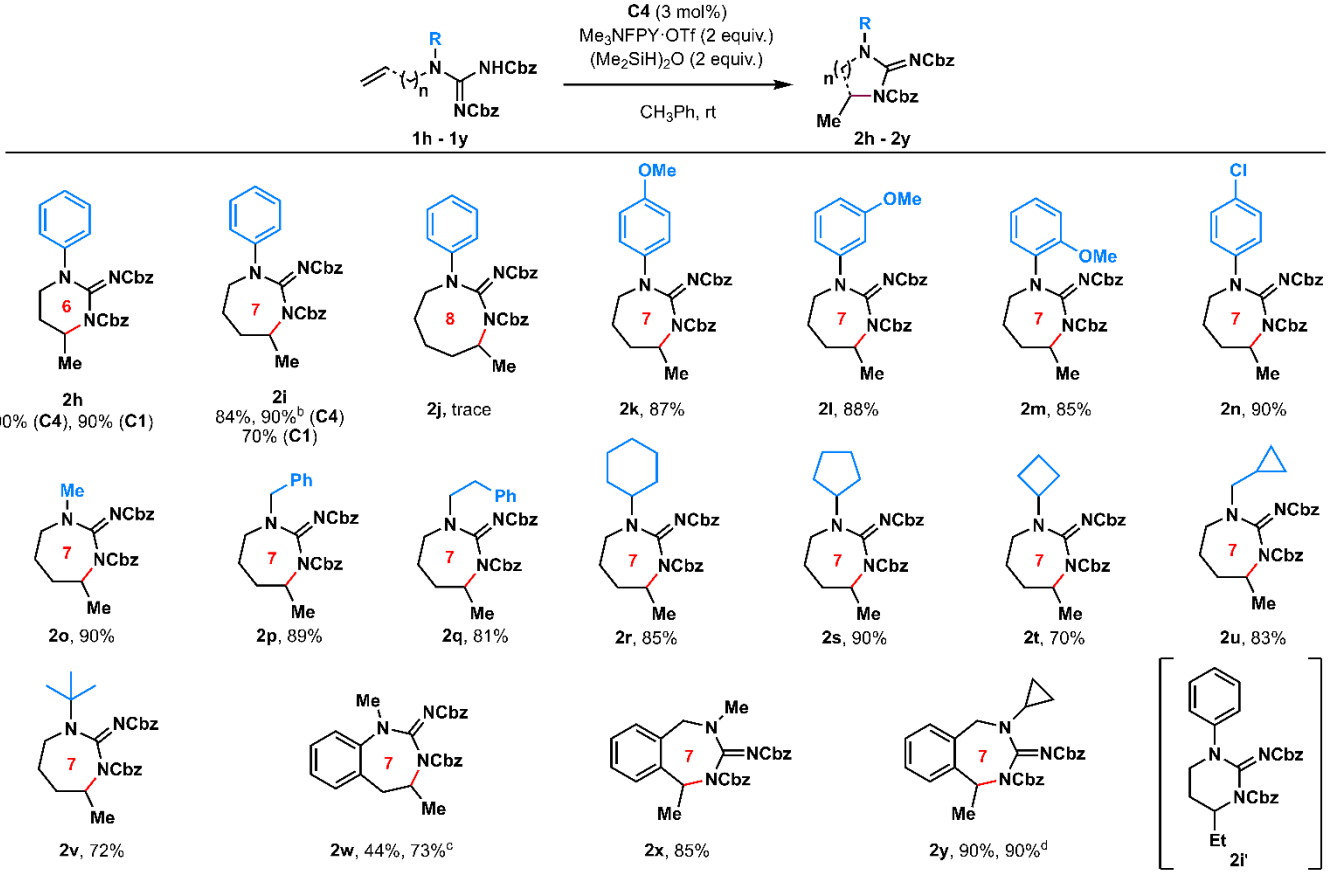
Conditions: alkenyl guanidine (0.1 mmol), catalyst (0.003 mmol), $Me_3NFPY{\cdot}X$ (0.2 mmol), silane (0.2 mmol), CH_3Ph (1.0 mL), room temperature, 20 h. [a]NMR yield using 1,4-bis(trifluoromethyl)benzene as the internal standard. [b]isolation yield [c]2.30 mmol scale

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]

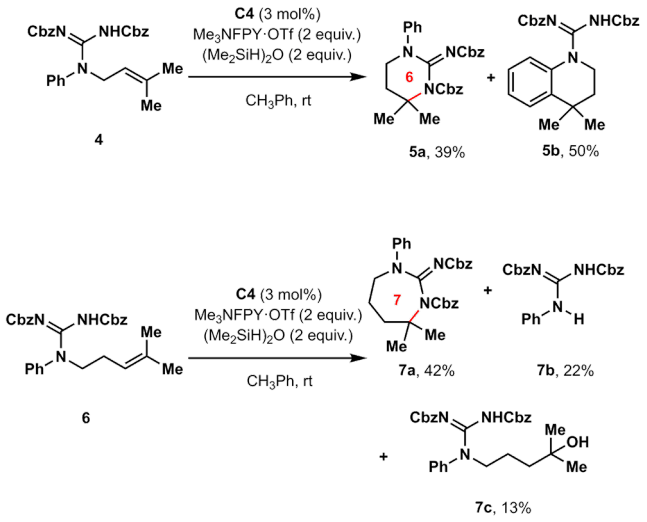


Conditions: alkenyl guanidine (0.1 mmol), **C4** (0.003 mmol), *N*-fluorocollidinium trifluoromethanesulfonate (0.2 mmol), 1,1,3,3-tetramethyldisiloxane (0.2 mmol), CH_3Ph (1.0 mL), room temperature, 20 h. [a]isolation yield [b]3.00 mmol scale [c]9 mol% of **C4** was used. [d]4.13 mmol scale

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. Replacing the aniline unit with aliphatic amines such as methylamine, benzylamine, and phenethylamine, resulted in comparable yields (**2o** – **2q**). Products bearing more hindered amine such as cyclohexylamine (**2r**), cyclopentylamine (**2s**), and *tert*-butylamine (**2v**), were prepared in good yields. Substrates bearing strained carbocycles such as cyclobutyl and cyclopropylmethyl group were also tolerated under these reaction condition and gave their respective products, **2t** and **2u**. Moreover, we could prepare benzocyclic guanidines (**2w** – **2y**) in good 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 the small amount of byproduct **2i′** (6%), which was likely produced via a 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**.

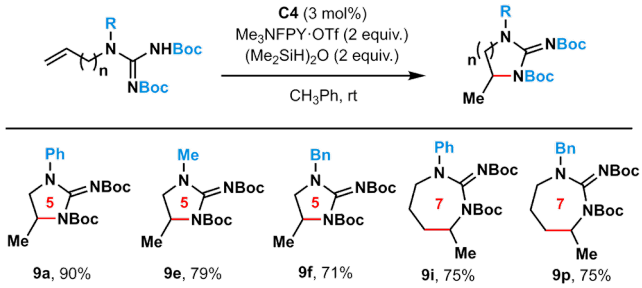
We also examined cyclizations using tri-substituted alkenyl guanidines (Scheme 5). Although the formation of 6-membered cyclic guanidine **5a** was amenable, the yield was less than moderate due to a side reaction, hydroarylation affording **5b**, which had also been observed in a previous study of ours.[19d] Additionally, 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



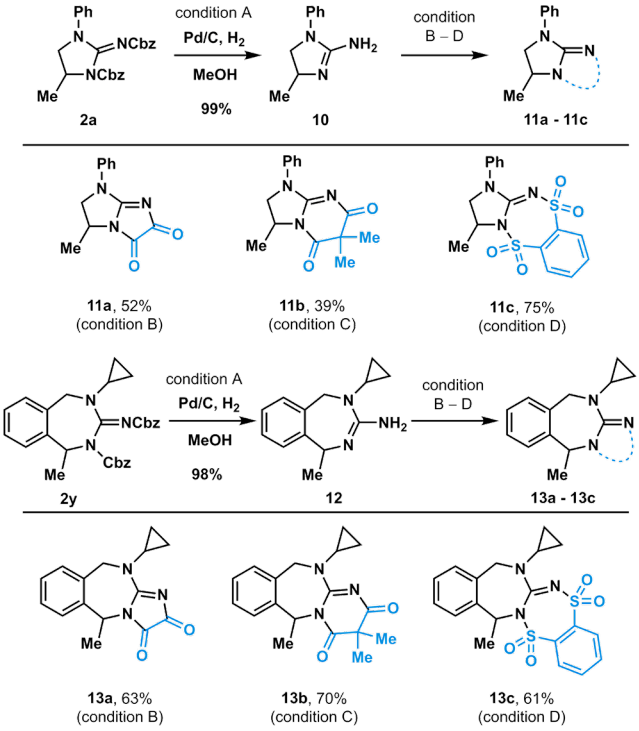
As expected, replacing the two Cbz groups of **1a** with Boc groups, another common protective group, resulted in a 90% yield of the 5-membered cyclic guanidine **9a** (Scheme 6). The products containing methylamine **9e** and benzylamine **9f** were also synthesized in good yields. It should be noted 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 an 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]

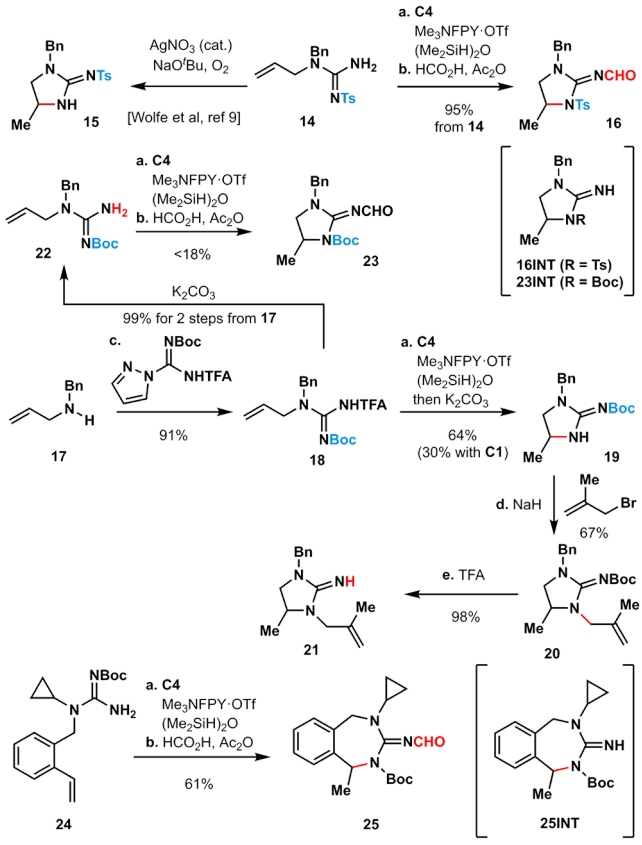


(A) Pd/C, H_2, MeOH, rt, 1 h (B) oxalyl chloride (2.0 equiv.), NEt_3 (5.0 equiv.), CH_2Cl_2 (0.03 M), rt, 12 h (C) dimethylmalonyl dichloride (2.0 equiv.), NEt_3 (5.0 equiv.), CH_2Cl_2 (0.03 M), rt, 12 h (D) 1,2-benzenedisulfonyl dichloride (2.0 equiv.), NEt_3 (5.0 equiv.), CH_2Cl_2 (0.03 M), rt, 12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

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 guanidine **11a** and **11b**, and tricyclic guanidine **11c** in moderate yields. We also derivatized 7-membered guanidine **2y** in the same way 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 highly polar compound (assumed as **16INT**), that could not be purified by silica gel chromatography. Formylation of this crude mixture enabled the isolation and structural determination to be **16**. Thus, this result indicates that the reactive nitrogen atom of the guanidine moiety used in Wolfe's conditions is different from ours.

Scheme 8. Selective Cyclization of Mono-protected or Hetero-protected (TFA 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 3h (c) *N*-Boc-*N'*-TFA-pyrazole-1-carboxamidine, THF, rt, 3h (d) NaH, 3-bromo-2-methylpropene, DMF, rt, 1h (e) TFA, CH_2Cl_2, rt 3h

Toward further examination of guanidine scope, we prepared alkenyl guanidines **18** and **22** by Baran's method.[17h] 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** gave highly polar compound (assumed as **23INT**). This structure was clearly elucidated by the formylation to be **23**. Unfortunately, the yield of Boc-guanidine **23** was significantly worse than that of Ts-guanidine **16**. This cyclization/formylation sequence also afforded **25** in 61% yield, although the cyclization of 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, 7-membered cyclic guanidines bearing common and easily removable Cbz or Boc under mild condition. At present, this is a unique and powerful method enabled to expand the chemical space of unusual 7-membered cyclic guanidines. Further diversifications of products through cobalt catalysis led to various heterocycles. Investigations and further transformations of alkenyl guanidines bearing mono-Boc or Boc-TFA protective groups revealed selective product formation and expansion of accessible cyclic guanidine 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.

AUTHOR INFORMATION

Corresponding Author

*Email: cgehisa@musashino-u.ac.jp

Funding Sources

JSPS KAKENHI Grant number 17K15426
The Takeda Science Foundation
The research foundation for pharmaceutical sciences

ACKNOWLEDGMENT

We thank Prof. Kou Hiroya (Musashino University) for our liberal research environment.

REFERENCES

(1) (a) Adina-Zada, A.; Sereeruk, C.; Jitrapakdee, S.; Zeczycki, T. N.; St Maurice, M.; Cleland, W. W.; Wallace, J. C.; Attwood, P. V., Roles of Arg427 and Arg472 in the binding and allosteric effects of acetyl CoA in pyruvate carboxylase. *Biochemistry* **2012**, *51,* 8208-8217. (b) Derbel, N.; Clarot, I.; Mourer, M.; Regnouf-de-Vains, J. B.; Ruiz-Lopez, M. F., Intramolecular interactions versus hydration effects on p-guanidinoethyl-phenol structure and pKa values. *J. Phys. Chem. A* **2012**, *116,* 9404-9411. (c) Chen, X.; Guo, Y.; Jia, G.; Zhao, H.; Liu, G.; Huang, Z., Arginine Promotes Slow Myosin Heavy Chain Expression via Akirin2 and the AMP-Activated Protein Kinase Signaling Pathway in Porcine Skeletal Muscle Satellite Cells. *J. Agric. Food Chem.* **2018**, *66,* 4734-4740. (d) Brezina, K.; Duboue-Dijon, E.; Palivec, V.; Jiracek, J.; Krizek, T.; Viola, C. M.; Ganderton, T. R.; Brzozowski, A. M.; Jungwirth, P., Can Arginine Inhibit Insulin Aggregation? A Combined Protein Crystallography, Capillary Electrophoresis, and Molecular Simulation Study. *J. Phys. Chem. B* **2018**, *122,* 10069-10076.

(2) Berlinck, R. G. S.; Bertonha, A. F.; Takaki, M.; Rodriguez, J. P. G., The chemistry and biology of guanidine natural products. *Nat. Prod. Rep.* **2017**, *34,* 1264-1301.

(3) Thottumkara, A. P.; Parsons, W. H.; Du Bois, J., Saxitoxin. *Angew. Chem. Int. Ed.* **2014**, *53,* 5760-5784.

(4) Ling, L. L.; Schneider, T.; Peoples, A. J.; Spoering, A. L.; Engels, I.; Conlon, B. P.; Mueller, A.; Schäberle, T. F.; Hughes, D. E.; Epstein, S.; Jones, M.; Lazarides, L.; Steadman, V. A.; Cohen, D. R.; Felix, C. R.; Fetterman, K. A.; Millett, W. P.; Nitti, A. G.; Zullo, A. M.; Chen, C.; Lewis, K., A new antibiotic kills pathogens without detectable resistance. *Nature* **2015**, *517,* 455-459.

(5) (a) Zhang, W.-X.; Xu, L.; Xi, Z., Recent development of synthetic preparation methods for guanidines via transition metal catalysis. *Chem. Commun.* **2015**, *51,* 254-265. (b) Lemrová, B.; Soural, M., Synthetic Strategies for Preparing Bicyclic Guanidines. *Eur. J. Org. Chem.* **2015**, *2015,* 1869-1886.

(6) (a) Kim, H.-O.; Mathew, F.; Ogbu, C., A Convenient Synthesis of Disubstituted Guanidines via the Mitsunobu Protocol. *Synlett* **1999**, *1999,* 193-194. (b) Sanière, L.; Leman, L. c.; Bourguignon, J.-J.; Dauban, P.; Dodd, R. H., Iminoiodane mediated aziridination of α-allylglycine: access to a novel rigid arginine derivative and to the natural amino acid enduracididine. *Tetrahedron* **2004**, *60,* 5889-5897. (c) Benohoud, M.; Leman, L.; Cardoso, S. H.; Retailleau, P.; Dauban, P.; Thierry, J.; Dodd, R. H., Total synthesis and absolute configuration of the natural amino acid tetrahydrolathyrine. *J. Org. Chem.* **2009**, *74,* 5331-5336. (d) O'Donovan, D. H.; Rozas, I., New methods for the preparation of aryl 2-iminoimidazolidines. *Tetrahedron Lett.* **2012**, *53,* 4532-4535. (e) Buck, M. L.; Evans, D. M.; Evans, V. A.; Herkt, D.; Sharp, H.; Hollinshead, J.; Mitschang, F.; Murphy, P. J.; Nash, R. J.; Wenbourne, J., A synthesis of tiruchanduramine and a reinvestigation of its glycosidase inhibitory activity. *Tetrahedron* **2017**, *73,* 4545-4548. (f) Imaoka, T.; Iwata, M.; Nagasawa, K., Synthesis of a Quaternary *N*,*N*′ -Aminal-Containing A-E Ring System of Palau′ amine via an Enamide-Type Overman Rearrangement Reaction. *Eur. J. Org. Chem.* **2018**, *2018,* 2572-2578.

(7) (a) Watanabe, M.; Okada, H.; Teshima, T.; Noguchi, M.; Kakehi, A., A facile and regio- and stereo-selective preparation of bicyclic guanidines by iodocyclization of 3-(alk-2-enyl)-2-(substituted amino)-1-imidazolin-4-ones. *Tetrahedron* **1996**, *52,* 2827-2838. (b) Chern, J. W.; Tao, P. L.; Wang, K. C.; Gutcait, A.; Liu, S. W.; Yen, M. H.; Chien, S. L.; Rong, J. K., Studies on quinazolines and 1,2,4-benzothiadiazine 1,1-dioxides. 8.1, 2 synthesis and pharmacological evaluation of tricyclic fused quinazolines and 1,2,4-benzothiadiazine 1,1-dioxides as potential alpha1-adrenoceptor antagonists. *J. Med. Chem.* **1998**, *41,* 3128-3141. (c) Hirota, S.; Kato, R.; Suzuki, M.; Soneta, Y.; Otani, T.; Saito, T., Synthesis of Diazaheterocyclic Ring-Fused 1,2,4-Benzothiadiazine 1,1-Dioxides by a Sequential Aza-Wittig/NH-Addition Cyclization/Nucleophilic Ring-Closure Methodology with *N*-Alkenyl-2-carbodiimidobenzenesulfonamides as Key Intermediates. *Eur. J. Org. Chem.* **2008**, *2008,* 2075-2083. (d) Al Shuhaib, Z.; Davies, D. H.; Dennis, M.; Evans, D. M.; Fletcher, M. D.; Franken, H.; Hancock, P.; Hollinshead, J.; Jones, I.; Kähm, K.; Murphy, P. J.; Nash, R.; Potter, D.; Rowles, R., Iodocyclisations reactions of Boc- and Cbz-protected *N*-allylguanidines. *Tetrahedron* **2014**, *70,* 4412-4419. (e) Daniel, M.; Blanchard, F.; Nocquet-Thibault, S.; Cariou, K.; Dodd, R. H., Halocyclization of Unsaturated Guanidines Mediated by Koser's Reagent and Lithium Halides. *J. Org. Chem.* **2015**, *80,* 10624-10633. (f) Nishikawa, T.; Sawayama, Y., Bromocyclization of Alkynyl Guanidine: A New Approach to the Synthesis of Cyclic Guanidines of Saxitoxin. *Synlett* **2011**, *2011,* 651-654. (g) Fedoseev, P.; Sharma, N.; Khunt, R.; Ermolat'ev, D. S.; Van der Eycken, E. V., Iodine-mediated regioselective guanylation-amination of propargylamines towards the synthesis of diversely substituted 2-aminoimidazoles. *RSC Adv.* **2016**, *6,* 75202-75206.

(8) (a) Huber, D.; Leclerc, G.; Ehrhardt, J. D.; Andermann, G., The 3,4-dimethoxybenzyl group: A protective group for new 2-imino-imidazolidine derivates. *Tetrahedron Lett.* **1987**, *28,* 6453-6456. (b) Shipman, M.; Nalli, S.; Clarkson, G.; Franklin, A.; Bellone, G., Iminophosphorane-Mediated Synthesis of Cyclic Guanidines: Application to the Synthesis of a Simplified NA22598A1 Analogue. *Synlett* **2008**, *2008,* 2339-2341. (c) Mailyan, A. K.; Young, K.; Chen, J. L.; Reid, B. T.; Zakarian, A., Stereoselective Synthesis of Cyclic Guanidines by Directed Diamination of Unactivated Alkenes. *Org. Lett.* **2016**, *18,* 5532-5535. (d) Rao Kovvuri, V. R.; Xue, H.; Romo, D., Generation and Reactivity of 2-Amido-1,3-diaminoallyl Cations: Cyclic Guanidine Annulations via Net (3 + 2) and (4 + 3) Cycloadditions. *Org. Lett.* **2020**, *22,* 1407-1413.

(9) Garlets, Z. J.; Silvi, M.; Wolfe, J. P., Synthesis of Cyclic Guanidines via Silver-Catalyzed Intramolecular Alkene Hydroamination Reactions of *N*-Allylguanidines. *Org. Lett.* **2016**, *18,* 2331-2334.

(10) (a) Zavesky, B. P.; Babij, N. R.; Fritz, J. A.; Wolfe, J. P., Synthesis of cyclic guanidines via Pd-catalyzed alkene carboamination. *Org. Lett.* **2013**, *15,* 5420-5423. (b) Peterson, L. J.; Luo, J.; Wolfe, J. P., Synthesis of Cyclic Guanidines Bearing *N*-Arylsulfonyl and *N*-Cyano Protecting Groups via Pd-Catalyzed Alkene Carboamination Reactions. *Org. Lett.* **2017**, *19,* 2817-2820.

(11) (a) Hövelmann, C. H.; Streuff, J.; Brelot, L.; Muñiz, K., Direct synthesis of bicyclic guanidines through unprecedented palladium(ii) catalysed diamination with copper chloride as oxidant. *Chem. Commun.* **2008**, 2334-2336. (b) Zhao, B.; Du, H.; Shi, Y., Cu(I)-Catalyzed Cycloguanidination of Olefins. *Org. Lett.* **2008**, *10,* 1087-1090. (c) Peterson, L. J.; Kirsch, J. K.; Wolfe, J. P., Pd-Catalyzed Alkene Diamination Reactions of Nitrogen Electrophiles: Synthesis of Cyclic Guanidines and Ureas Bearing Dialkylaminomethyl Groups. *Org. Lett.* **2018**, *20,* 3513-3517.

(12) (a) Gainer, M. J.; Bennett, N. R.; Takahashi, Y.; Looper, R. E., Regioselective rhodium(II)-catalyzed hydroaminations of propargylguanidines. *Angew. Chem. Int. Ed.* **2011**, *50,* 684-687. (b) Kwon, K. H.; Serrano, C. M.; Koch, M.; Barrows, L. R.; Looper, R. E., Synthesis of bicyclic guanidines via cascade hydroamination/Michael additions of mono-*N*-acryloylpropargylguanidines. *Org. Lett.* **2014**, *16,* 6048-6051.

(13) Zavesky, B. P.; Babij, N. R.; Wolfe, J. P., Synthesis of substituted 2-aminoimidazoles via Pd-catalyzed alkyne carboamination reactions. Application to the synthesis of preclathridine natural products. *Org. Lett.* **2014**, *16,* 4952-4955.

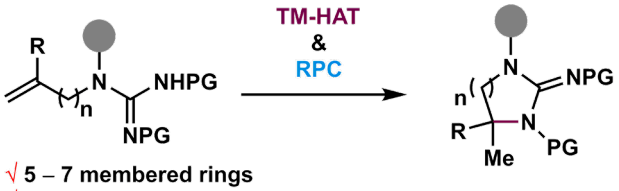
(14) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J., Expanding the substrate scope for C-H amination reactions: oxidative cyclization of urea and guanidine derivatives. *Org. Lett.* **2006**, *8,* 1073-1076.

(15) (a) Buchi, G.; Rodriguez, A. D.; Yakushijin, K., Syntheses of (+/-)-alchorneine and (+/-)-isoalchorneine. *J. Org. Chem.* **1989**, *54,* 4494-4496. (b) Butler, D. C.; Inman, G. A.; Alper, H., Room temperature ring-opening cyclization reactions of 2-vinylaziridines with isocyanates, carbodiimides, and isothiocyanates catalyzed by. *J. Org. Chem.* **2000**, *65,* 5887-5890.

(16) Kitamura, M.; Yuasa, R.; Van Vranken, D. L., Synthesis of the cyclic prenylguanidine nitensidine E using a palladium-catalyzed carbenylative amination. *Tetrahedron Lett.* **2015**, *56,* 3027-3031.

(17) (a) Mulcahy, J. V.; Du Bois, J., A stereoselective synthesis of (+)-gonyautoxin 3. *J. Am. Chem. Soc.* **2008**, *130,* 12630-12631. (b) Su, S.; Rodriguez, R. A.; Baran, P. S., Scalable, stereocontrolled total syntheses of (+/-)-axinellamines A and B. *J. Am. Chem. Soc.* **2011**, *133,* 13922-13925. (c) Perl, N. R.; Ide, N. D.; Prajapati, S.; Perfect, H. H.; Duron, S. G.; Gin, D. Y., Annulation of thioimidates and vinyl carbodiimides to prepare 2-aminopyrimidines, competent nucleophiles for intramolecular alkyne hydroamination. Synthesis of (-)-crambidine. *J. Am. Chem. Soc.* **2010**, *132,* 1802-1803. (d) Bhonde, V. R.; Looper, R. E., A stereocontrolled synthesis of (+)-saxitoxin. *J. Am. Chem. Soc.* **2011**, *133,* 20172-20174. (e) Gibbons, J. B.; Gligorich, K. M.; Welm, B. E.; Looper, R. E., Synthesis of the reported structures for kealiinines B and C. *Org. Lett.* **2012**, *14,* 4734-4737. (f) Rodriguez, R. A.; Barrios Steed, D.; Kawamata, Y.; Su, S.; Smith, P. A.; Steed, T. C.; Romesberg, F. E.; Baran, P. S., Axinellamines as broad-spectrum antibacterial agents: scalable synthesis and biology. *J. Am. Chem. Soc.* **2014**, *136,* 15403-15413. (g) Gibbons, J. B.; Salvant, J. M.; Vaden, R. M.; Kwon, K. H.; Welm, B. E.; Looper, R. E., Synthesis of Naamidine A and Selective Access to N^2-Acyl-2-aminoimidazole Analogues. *J. Org. Chem.* **2015**, *80,* 10076-10085. (h) Tian, M.; Yan, M.; Baran, P. S., 11-Step Total

Synthesis of Araiosamines. *J. Am. Chem. Soc.* **2016**, *138,* 14234-14237.
(18) (a) Halpern, J., Free radical mechanisms in organometallic and bioorganometallic chemistry. *Pure Appl. Chem.* **1986**, *58,* 575-584. (b) Isayama, S.; Mukaiyama, T., A New Method for Preparation of Alcohols from Olefins with Molecular Oxygen and Phenylsilane by the Use of Bis(acetylacetonato)cobalt(II). *Chem. Lett.* **1989**, *18,* 1071-1074. (c) Eisenberg, D. C.; Norton, J. R., Hydrogen-Atom Transfer Reactions of Transition-Metal Hydrides. *Isr. J. Chem.* **1991**, *31,* 55-66. (d) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M., Hydrazines and Azides via the Metal-catalyzed Hydrohydrazination and Hydroazidation of Olefins. *J. Am. Chem. Soc.* **2006**, *128,* 11693-11712. (e) Choi, J.; Tang, L.; Norton, J. R., Kinetics of hydrogen atom transfer from (η^5-C_5H_5)Cr(CO)$_3$H to various olefins: influence of olefin structure. *J. Am. Chem. Soc.* **2007**, *129,* 234-240. (f) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L., Total Synthesis of Vinblastine, Vincristine, Related Natural Products, and Key Structural Analogues. *J. Am. Chem. Soc.* **2009**, *131,* 4904-4916. (g) King, S. M.; Ma, X.; Herzon, S. B., A Method for the Selective Hydrogenation of Alkenyl Halides to Alkyl Halides. *J. Am. Chem. Soc.* **2014**, *136,* 6884-6887. (h) Kuo, J. L.; Hartung, J.; Han, A.; Norton, J. R., Direct Generation of Oxygen-Stabilized Radicals by H• Transfer from Transition Metal Hydrides. *J. Am. Chem. Soc.* **2015**, *137,* 1036-1039. (i) Crossley, S. W.; Obradors, C.; Martinez, R. M.; Shenvi, R. A., Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116,* 8912-9000. (j) Obradors, C.; Martinez, R. M.; Shenvi, R. A., Ph(*i*-PrO)SiH$_2$: An Exceptional Reductant for Metal-Catalyzed Hydrogen Atom Transfers. *J. Am. Chem. Soc.* **2016**, *138,* 4962-4971. (k) Lo, J. C.; Kim, D.; Pan, C. M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutierrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P. L.; Baran, P. S., Fe-Catalyzed C-C Bond Construction from Olefins via Radicals. *J. Am. Chem. Soc.* **2017**, *139,* 2484-2503. (l) Green, S. A.; Crossley, S. W. M.; Matos, J. L. M.; Vásquez-Céspedes, S.; Shevick, S. L.; Shenvi, R. A., The High Chemofidelity of Metal-Catalyzed Hydrogen Atom Transfer. *Acc. Chem. Res.* **2018**, *51,* 2628-2640. (m) Shevick, S. L.; Obradors, C.; Shenvi, R. A., Mechanistic Interrogation of Co/Ni-Dual Catalyzed Hydroarylation. *J. Am. Chem. Soc.* **2018**, *140,* 12056-12068. (n) Wang, Y. Y.; Bode, J. W., Olefin Amine (OLA) Reagents for the Synthesis of Bridged Bicyclic and Spirocyclic Saturated *N*-Heterocycles by Catalytic Hydrogen Atom Transfer (HAT) Reactions. *J. Am. Chem. Soc.* **2019**, *141,* 9739-9745. (o) Zhou, X. L.; Yang, F.; Sun, H. L.; Yin, Y. N.; Ye, W. T.; Zhu, R., Cobalt-Catalyzed Intermolecular Hydrofunctionalization of Alkenes: Evidence for a Bimetallic Pathway. *J. Am. Chem. Soc.* **2019**, *141,* 7250-7255. (p) Shevick, S. L.; Wilson, C. V.; Kotesova, S.; Kim, D.; Holland, P. L.; Shenvi, R. A., Catalytic hydrogen atom transfer to alkenes: a roadmap for metal hydrides and radicals. *Chem. Sci.* **2020**. (q) Yao, C.; Wang, S.; Norton, J.; Hammond, M., Catalyzing the Hydrodefluorination of CF_3-Substituted Alkenes by $PhSiH_3$. H• Transfer from a Nickel Hydride. *J. Am. Chem. Soc.* **2020**, *142,* 4793-4799. (r) Wu, B.; Zhu, R., Radical Philicity Inversion in Co- and Fe-Catalyzed Hydrogen-Atom-Transfer-Initiated Cyclizations of Unsaturated Acylsilanes. *ACS Catal.* **2020**, *10,* 510-515. (s) Kattamuri, P. V.; West, J. G., Hydrogenation of Alkenes via Cooperative Hydrogen Atom Transfer. *J. Am. Chem. Soc.* **2020**, *142,* 19316-19326.
(19) (a) Shigehisa, H.; Aoki, T.; Yamaguchi, S.; Shimizu, N.; Hiroya, K., Hydroalkoxylation of Unactivated Olefins with Carbon Radicals and Carbocation Species as Key Intermediates. *J. Am. Chem. Soc.* **2013**, *135,* 10306-10309. (b) Shigehisa, H.; Koseki, N.; Shimizu, N.; Fujisawa, M.; Niitsu, M.; Hiroya, K., Catalytic Hydroamination of Unactivated Olefins Using a Co Catalyst for Complex Molecule Synthesis. *J. Am. Chem. Soc.* **2014**, *136,* 13534-13537. (c) Shigehisa, H., Functional Group Tolerant Markovnikov-Selective Hydrofunctionalization of Unactivated Olefins Using a Cobalt Complex as Catalyst. *Synlett* **2015**, *26,* 2479-2484. (d) Shigehisa, H.; Ano, T.; Honma, H.; Ebisawa, K.; Hiroya, K., Co-Catalyzed Hydroarylation of Unactivated Olefins. *Org. Lett.* **2016**, *18,* 3622-3625. (e) Shigehisa, H.; Hayashi, M.; Ohkawa, H.; Suzuki, T.; Okayasu, H.; Mukai, M.; Yamazaki, A.; Kawai, R.; Kikuchi, H.; Satoh, Y.; Fukuyama, A.; Hiroya, K., Catalytic Synthesis of Saturated Oxygen Heterocycles by Hydrofunctionalization of Unactivated Olefins: Unprotected and Protected Strategies. *J. Am. Chem. Soc.* **2016**, *138,* 10597-10604. (f) Date, S.; Hamasaki, K.; Sunagawa, K.; Koyama, H.; Sebe, C.; Hiroya, K.; Shigehisa, H., Catalytic Direct Cyclization of Alkenyl Thioester. *ACS Catal.* **2020**, *10,* 2039-2045. (g) Ebisawa, K.; Izumi, K.; Ooka, Y.; Kato, H.; Kanazawa, S.; Komatsu, S.; Nishi, E.; Shigehisa, H., Catalyst- and Silane-Controlled Enantioselective Hydrofunctionalization of Alkenes by Cobalt-Catalyzed Hydrogen Atom Transfer and Radical-Polar Crossover. *J. Am. Chem. Soc.* **2020**, *142,* 13481-13490. (h) Nagai, T.; Mimata, N.; Terada, Y.; Sebe, C.; Shigehisa, H., Catalytic Dealkylative Synthesis of Cyclic Carbamates and Ureas via Hydrogen Atom Transfer and Radical-Polar Crossover. *Org. Lett.* **2020**, *22,* 5522-5527.
(20) (a) Touney, E. E.; Foy, N. J.; Pronin, S. V., Catalytic Radical-Polar Crossover Reactions of Allylic Alcohols. *J. Am. Chem. Soc.* **2018**, *140,* 16982-16987. (b) Discolo, C. A.; Touney, E. E.; Pronin, S. V., Catalytic Asymmetric Radical–Polar Crossover Hydroalkoxylation. *J. Am. Chem. Soc.* **2019**, 17527-17532. (c) Huang, G.; Ke, M.; Tao, Y.; Chen, F., Specific *Z*-Selectivity in the Oxidative Isomerization of Allyl Ethers to Generate Geometrically Defined *Z*-Enol Ethers Using a Cobalt(II)(salen) Complex Catalyst. *J. Org. Chem.* **2020**, *85,* 5321-5329. (d) Vrubliauskas, D.; Vanderwal, C. D., Cobalt-Catalyzed Hydrogen-Atom Transfer Induces Bicyclizations that Tolerate Electron-Rich and Electron-Deficient Intermediate Alkenes. *Angew. Chem. Int. Ed.* **2020**, *59,* 6115-6121. (e) Yahata, K.; Kaneko, Y.; Akai, S., Cobalt-Catalyzed Intermolecular Markovnikov Hydroamination of Nonactivated Olefins: N_2-Selective Alkylation of Benzotriazole. *Org. Lett.* **2020**, *22,* 598-603.



√ 5 – 7 membered rings
√ Common PG (Cbz & Boc)
√ Broad substrate scope
√ Scalable

cyclic guanidines
[31 examples]