Rhodium Catalysis

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Regioselective Rhodium(II)-Catalyzed Hydroaminations of Propargylguanidines**

*Morgan J. Gainer, Nitasha R. Bennett, Yu Takahashi, and Ryan E. Looper**

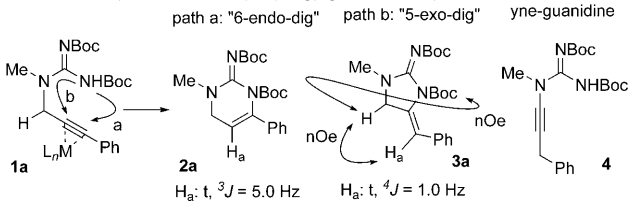
Cyclic and polycyclic guanidinium ion natural products have been shown to modulate a variety of important biological processes and their activities are often reliant on the unique hydrogen bond donor–acceptor topologies that these substructures display.[1] While most synthetic methods to prepare guanidines rely on the addition of an amine (guanylation) of an activated thiourea or urea,[2] alternative methodologies that generates peripheral C–N bonds from an intact guanidine nucleus have proven powerful for the preparation of polycyclic guanidine natural products.[3a–e]

Our interest in the biological activity of guanidine natural products has prompted us to develop a synthetic platform that is capable of delivering cyclic guanidines having multiple ring sizes, substitution patterns, and oxidation states in short order. To this end we have been interested in the addition of guanidine N–H bonds across C–C π systems and recently reported a La^{III}-catalyzed tandem addition–hydroamination reaction of propargylcyanamides which required forcing conditions, and resulted in exclusive 5-*exo*-dig cyclization.[4] This led us to study the hydroamination of preformed di-Boc protected propargylguanidines of the type **1**, in hopes of finding a 6-*endo*-dig selective process. Traditionally, metal-catalyzed cyclizations on alkynes favor a 5-*exo*-dig pathway. This can be seen in Au^{I}- and Au^{III}-catalyzed cyclization of propargylcarbamates, propargylureas, and propargylamides,[5,6] as well as the Ti^{IV}–amide hydroamination reactions of homopropargylamines.[7,8] Examples of cyclization of heteroatom nucleophiles onto alkynes leading to 6-*endo*-dig cyclization, although as synthetically significant as the 5-*exo*-dig products, are nevertheless much less common and usually observed with substrates in which the tether is largely sp^2 hybridized.[9,10]

During the preparation of this manuscript, Gin and coworkers described the $AuCl_3$-catalyzed hydroamination of alkynes with 2-aminopyrimidines in the synthesis of crambedine.[11] Their gold-catalyzed 6-*exo*-dig cyclization highlights the power of this approach in total synthesis. Achieving selectivity in these hydroaminations, particularly 5-*exo*-dig vs. 6-*endo*-dig, would present a valuable tool for the synthesis of complex guanidine-containing natural products. Here, we describe the discovery of an unusual reactivity of dirhodium(II) carboxylates as highly 6-*endo*-dig selective hydroamination catalysts in the cyclization of propargylguanidines, while Ag^{I} is typically 5-*exo*-dig selective.

We first examined the ability of traditional π-Lewis acids to catalyze the hydroamination of **1a** (Table 1). Initial

Table 1: Catalyst screen for propargylguanidine hydroamination.



Entry	Catalyst[a]	Solvent	*t* [h]	Selectivity[b] **2**:**3**:**4**	Yield [%][c]
1	$(CuOTf)_2{\cdot}Ph$	CH_2Cl_2	48	1:4.6:1	31
2	$Pd(OAc)_2$	CH_2Cl_2	12	1:4:0	55
3	AgOTf	CH_2Cl_2	3	1:16:0	52
4	AgOAc	CH_2Cl_2	5	1:>20:0	55
5[d]	AgOAc	CH_2Cl_2	2	1:>20:0	90
6	$NaAuCl_4$	CH_2Cl_2	168	4:1:0	21
7	$AuCl_3$	CH_2Cl_2	60	3:1:0	n.d.
8	$[Rh_2(tfa)_4]$	CH_2Cl_2	60	6:1:0	n.d.
9	$[Rh_2(OAc)_4]$	CH_2Cl_2	60	13:1:0	47
10	$[Rh_2(oct)_4]$	CH_2Cl_2	16	>20:1:0	81

[a] All catalysts were screened at 10 mol% loading. OTf = trifluoromethanesulfonate, OAc = acetate, tfa = trifluoroacetate, oct = octanoate, AcOH = acetic acid. [b] Product selectivities determined by ^{1}H NMR spectroscopy; >20:1 indicates a single regioisomer. [c] Yields of isolated product. [d] 3 equiv of AcOH were used as additive.

experiments highlighted that there were multiple reaction pathways available (Table 1, entry 1). Cyclization of **1a** in the presence of Cu^{I} salts reliably gave a mixture of 6-*endo*-dig and 5-*exo*-dig products (**2a** and **3a**, respectively) that are easily identified by the magnitude of either ^3J or ^4J coupling. From nOe experiments it was also confirmed that the 5-*exo* product **3a** carried the *Z*-alkene configuration. The unanticipated product was the yne-guanidine **4**, which may arise from a [1,3]-prototropic shift followed by isomerization as detailed by Gevorgyan et al. for propargyl acetates.[12]

Ag^{I} catalysis proved to be optimal for the generation of **3a** with AgOAc giving a 1:>20 ratio of **2a**:**3a** in 55% yield (Table 1, entry 4). It was further found that addition of AcOH

[*] M. J. Gainer, N. R. Bennett, Y. Takahashi, Prof. Dr. R. E. Looper
Department of Chemistry, University of Utah
315 South 1400 East, Salt Lake City, UT 84112 (USA)
Fax: (+1) 801-581-8433
E-mail: r.looper@utah.edu

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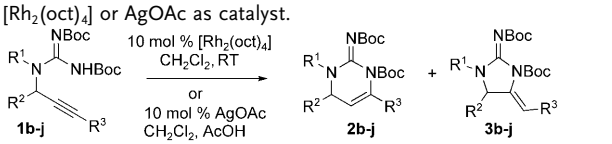
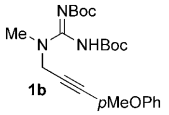
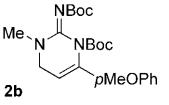
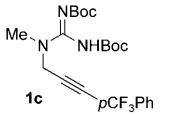
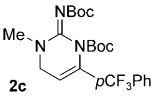
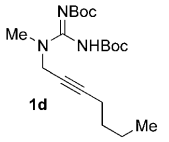
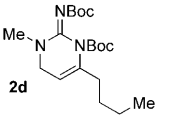
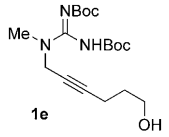
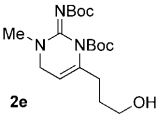
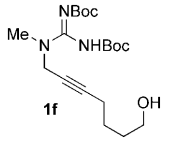
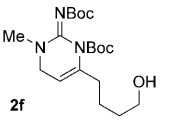
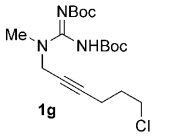
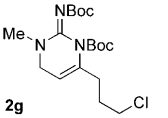
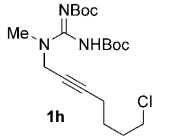
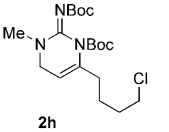
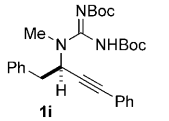
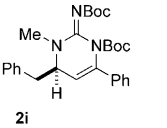
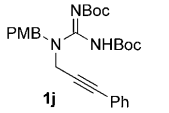
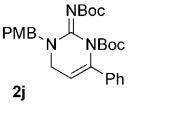
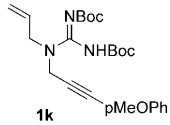
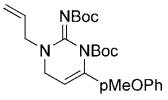
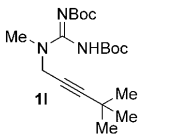
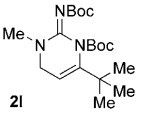
to the AgOAc-catalyzed reaction gave significant rate enhancements (Table 1, entry 5) suggesting that protonolysis of the vinyl metal species was rate limiting, consistent with the known electrophilic hydroamination mechanism.[13] Our first success in reversing the selectivity was found with gold(III) catalysts that favored the 6-*endo* product (Table 1, entries 6 and 7). The sluggishness of the Au-catalyzed reactions directed our attention to Rh^{II}. Dirhodium(II) carboxylates have rarely been used to activate alkynes,[14] however Murai et al. have shown that $[Rh_2(tfa)_4]$ is a competent ene–ene–yne cycloisomerization catalyst and gives different product distributions than Pt^{II} or Ru^{II}.[15] Gratifyingly, $[Rh_2(tfa)_4]$ turned the selectivity over favoring the 6-*endo* product (Table 1, entry 8). Quite to our surprise, given its decreased Lewis acidity, $[Rh_2(OAc)_4]$ was a very selective catalyst favoring the 6-*endo* product 13:1 (Table 1, entry 9). The reaction times were long and we suspected that this was due to catalyst solubility. The reaction was enhanced with $[Rh_2(oct)_4]$ giving the 6-*endo* product in 81% yield after 16 h in >20:1 (**2a:3a**) selectivity (Table 1, entry 10).

Having identified a selective catalyst set, a substrate selectivity profile was developed for the reaction (Table 2) and it was immediately apparent that the reactivity of the dirhodium(II) carboxylates was quite unique. For example, cyclization of the *p*-methoxyphenyl alkyne (Table 2, entry 1) with Ag^I favored the 5-*exo* product, however with poor selectivity, consistent with the ability of this substituent to competitively stabilize a vinyl cation for 6-*endo* cyclization. In contrast, Rh^{II} gave exclusively the 6-*endo* product **2b**. Cyclization of electron-poor aryl alkynes showed the opposite trend, with Ag^I giving high 5-*exo* selectivity while Rh^{II} was more modestly selective for the 6-*endo* product **2c** (Table 2, entry 2). Alkyl-substituted alkynes gave the 6-*endo* products exclusively with Rh^{II} (Table 2, entries 3–7). This is in direct contrast to the Ag^I-catalyzed reactions, where modest selectivities for the 5-*exo* products are seen when the alkyne termini are electronically indistinguishable. Importantly for subsequent annulations and access to polycyclic skeletons, $[Rh_2(oct)_4]$ tolerates useful functional groups (e.g. alcohols and alkyl chlorides, Table 2, entries 4–7). These primary alkyl chlorides were also cleanly cyclized to the 5-*exo*-dig isomers **2g,h** with Ag^I. Substitution is also permitted at the propargylic position wherein good selectivities are seen with Ag^I for the 5-*exo* product and with Rh^{II} for the 6-*endo* product (Table 2, entry 8). Substituents on the guanidine nitrogen had modest effects on selectivity, with the 6-*endo* product always favored under Rh^{II} catalysis (Table 2, entries 9,10). The *tert*-butyl alkyne **1l** (Table 2, entry 11) reacted well in the Ag^I-catalyzed process but was unreactive toward Rh^{II}, presumably due to the size of the Rh^{II} catalyst.

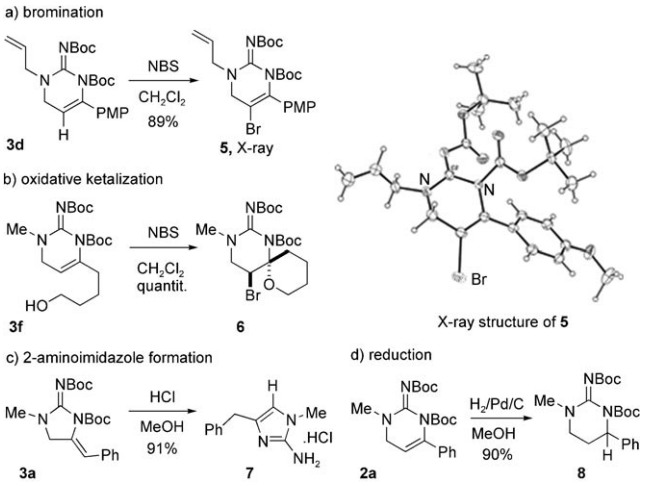
The resultant cyclic ene-guanidines contain a rich functional group handle for further manipulations (Scheme 1). For example bromination proceeds to give the 5-bromodihydropyrimidine **5** the structure of which was further confirmed by X-ray crystallography (Scheme 1 a). Oxidative cyclization of pendant nucleophiles gives the spirocyclic hemiaminal **6**, reminiscent of the crambescidins Scheme 1 b. Deprotection of the 5-membered ene-guanidine **3a** under acidic conditions was accompanied by isomerization to give the 2-amino-

Table 2: Substrate scope for the hydroamination of propargylguanidines with $[Rh_2(oct)_4]$ or AgOAc as catalyst.



Entry	Substrate	Catalyst	Yield [%][a]	Select. 2:3	6-endo product 2
1		$[Rh_2(oct)_4]$ AgOAc	92 65	>20:1 1:2	
2		$[Rh_2(oct)_4]$ AgOAc	60 80	5:1 1:>20	
3		$[Rh_2(oct)_4]$ AgOAc	95 90	>20:1 1:2	
4		$[Rh_2(oct)_4]$ AgOAc	95[b] 65	>20:1 1:2	
5		$[Rh_2(oct)_4]$ AgOAc	95 60	>20:1 1:3	
6		$[Rh_2(oct)_4]$ AgOAc	98 55	>20:1 1:5	
7		$[Rh_2(oct)_4]$ AgOAc	80 63	>20:1 1:7	
8		$[Rh_2(oct)_4]$ AgOAc	41 95	12:1 1:>20	
9[c]		$[Rh_2(oct)_4]$ AgOAc	68 71	7:1 1:>20	
10		$[Rh_2(oct)_4]$ AgOAc	68 71	11:1 1:2	
11		$[Rh_2(oct)_4]$ AgOAc	n.d. 70	– 1:11	

[a] Yields of isolated product. [b] Products were inseparable by chromatography; combined yield. [c] PMB = *p*-methoxybenzyl.

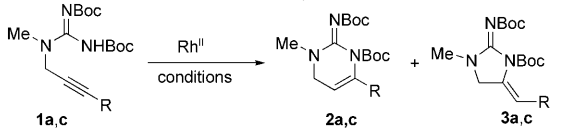


Scheme 1. Transformations of the resultant ene-guanidines. PMP = *p*-methoxyphenyl, NBS = *N*-bromosuccinimide.

imidazole **7** (Scheme 1 c).[16] Reduction was also cleanly performed on **2a** to give tetrahydropyrimidine **8** (Scheme 1 d).

Examples of alkyne activation by dirhodium(II) carboxylates are quite rare.[8,17] Given the fact that reactions of internal alkynes have only been observed with $[Rh_2(tfa)_4]$,[18] and that $[Rh_2(oct)_4]$ is not able to activate alkynes independently,[8] we were surprised that the dirhodium(II) alkylcarboxylates were competent catalysts for this transformation especially at room temperature.[19] This was especially true for the cyclization of electron-deficient alkynes such as the *p*CF_3Ph-substituted alkyne **1c**. We were even more surprised by the observation that **1c** reacted ten times faster than the *p*-methoxy-substituted alkyne **1b**. Regardless of the poor π-Lewis acidity of these catalysts, this suggested that coordination of the alkyne was not rate limiting. Addition of 3 equivalents of acetic acid changed the selectivity from 5:1 to 1:1.7 (**2c:3c**, Table 3, entries 1 and 2) suggesting that protonation of a vinyl–rhodium intermediate might be involved in the product-determining step. The use of $[Rh_2(tfa)_4]$ as a catalyst also favored the 5-*exo*-dig product with **1c** (Table 3, entry 3). Taken together this may suggest a Curtin–Hammett scenario wherein the initial cyclization to form a 5- or 6-membered vinyl–rhodium anion is highly reversible and that perturbation of this pre-equilibrium by stabilizing the kinetically favored 5-*exo*-dig intermediate leads to poor selectivity.[20]

Table 3: Condition effects on selectivity.



Entry	R	Catalyst	Conditions	Selectivity **2**:**3**
1	*p*CF_3Ph	$[Rh_2(oct)_4]$	CH_2Cl_2, 0.05 M, 23 °C	5:1
2	*p*CF_3Ph	$[Rh_2(oct)_4]$	CH_2Cl_2, 0.05 M, 23 °C, AcOH[a]	1:1.7
3	*p*CF_3Ph	$[Rh_2(tfa)_4]$	CH_2Cl_2, 0.05 M, 23 °C	1:5
4	Ph	$[(Ph_3P)_3RhCl]$	CH_2Cl_2, 60 °C, 12 h	10:1
5	Ph	$[(Ph_3P)_3RhCl]$	$AgSbF_6$, CH_2Cl_2, RT, 12 h	1:10

[a] 3 equivalents of AcOH were used.

Mechanistically it is difficult to rationalize oxidation state changes in the dirhodium(II) carboxylates upon arriving at a vinyl–rhodium intermediate (in this case the formation of Rh^I in the dimer). This prompted us to examine better defined catalysts known to proceed through vinyl–rhodium intermediate.[21] Although sluggish, Wilkinson's catalyst promoted the cyclization and favored the 6-*endo* product in 10:1 selectivity (Table 3, entry 4). Cationic Rh^I, however, reversed the selectivity favoring the 5-*exo* product in 10:1 selectivity (Table 3, entry 5). Again this may support the necessity for the initial cyclization event to be reversible in order to access the 6-*endo* product. More importantly this suggests access to more defined vinyl–rhodium intermediates that might be exploited for cascade reactivity.

In conclusion we have demonstrated the unique ability of dirhodium(II) carboxylates to catalyze the 6-*endo*-dig selective hydroamination of propargylguanidines. The resultant cyclic ene-guanidines contain a rich latent functional group for the preparation of skeletally diverse cyclic guanidine natural product substructures. Studies to further understand the reactivity of dirhodium(II) carboxylates and the application of these products to more complex targets are ongoing and will be reported in due course.

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Keywords: alkyne activation · guanidine · heterocycles · hydroamination · rhodium

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