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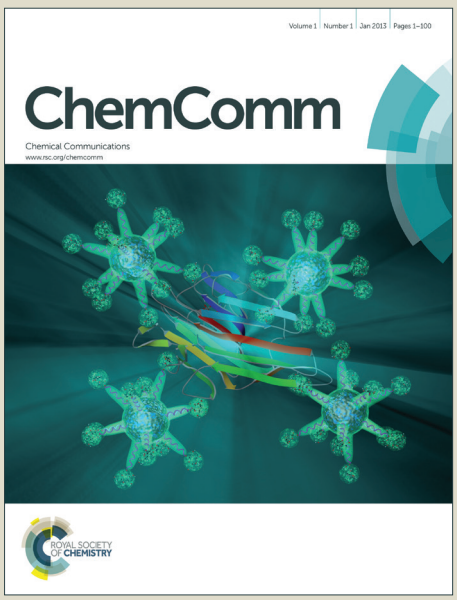

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Rh(III)-Catalyzed [5+1] Oxidative Cycloaddition of Arylguanidines with Alkynes: A Novel Access to C4-Disubstituted 1,4-Dihydroquinazolin-2-amines

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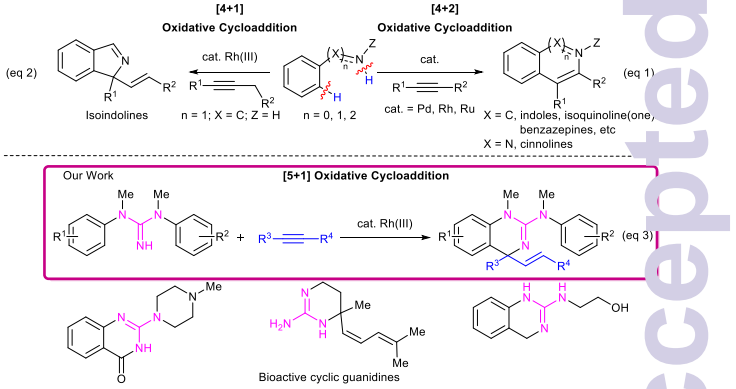
The novel and mild Rh^{III}-catalyzed [5+1] oxidative cycloaddition between arylguanidines and alkynes efficiently affords C4-disubstituted 1,4-dihydroquinazolin-2-amines. Members of this family of heterocycles, which contain the relevant cyclic guanidine units, have shown interesting pharmacological properties. The mechanism probably involves the formation of an eight-membered rhodacycle in which the imine unit of the guanidine is coordinated to the Rh center. This rhodacycle would evolve to give the C-4 disubstituted 1,4-dihydroquinazolin-2-amine skeleton.

Benzofused nitrogenated heterocycles are privileged structural units that are found in many natural products and pharmaceuticals with important physiological and biological activities.[1] In the last few decades, the most common synthetic methods for the preparation of these compounds have relied on transition metal-catalyzed processes.[2] In this regard, directed C–H activation towards the formation of C–C and C–N bonds has received the most attention owing to its sustainable and environmentally benign features.[3] For dehydrogenative N–H/C–H coupling processes, besides oxidative annulations[4] (intramolecular processes with the formation of C–N bonds), typical [n+2] oxidative cycloadditions[5] of monofunctionalized substrates (n atoms = 3, 4, 5) with unsaturated two-carbon partners, *e.g.* alkynes, provide an easy entry to a wide variety of azaheterocycles such as indoles ([3+2]), isoquinolines and isoquinolones ([4+2]), benzazepines ([5+2]) (Scheme 1, eq 1). Similar metal-catalyzed C–H activation strategies have also proven reliable for the formation of the corresponding benzofused dinitrogenated heterocycles bearing N–N bonds.[6] Alkynes can also participate in more unusual [n+1] oxidative cycloadditions. Thus, isoindolines were obtained by Rh-catalyzed [4+1] oxidative cycloaddition of primary benzylamines with internal aliphatic alkynes (Scheme 1, eq 2).[7]

On the other hand, [4+1] and [5+1] oxidative cycloadditions of oxygenated substrates with allenes[8] and enynes[9] have been recently described.



Scheme 1 Azaheterocycles by Metal-Catalyzed Oxidative Cycloadditions.

However, to our knowledge, [5+1] oxidative cycloadditions of di(tri)nitrogenated substrates with alkynes are unknown. Herein, we report the novel Rh(III)-catalyzed [5+1] oxidative cycloaddition of arylguanidines with alkynes to give C-4 disubstituted 1,4-dihydroquinazolin-2-amines containing the guanidine moiety, interesting structural motif present in many bioactive compounds (Scheme 1, eq 3).[10]

We began our investigation by examining the reaction between *N*,*N*′-dimethyl-*N*,*N*′-diphenylguanidine **1a**[11] and 1-hexyne **2a** under our previously reported conditions:[12] *t*-AmOH at 60 °C under argon, using $[Cp^*RhCl_2]_2$ (2.5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv) as the oxidant (Table 1). Only traces of the six-membered 1,4-dihydroquinazolin-2-amine **3a** were observed by GCMS (entry 1). Pleasingly, replacement of the oxidant $Cu(OAc)_2{\cdot}H_2O$ by AgOAc gave **3a** in 73% yield on using an air atmosphere (entry 2). This new oxidative cycloaddition strongly depends on the choice of solvent.[13] To our delight, the use of protic solvents such as *i*-PrOH was beneficial to the reaction and gave **3a** in an excellent 91% yield (entry 3). Control experiments showed that both $[Cp^*RhCl_2]_2$ and AgOAc were necessary as the reaction failed in their absence (entries 4 and 5). The third row catalyst $[Cp^*IrCl_2]_2$ or other oxidants

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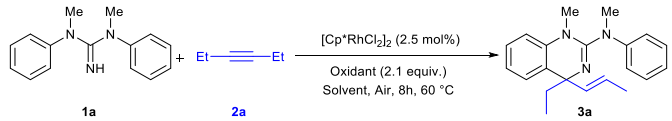
like O_2, AgOPiv and $AgOCOCF_3$ gave low-to-moderate yields of **3a** (entries 6-9).[13] Interestingly, both the reaction with a lower concentration of **1a** and a scaled-up process gave fairly good yields of 1,4-dihydroquinazolin-2-amine **3a** (entries 10–11).

Table 1 Reaction Optimization.[a]



1a 2a 3a

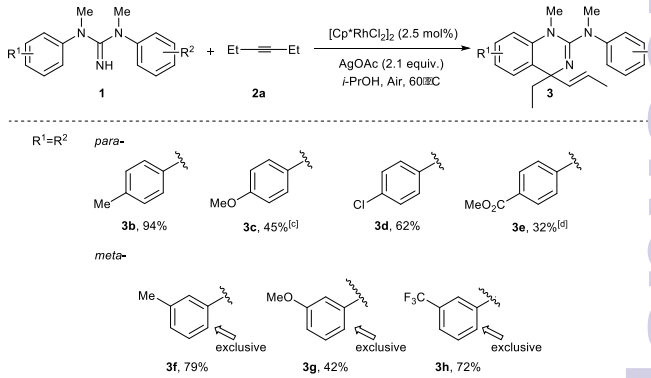
Entry	Oxidant	Additive	Solvent	Yield of **3a** (%)[b]
1[c]	$Cu(OAc)_2.H_2O$	$AgSbF_6$	^{t}AmOH	trace
2	AgOAc	-	^{t}AmOH	73
3	AgOAc	-	^{i}PrOH	91
4[d]	AgOAc	-	^{i}PrOH	-
5[e]	-	Na_2CO_3	^{i}PrOH	-
6[f]	AgOAc	-	^{i}PrOH	trace
7[g]	O_2	Na_2CO_3	^{t}AmOH	39
8	Ag(OPiv)	-	^{i}PrOH	51
9	$Ag(O_2CCF_3)$	-	^{t}AmOH	trace
10[h]	AgOAc	-	^{i}PrOH	86
11[i]	AgOAc	-	^{i}PrOH	70

[a] Conditions: **1a**, 0.4 mmol; **2a**, 0.4 mmol; [**1a**] = 0.2 M. [b] Isolated yields. [c] Under an argon atmosphere. [d] No catalyst was used. [e] No AgOAc was used. [f] Catalyst: $[Cp^*IrCl_2]_2$ (2.5 mol%). [g] AgOAc (25 mol%). [h] [**1a**] = 0.037 M. [i] Conditions: **1a**, 1.3 mmol; **2a**, 1.3 mmol; [**1a**] = 0.2 M.

Once the conditions had been optimized, we proceeded to evaluate the scope and limitations of both partners in the oxidative cycloaddition reaction. Gratifyingly, *para*- and *meta*-substituted aryl guanidines **1b–h** were well tolerated and they afforded 1,4-dihydroquinazolin-2-amines **3b–h** in moderate-to-good yields (Table 2).[14] The electronic properties of the *para*-substituted aryl guanidines had a significant effect on the reaction. Thus, the moderate electron-donating methyl group provided the stable 1,4-dihydroquinazolin-2-amine **3b** in 94% yield while the highly electron-donating methoxy group afforded the unstable 1,4-dihydroquinazolin-2-amine **3c** in a moderate 45% yield. By contrast, electron-poor substituents on aryl guanidines, *e.g.*, chloro **1d** and methoxycarbonyl **1e**, gave low-to-moderate yields of the corresponding 1,4-dihydroquinazolin-2-amines **3d,e**.[13] Interestingly, reaction of the *meta*-substituted arylguanidines was completely regioselective through activation of the less-hindered C–H bond, affording the 1,4-dihydroquinazolin-2-amines **3f–h** in moderate-to-good yields. Note that the electronic properties of the substituents at the *meta*-position of the arylguanidine did not have an appreciable effect on the reaction yield. Thus, either electron-releasing or electron-withdrawing groups in arylguanidines **1f,h** provided the corresponding 1,4-dihydroquinazolin-2-amines **3f,h** in similar yields.

We proceeded to examine the oxidative cycloaddition of aryl guanidines **1a** and **1f** with several alkynes **2** (Table 3). The symmetrically substituted aliphatic alkynes with long chains, 4-octyne **2b** ($R^3 = R^4 =$ *n*-Pr) and **2c** ($R^3 = R^4 =$ *n*-Bu) gave the corresponding 1,4-dihydroquinazolin-2-amines **3ab**, **3fb** and **3ac** in fairly good yields, whereas the parent internal alkyne, 2-butyne **2d** ($R^3 = R^4$ = Me), was less effective and gave the 1,4-dihydroquinazolin-2-amine **3ad** in moderate yield.

Table 2 Rh^{III}-Catalyzed [5+1] Oxidative Cycloaddition of *p*- and *m*-Substituted Arylguanidines **1b–h** and 3-Hexyne **2a** to 1,4-Dihydroquinazolin-2-amines **3b–h.**[a,b]



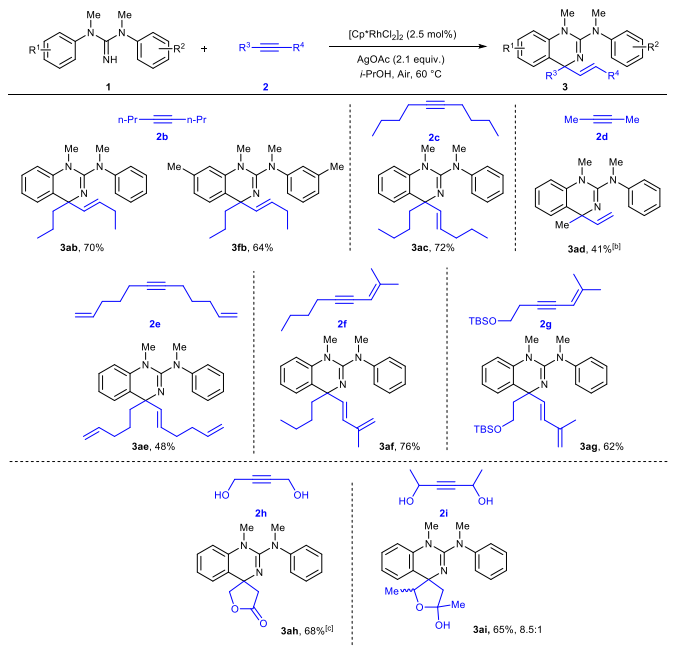
[a] Optimized conditions: **1**, 0.4 mmol; **2a**, 0.4 mmol; [**1**] = 0.2 M in *i*-PrOH (2 mL); 60 °C, air, 8 h. [b] Isolated yields. [c] Conditions: 40 °C, 8 h. [d] Indole **4e** (19%) was also isolated.[13]

Functionalized aliphatic alkynes were analyzed next.[15] Symmetrical α,ω-enyne **2e** gave the C-4 disubstituted 1,4-dihydroquinazolin-2-amine **3ae**, which contains three double bonds susceptible to further manipulation. Notably, 1,3-enynes **2f** and **2g** reacted smoothly to give the C-4 difunctionalized 1,4-dihydroquinazolin-2-amines **3af** and **3ag** as single regioisomers in 76% and 62% yield. Gratifyingly, alkynyl 1,4-diols were also well tolerated by the reaction conditions, thus providing a one-pot synthesis of interesting functionalized spiro-1,4-dihydroquinazolin-2-amines **3ah** and **3ai** (as an 8.5:1 diastereoisomeric mixture), thereby making the one-carbon oxidative annulation protocol attractive to medicinal chemistry.[17]

In an effort to gain an insight into the reaction mechanism, several experiments to form the cyclometalated rhodium complexes were conducted. The new six-membered cyclometalated Rh(III) complex **5a** was isolated in 81% yield by reacting $[Cp^*RhCl_2]_2$ with 2.2 equivalents of guanidine **1a** in MeOH at rt for 2 h (Scheme 2, eq 1). The structure of **5a** was characterized by X-ray crystallography[18] and by NMR spectroscopy.[13] Gratifyingly, further reaction of **5a** with 2 (1.2 equiv) at room temperature led to the quantitative formation of air-stable complex **6a** in 5 min (Scheme 2, eq 2). The X-ray structure of **6a** confirmed a characteristic eight-ring boat structure (torsion angle C(1)-C(2)-C(21)-C(22) = 60.5°) in which the RhCp* fragment displays a three-legged piano stool environment completed by the imino NH group of the guanidine and the C atom of the vinyl moiety. The Rh(1)-N(10) and Rh(1)-C(22) bond lengths of 2.092(5) and 2.060(6) Å, respectively, compare well with those found in other rhodium cyclometalated complexes reported by Jones,[19] and support the dative and single character of the bonds. Both chloro-complexes **5a** and **6a** were quantitatively transformed into the corresponding acetate derivatives **5b** and **6b** by treatment with AgOAc (1 equiv) in dichloromethane.

To our delight, a stoichiometric experiment using complex **6b** in ^{i}PrOH/AcOH showed the presence of two reaction products, the major quinazoline **3a** and the minor styrene **7a**, the latter probably derived from protonolysis of complex **6b** (Scheme 3).[20]

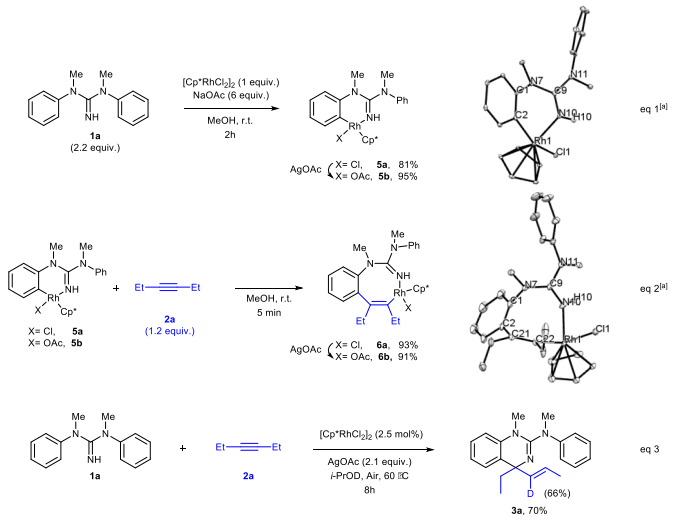
Table 3 Rh-Catalyzed [5+1] Oxidative Cyclization of Arylguanidine **1a** with Substituted Aliphatic Alkynes.[a]



[a] Optimized conditions: **1**, 0.4 mmol; **2a**, 0.4 mmol; [**1**] = 0.2 M in *i*-PrOH (2 mL); 60 °C, Air, 8 h. [b] Conditions: 40 °C in a sealed tube, 24 h. [c] AgOAc: 4 eq.

After heating styrene **7a** under the typical catalytic conditions for 24h was recovered unchanged, which suggests that is a side product instead of a reaction intermediate. In addition, quinazoline **3a-*d***, which is deuterated at the vinylic position (66% D incorporation), was obtained when the catalytic reaction of arylguanidine **1a** and alkyne **2a** was performed in deuterated isopropanol (Scheme 2, eq 3).[13]

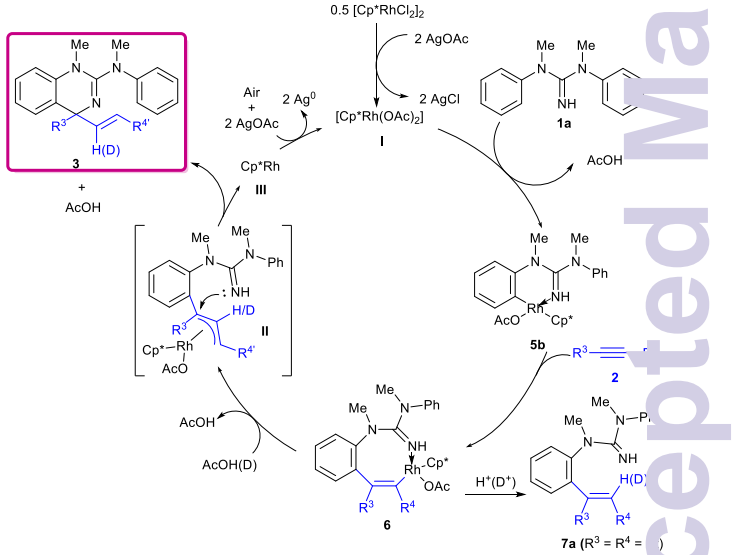
Scheme 2 Mechanistic Studies.



[a] Diamond plots of the structures of complexes **5a** and **6a** in the crystal with ellipsoids at 30% probability and the Cp* methyl groups omitted for clarity.

On the basis of the above results and previous reports,[21] a tentative reaction mechanism for the Rh(III)-catalyzed [5+1] oxidative cycloaddition is shown in Scheme 3. Initial coordination of the guanidine to the catalytically active $Cp^*Rh(OAc)_2$ **I** followed by ortho C–H bond activation generates a six-membered rhodacycle **5b**. Coordination and insertion of the alkyne **2** into the Rh–C bond of **5b** gives a new eight-membered rhodacycle **6**.[22] β-hydride elimination with concomitant loss of AcOH[23] followed by protonolysis at central carbon of the transient allene formed[24] would afford the π-allylrhodium intermediate **II**.[25] Finally, nucleophilic attack by the imine at the more electrophilic position of **II** delivers the C4-disubstituted-1,4-dihydroquinazolin-2-amine **3**[26] and a Cp^*Rh^I species, which is reoxidized by silver acetate under air to the next catalytic cycle.

Scheme 3 Proposed Catalytic Cycle.



Conclusions

In summary, we have successfully developed a new and efficient rhodium-catalyzed [5+1] oxidative cycloaddition between guanidines and internal aliphatic alkynes to give C4-disubstituted 1,4-dihydroquinazolin-2-amines. The reaction tolerates a wide range of functional groups in both the guanidine and alkyne partners, and provides an easy access to relevant functionalized heterocycles containing the guanidine moiety. Further mechanistic studies and investigations on the application of this novel oxidative cycloaddition are currently underway in our laboratory.

Acknowledgements

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13 See Supporting Information for details.

14 *Ortho*-substituted arylguanidines remained unchanged.

15 Diaryl and unsymmetrical alkyl arylalkyne partners did not participate in the [5+1] cycloaddition, only traces of indoles are isolated. See Supporting Information for details.

16 Arylguanidine **1a** remains unreactive under the acidic Lam conditions, $[\{Cp^*RhCl_2\}_2]$ (2.5 mol%), $Cu(OAc)_2$ (2.1 equiv.), AcOH (0.1 equiv.), dioxane, 60 °C. See ref 9.

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18 CCDC 1053853 (**5a**) and 1053854 (**6a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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26 (*a*) With enynes **2f** and **2g**, rhodacycles **6** would undergo [1,4]-H migrations to form intermediates **II** (see ref. 9). (*b*) With alkynyl-1,4-diols **2h** and **2i** as partners, tautomerization to the aldehyde (of the initial enol formed) followed by hemiacetalization (**3ai**) and oxidation to the lactone (**3ah**) is observed.