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# Ruthenium-Catalyzed Azide−Alkyne Cycloaddition: Scope and Mechanism

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***Abstract:*** The catalytic activity of a series of ruthenium(II) complexes in azide−alkyne cycloadditions has been evaluated. The [Cp*RuCl] complexes, such as Cp*RuCl($PPh_3$)$_2$, Cp*RuCl(COD), and Cp*RuCl(NBD), were among the most effective catalysts. In the presence of catalytic Cp*RuCl($PPh_3$)$_2$ or Cp*RuCl(COD), primary and secondary azides react with a broad range of terminal alkynes containing a range of functionalities selectively producing 1,5-disubstituted 1,2,3-triazoles; tertiary azides were significantly less reactive. Both complexes also promote the cycloaddition reactions of organic azides with internal alkynes, providing access to fully-substituted 1,2,3-triazoles. The ruthenium-catalyzed azide−alkyne cycloaddition (RuAAC) appears to proceed via oxidative coupling of the azide and alkyne reactants to give a six-membered ruthenacycle intermediate, in which the first new carbon−nitrogen bond is formed between the more electronegative carbon of the alkyne and the terminal, electrophilic nitrogen of the azide. This step is followed by reductive elimination, which forms the triazole product. DFT calculations support this mechanistic proposal and indicate that the reductive elimination step is rate-determining.

## Introduction

1,2,3-Triazoles have been known for over a century,[1] yet they have not been utilized as widely as other members of the azole family. The conspicuous lack of 1,2,3-triazoles in the literature is likely due to the limited repertoire of synthetic methods leading to these heterocycles. Among those,[2] the Huisgen 1,3-dipolar cycloaddition[3,4] of azides and alkynes prominently stands out as the most direct way to assemble the 1,2,3-triazole functionality.[5] Although the reaction is highly exothermic (*ca.* −50 to 65 kcal/mol), its high activation barrier (25−26 kcal/mol for methyl azide and propyne[6]) results in exceedingly low reaction rates for unactivated reactants even at elevated temperature. Furthermore, since the difference in HOMO−LUMO energy levels for both azides and alkynes are of similar magnitude, both dipole-HOMO- and dipole-LUMO-controlled pathways operate in these cycloadditions. As a result, a mixture of regioisomeric 1,2,3-triazole products is usually formed when an alkyne is unsymmetrically substituted.

The copper-catalyzed 1,3-dipolar *a*zide−*a*lkyne *c*ycloaddition (CuAAC) was an important advance in the chemistry of 1,2,3-triazoles.[7,8] An enormous rate acceleration ($10^7$ to $10^8$ comparing to the uncatalyzed process[6]), a remarkably broad scope, a tolerance to aqueous and oxic conditions, and an exclusive regioselectivity have enabled a number of applications in the relatively short time since the reaction was discovered.[9−14] The especially narrow reactivity profiles of azides and alkynes and the efficiency of their copper-catalyzed union have been recognized across disciplines, as evidenced by its the applications in bioorganic chemistry, organic synthesis, and materials and polymer science.

While Cu(I) catalysis provides a reliable means for the assembly of 1,4-disubstituted 1,2,3-triazoles, a general method for the generation of 1,5-disubstitued regioisomers is lacking. Among the available methods are the reactions of stabilized phosphonium ylides[15−20] or enamines[2,21] with aryl azides and the addition of magnesium acetylides to azides.[22] However, these methods have considerable limitations.

We recently disclosed that pentamethylcyclopentadienyl ruthenium chloride [Cp*RuCl] complexes catalyze the facile

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cycloaddition of azides with terminal alkynes, regioselectively leading to 1,5-disubstituted 1,2,3-triazoles.[23] Furthermore, and in stark contrast to the CuAAC, its sister ruthenium-catalyzed process, RuAAC, readily engages internal alkynes in catalysis, providing access to fully substituted 1,2,3-triazoles. In this report, we summarize the results of our studies of the scope, limitations, and mechanism of the RuAAC reaction.

## Experimental Section

Unless stated otherwise, all reagents and solvents were purchased from commercial suppliers and used without further purification. Most manipulations were carried out under a nitrogen atmosphere using standard Schlenck techniques unless otherwise stated. See Supporting Information for complete details.

**Procedure A.** General procedure for $Cp^*RuCl(PPh_3)_2$ catalyzed reactions as exemplified for the synthesis of triazole **3**: A solution of 1-ethynylcyclohexanol (51 $\mu$L, 0.40 mmol) and ethyl 2-(2-azidoacetamido)-3-hydroxypropanoate (86 mg, 0.40 mmol) in 0.5 mL of dioxane was added to $Cp^*RuCl(PPh_3)_2$ (6.4 mg, 0.008 mmol) dissolved in 2.5 mL of dioxane. The vial was purged with nitrogen, sealed, and heated in an oil bath at 60 °C for 12 h, at which point TLC and LC−MS analyses indicated complete consumption of the alkyne and the azide starting materials. The mixture was adsorbed onto silica and chromatographed with hexanes/ethyl acetate (1:1) to remove nonpolar impurities, followed by ethyl acetate to elute the product, which was isolated as a pale yellow oil. (Note: in all reactions the alkyne was added first, followed by the addition of the azide, or azide and alkyne were dissolved in the reaction solvent and added to the solution of the catalyst.)

**Procedure B.** General procedure for Cp*RuCl(COD) catalyzed reactions as exemplified for the synthesis of triazole **14**: Cp*RuCl(COD) (4.0 mg, 0.010 mmol) was added to a tube with a septa cap. The tube was sealed, then evacuated, and filled with nitrogen three times. Toluene (5 mL, degassed for 1 h with nitrogen purge) was added followed by 2-methyl-4-phenylbut-3-yn-2-ol (80 mg, 0.50 mmol) and 1-azido-4-methylbenzene (67 mg, 0.50 mmol). The reaction was stirred at room temperature for 30 min, at which time TLC analysis indicated complete consumption of the starting materials. The mixture was adsorbed onto silica and chromatographed with 4:1 hexanes/ethyl acetate and then 2:1 hexanes/ethyl acetate to afford the pure product as a white solid. (Note: in all reactions the alkyne was added first, followed by the addition of the azide, or azide and alkyne were dissolved in the reaction solvent and added to the solution of the catalyst; azide should not be added first.)

**Computational Details.** See Supporting Information.

## Results and Discussion

In the past three decades, ruthenium-catalyzed transformations of alkynes have received considerable attention.[24–28] An impressive number of ruthenium mediated reactions of alkynes have been developed, especially those involving vinylidene, allenylidene, metallacyclopentene, and metallacyclopentadiene intermediates. Direct addition processes include cyclotrimerization to generate benzene rings,[29–34] [2 + 2] cycloadditions of alkynes with olefins,[35–38] Alder ene reactions of alkynes and alkenes,[39] and enyne metathesis.[40] Formal cycloadditions in which the third component is an oxygen nucleophile[41] or carbon monoxide, as in the Pauson−Khand reaction, are known as well.[42,43] Ruthenium-mediated propargylic substitution,[44–46] anti-Markovnikov addition,[26] and related methods have also found broad utility. However, catalytic dipolar cycloadditions are absent in this list.[47] Keeping in mind the wide variety of transformations of alkynes catalyzed by ruthenium species,[48] we began our study with ruthenium complexes known to engage alkynes in catalysis.

**Catalysts, Ligands, and Experimental Conditions.** The catalytic activity of several ruthenium(II) complexes was evaluated using the cycloaddition of benzyl azide and phenylacetylene. Solvents such as dioxane, benzene, 1,2-dichloroethane, toluene, or THF were employed. As previously reported, $\eta^5$-pentamethylcyclopentadienyl ruthenium [Cp*RuCl] complexes were particularly effective in promoting the reaction (Table 1). The unique catalytic properties of these complexes can be ascribed to the presence of the electron-rich Cp* ligand, which stabilizes higher formal oxidation states of the metal center. Ruthenium(II) complexes lacking this ligand, such as $(COD)RuCl_2$, $[(p\text{-cym})RuCl_2]_2$, $(p\text{-cym})RuCl_2(PPh_3)$, $RuCl_2(PPh_3)_3$, and $RuHCl(CO)(PPh_3)_3$, showed no appreciable catalytic activity; $CpRuCl(PPh_3)_2$, $RuH_2(CO)(PPh_3)_3$, and $Ru(OAc)_2(PPh_3)_2$ were marginally effective in catalyzing the cycloaddition. It is noteworthy that reactions catalyzed by $RuCl_2(PPh_3)_3$, $RuHCl(CO)(PPh_3)_3$, $RuH_2(CO)(PPh_3)_3$, and $Ru(OAc)_2(PPh_3)_2$ resulted in the formation of the 1,4-substituted triazole regioisomer, albeit in low yields. $CpRuCl(PPh_3)_2$ was a modestly active


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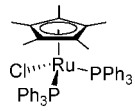
***Table 1.*** Performance of Ruthenium(II) Catalysts in Cycloaddition of Benzyl Azide and Phenyl Acetylene[a]

| Ru catalyst | 1,5 | 1,4 |
|---|---|---|
| $[RuCl_2(COD)]_x$ | - | - |
| $[(p\text{-cym})RuCl_2]_2$ | - | - |
| $[(p\text{-cym})RuCl_2(PPh_3)$ | - | - |
| $[Cp^*Ru(H_2O)(NBD)]BF_4$ | - | - |
| $RuCl_2(PPh_3)_3$ | - | <5% |
| $Ru(OAc)_2(PPh_3)_2$ | - | 46% |
| $RuHCl(CO)(PPh_3)_3$ | - | <5% |
| $RuH_2(CO)(PPh_3)_3$ | - | 56% |
| $CpRuCl(PPh_3)_2$ | 13% | 1% |
| $Cp^*RuCl(PPh_3)_2$ | 100% | |
| Cp*RuCl(COD) | 100% | |
| Cp*RuCl(NBD) | 93% | |
| $[Cp^*RuCl]_4$ | 100% | |

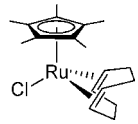
[a] Reaction conditions: refluxing THF (oil bath temp = 75 °C), 2 mol% [Ru], azide/alkyne = 1:1.2, 4 h. The yields are estimated based on the integration of triazole and the unreacted azide. "-" means not detected or trace.

catalyst as well, resulting in the formation of a 5.8:1 (in benzene) or 10:1 (in THF) mixture of 1,5- and 1,4-regioisomers.

[Cp*RuCl] complexes, e.g., $[Cp^*RuCl]_4$, $Cp^*RuCl(PPh_3)_2$, Cp*RuCl(COD), and Cp*RuCl(NBD), were especially active and selective catalysts, producing the 1,5-disubstituted triazole product in excellent yields. Further studies described below focused on the bis(triphenylphosphine) (**1**) and cyclooctadiene (**2**) catalysts due to their ready synthetic availability and stability. Both complexes can be conveniently obtained by treatment of the $[Cp^*RuCl]_4$ precursor with an excess of $PPh_3$ or cyclooctadiene, respectively.[26]




**1**




**2**

The [Cp*RuCl]-catalyzed cycloadditions proceed well in a variety of aprotic organic solvents including tetrahydrofuran, dioxane, toluene, benzene, dimethylformamide, and 1,2-dichloroethane. Performing the reaction in protic solvents (MeOH, *i*-PrOH) resulted in reduced yields and caused formation of byproducts. Nevertheless, the presence of adventitious water or protic functional groups in the reactants (*vide infra*) usually did not affect the performance of the catalysts; in other words, the solvents employed need not be scrupulously dried. As reported earlier, the cycloadditions with $Cp^*RuCl(PPh_3)_2$ can be carried out at temperatures ranging from ambient to 110 °C. The reaction does not appear to be very sensitive to atmospheric oxygen. Indeed, the cycloaddition of benzylazide and $Ph_2C(OH)C{\equiv}CH$ in the presence of 1 mol % of $Cp^*RuCl(PPh_3)_2$ in benzene also proceeded smoothly even when the reaction was performed without exclusion of oxygen (4 h at reflux, >99% conversion). It should be noted that $Cp^*RuCl(PPh_3)_2$ is known to react with dioxygen to give $Cp^*RuCl(O_2)(PPh_3)$. The dioxygen ligand in the latter complex is not tightly bound and can be replaced with a phosphite ligand L to give $Cp^*RuCl(L)(PPh_3)$.[28] Evidently, in our catalytic reactions, atmospheric oxygen does not effectively compete with the reactants.

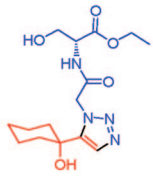
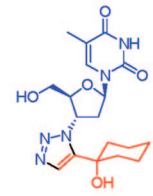
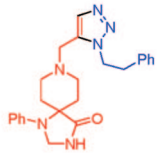
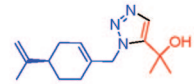
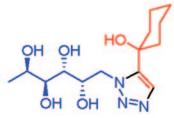
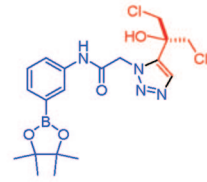
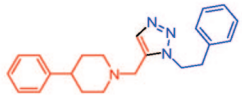
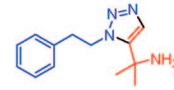
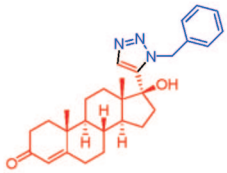
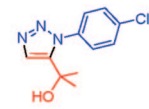
The cyclooctadiene ligand in Cp*RuCl(COD) catalyst is more labile than phosphines and is displaced more readily than phosphine ligands in the bis(triphenylphosphine) complex. This is evidenced by the activity of the former catalyst even at room temperature. This feature of the Cp*RuCl(COD) catalyst is particularly advantageous for the reactions involving internal alkynes or aryl azides. The deactivation of the catalyst via the formation of the tetraazadiene complex, discussed below, is common for aryl azides, but it is minimized at room temperature, and the triazoles are obtained in good to excellent yields and with excellent regioselectivity.

**Scope of the [Cp*RuCl]-Catalyzed Cycloadditions.** The ruthenium-catalyzed reactions described herein exhibit excellent scope with respect to both reactants, successfully engaging a wide range of azides and alkynes in the catalysis. The steric demands of the azide substituent significantly affect the outcome of the cycloaddition. Thus, reactions involving primary azides were most efficient and cycloadditions of secondary azides often took longer and resulted in slightly lower yields, whereas tertiary azides, with a few exceptions, reluctantly participated in catalysis. On the other hand, the catalysis is not very sensitive to the substituents on the alkyne. Worthy of note, certain alkyne classes, such as 1,1-disubstituted propargyl alcohols, exhibited especially high reactivity (*vide infra*). Table 2 highlights reactions of terminal alkynes with alkyl azides catalyzed by $Cp^*RuCl(PPh_3)_2$ and Cp*RuCl(COD) complexes (either catalyst can be used in most cases). As seen from these examples, terminal alkynes containing halide, alcohol, ether, acetal, nitrile, ester, amine, sulfonamide, and pyridine functionalities readily participated in the catalysis. In most cases 2 mol % of the catalyst was used, and the reactions were carried out in THF or dioxane at temperatures ranging from ambient to 80 °C. In all cases involving terminal alkynes, only the 1,5-disubstituted triazoles were formed. The only combination of the reactants that gave a mixture of 1,4- and 1,5-regioisomers we have found is benzyl azide and trimethylsilyl acetylene. Their reaction in refluxing benzene in the presence of 2 mol % $Cp^*RuCl(PPh_3)_2$ catalyst resulted in a mixture of 1,5- and 1,4-disubstituted triazoles in 98:2 ratio.

As already mentioned, the [Cp*RuCl]-catalyzed reactions appear to be more sensitive to the steric demands of the azide than those of the alkyne. Thus, secondary azides reacted significantly slower than primary ones, and tertiary azides were even less reactive under the current conditions. Nevertheless, as demonstrated by the examples in Table 2, cycloaddition products of secondary azides were obtained in good yields. Azides containing complex functional groups, such as 3′-azido-2′-deoxythymidine (AZT), could also be readily coupled under these conditions. As in the case of the Cu(I)-catalyzed cycloaddition, the ability to carry out Ru-catalyzed triazole formation from highly functionalized reactants is especially valuable, and we anticipate that the present method may serve as a useful platform for the generation of diversely substituted molecules that are structurally distinct from the compounds available from the CuAAC reaction.

A remarkable feature of the [Cp*RuCl] catalytic system is its ability to engage *internal* alkynes in the cycloaddition with organic azides resulting in the formation of 1,4,5-trisubstituted 1,2,3-triazoles. To date, these fully substituted triazoles were only accessible from particularly activated, electron-deficient alkynes (such as acetylene dicarboxylic acid derivatives) by thermal cycloadditions, which are generally not regioselective and often provide triazole products only in modest yields. In contrast, in the presence of [Cp*RuCl], organic azides react with a range of internal alkynes to provide 1,4,5-trisubstituted triazole products (Table 3). Regioselectivity of the cycloaddition is

***Table 2.*** [Cp*RuCl]-Catalyzed Reactions of Azides with Terminal Alkynes

| entry | product | procedure | yield, % | m.p., °C | entry | product | procedure | yield, % | m.p., °C |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  **3** | A | 80 | oil | 6 |  **8** | A | 72 | 213.0-216.0 |
| 2 |  **4** | A | 81 | 220.0-223.0 | 7 |  **9** | A | 93 | oil |
| 3 |  **5** | A | 75 | 165.0-168.0 | 8 |  **10** | B | 76 | 75.0-80.0 Decomp. |
| 4 |  **6** | A | 90 | oil | 9 |  **11** | A | 83 | 60.2-62.6 |
| 5 |  **7** | A | 78 | 258.0-263.3 | 10 |  **12** | A | 80 | 82.5-84 |

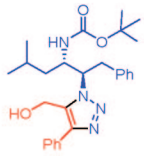
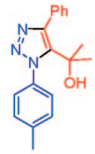
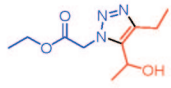
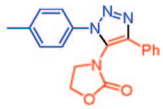
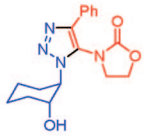
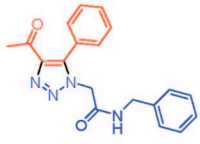
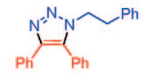
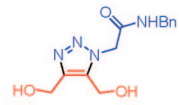
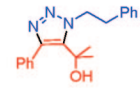
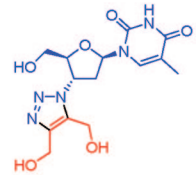
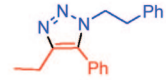
influenced by several factors in these cases. Alkynes containing a hydrogen bond donor group (e.g., propargylic alcohols and amines) exhibit virtually exclusive regioselectivity: the new bond is always formed between the $\beta$-carbon of the alkyne and the terminal nitrogen of the azide. This directing effect can be attributed to the formation of a strong H-bond between the alcohol or amine and the chloride ligand on the ruthenium. In the absence of such directing groups, regioselectivity seems to be governed primarily by the electronic (and possibly by steric) properties of the alkyne: the new bond in the metallacycle intermediate **28** (Scheme 3) is formed between the more nucleophilic carbon of the alkyne. In other words, the more electronegative carbon of the alkyne becomes C-4 in the triazole.

Cp*RuCl(PPh$_3$)$_2$ readily catalyzes reactions of aliphatic azides with internal alkynes at 60 °C, whereas the cyclooctadiene analogue (**2**) exhibits excellent activity already at room temperature. The advantages of the Cp*RuCl(COD) catalyst are also evidenced by the reactions of aryl azides, which often suffer from decomposition and catalyst deactivation at elevated temperatures. In fact, we found that heating is often detrimental in the reactions catalyzed by Cp*RuCl(COD), resulting in rapid deactivation of the catalyst and low yields of the cycloaddition product.

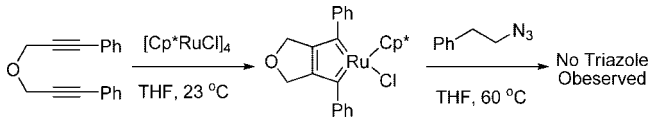
Possible pathways of deactivation of the ruthenium catalyst were also examined. Although [Cp*RuCl] can catalyze cyclotrimerization of alkynes, we did not observe formation of the benzenoid products. Likewise, ruthenacycles, whose intermediacy has been postulated in the catalytic alkyne trimerizations and which are known to form quite rapidly even at 0 °C,[49,50] were not detected among the species present in the reaction mixture. Furthermore, ruthenacycle **24** prepared from the 1,6-diyne shown in Scheme 1 using a slightly modified procedure reported by Yamamoto et al.[51] was not reactive with an organic azide even after prolonged (several days) heating. Similarly, other 1,6-diynes failed to produce triazole products when they were added, regardless of the order of addition, to the solution of the Cp*RuCl(COD) catalyst. It appears that the formation of ruthenacyclopentatrienes similar to **24** still prevails when 1,6-diynes are used as substrates, and the catalyst is effectively taken out of the catalytic cycle. With other alkynes, the formation of the ruthenacyclopentatriene complexes is suppressed and the

(49) Ernst, C.; Walter, O.; Dinjus, E. *J. Organomet. Chem.* **2001**, *627*, 249.
(50) Ernst, C.; Walter, O.; Dinjus, E.; Arzberger, S.; Gorls, H. *J. Prakt. Chem.* **1999**, *341*, 801.
(51) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605.

***Table 3.*** [Cp*RuCl]-Catalyzed Cycloadditions of Azides and Internal Alkynes

| entry | product | procedure | yield, % | m.p., °C |
|---|---|---|---|---|
| 1 |  **13** | B | 69 | 205.0-207.0 |
| 2 |  **14** | B | 93 | 161.8-163.3 |
| 3 |  **15** | B | 71 | oil |
| 4 |  **16** | B | 97 | 181.3-182.5 |
| 5 |  **17** | B | 95 | 144 -145 |
| 6 |  **18** | B | 79 | 155.5-156.5 |
| 7 |  **19** | A | 63 | 164-166 |
| 8 |  **20** | A | 78 | 145-147 |
| 9 |  **21** | A | 80 (>20:1) | 133.5-135 |
| 10 |  **22** | A | 80 | 153-156 |
| 11 |  **23** | B | 82 (9:1) | n.d. |

***Scheme 1.*** Syntheis of Ruthenacycle **24** and Its Reaction with (2-Azidoethyl)benzene



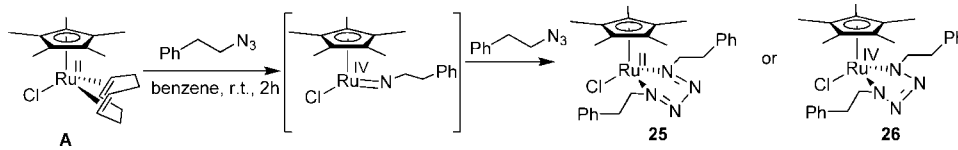

**24**

desired azide−alkyne cycloaddition takes place, likely as a consequence of the strong $\sigma$-coordination of the azide to ruthenium via the N-1 of the azide.

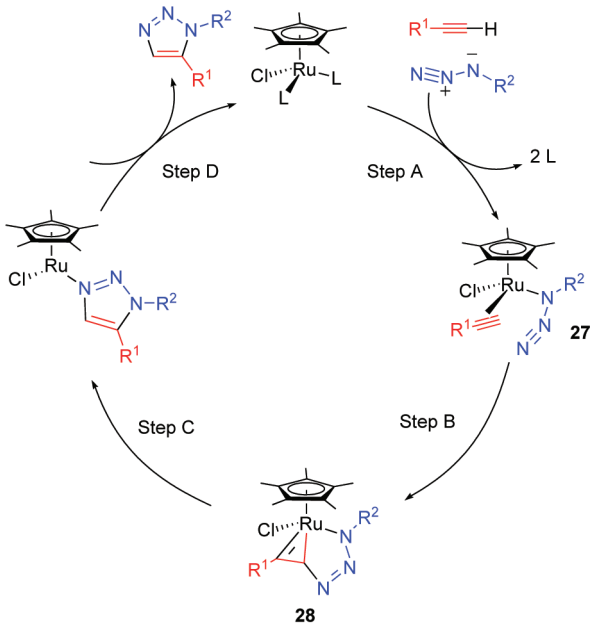
However, treatment of the Cp*RuCl(COD) catalyst at room temperature with 2 equiv of (2-azidoethyl)benzene readily produced ruthenium tetraazadiene complex **25** (or possibly tetrazenide **26**), shown in Scheme 2. This complex was isolated by flash chromatography and appeared to be exceedingly stable. Like ruthenacyclopentatriene **24**, it failed to react further with either alkynes or azides. While isolation of this compound is significant in itself (only a few similar ruthenium complexes have been reported in the literature[52,53]), more important is the realization that formation of **25** is a likely cause of diminished catalytic activity of certain [Cp*RuCl] systems, especially in cases involving organic azides which are prone to decomposition and can readily engage in the formation of the imido complexes. This finding leads to two practical conclusions: (a) reactions of aryl azides, which are less stable than their aliphatic counterparts and are prone to the formation of the ruthenium imido complexes, are best performed at room temperature and (b) azide should not be added to the catalyst before the alkyne. In our experience, the best results are obtained when a mixture of the azide and the alkyne is added to the solution of the catalyst.

(52) Danopoulos, A. A.; Hay-Motherwell, R. S.; Wilkinson, G.; Cafferkey, S. M.; Sweet, T. K. N.; Hursthouse, M. B. *J. Chem. Soc., Dalton Trans.* **1997**, 3177.
(53) Danopoulos, A. A.; Wilkinson, G.; Sweet, T. K. N.; Hursthouse, M. B. *J. Chem. Soc., Dalton Trans.* **1996**, 3771.

***Scheme 2.*** Formation of Catalytically Inactive [Cp*RuCl] Tetraazadiene Complexes




***Scheme 3.*** Proposed Intermediates in the Catalytic Cycle of the RuAAC Reaction




**Mechanistic Considerations and DFT Studies.** Participation of both terminal and internal alkynes in catalysis suggests that ruthenium acetylides are not involved in the catalytic cycle, and our experiments with isolated ruthenium(II) acetylides, as well as with vinylidene complexes, support this hypothesis. Since different Ru(II) complexes, such as Cp*RuCl(PPh$_3$)$_2$, Cp*RuCl(COD), Cp*RuCl(NBD), and [Cp*RuCl]$_4$ are competent catalysts, we propose that the neutral [Cp*RuCl] is the catalytically active species, especially in reactions mediated by Cp*RuCl(diolefin) and [Cp*RuCl]$_4$. This hypothesis is supported by the observations that (a) [Cp*RuBr] and [Cp*RuI] complexes are significantly less active catalysts, (b) [Cp*Ru]$^+$ cationic complexes obtained by the removal of the chloride with Ag$^+$ are devoid of the catalytic activity altogether, and (c) chelating diphosphines, such as bis(diphenylphosphino)ethane, completely deactivate the catalyst.

Catalytic cyclotrimerization of alkynes catalyzed by [Cp*RuCl] and similar complexes is, of course, well-known,[29,30,32,33,51,54] and we believe that the RuAAC is related to it. Cyclotrimerization catalyzed by the Cp*RuCl(COD) has been shown to proceed via ruthenacyclopentadiene intermediates. Therefore, we hypothesize that RuAAC represents a simple case that shunts off the usual alkyne oligomerization sequence, as schematically outlined in Scheme 3. The displacement of the spectator ligands (step A) produces the activated complex **27**, which is converted, via the oxidative coupling of an alkyne and an azide (step B), to the ruthenacycle **28**. This step controls the regioselectivity of the overall process. The new C—N bond is formed between the more electronegative and less sterically-demanding carbon of the alkyne and the terminal nitrogen of the azide. The metallacycle intermediate then undergoes reductive elimination (step C) releasing the aromatic triazole product and regenerating the catalyst (step D) or the activated complex **27**.

As noted above, the [CpRuCl] complexes, such as CpRuCl(PPh$_3$)$_2$, also catalyze the reaction, albeit much less efficiently and not regioselectively. The higher catalytic activity of [Cp*RuCl] catalysts can be attributed to the lability of the bystander ligands in such systems[34] (thus facilitating the formation of the activated complex **27**), the more sterically demanding nature of the Cp* ligand (which, in turn, facilitates the reductive elimination, step C, in the catalytic cycle), and prevents formation of the stabilized ruthenacycle **IN2A** (vide infra).

The proposed reaction mechanism was examined computationally employing DFT calculations using the B3LYP hybrid functional. In this computational study, methyl azide and propyne were used as the model reactants with [CpRuCl] as a catalyst. Methyl azide can, in principle, coordinate to the metal center via the nitrogen proximal to carbon or via the distal nitrogen atom. Both modes of coordination are known, although the former is observed by far more commonly.[55] The alkyne can also coordinate to the metal center in a $\pi$-fashion in two distinct orientations. Therefore, four activated azide/[Ru]/alkyne complexes, **PCA**, **PCB**, **PCC** and **PCD**, are possible, as shown in Figure 1. **PCA** and **PCC** complexes lead to the 1,5-disubstituted triazole product, whereas **PCB** and **PCD** would result in the formation of the 1,4-regioisomer. The computed energies of the complexes are within 1 kcal/mol. The results are consistent with those of a recent theoretical study.[56]

The energy profile for the reaction of **PCA** is illustrated in Figure 2. The first step, oxidative coupling of methyl azide and propyne, results in the formation of the six-membered ruthenacycle **IN1A**. This step is exothermic by 13.2 kcal/mol, and the calculated barrier is only 4.3 kcal/mol. **IN1A** can undergo reductive elimination via transition state **TS3A** (the rate-determining step, 13 kcal/mol activation energy) forming the metal—triazole complex **PRA** or can isomerize to a more stable ruthenacycle **IN2A** with a very low barrier of 1.6 kcal/mol (**TS2A**). In other words, the facility and the outcome of the overall process are influenced by the relative energies and the ease of interconversion of intermediates **IN1A** and **IN2A**. We propose that the formation of the **IN2A** is disfavored in [Cp*RuCl]-catalyzed reactions, and **IN1A** is directly converted to **PRA**. The activation energy of the reaction is therefore

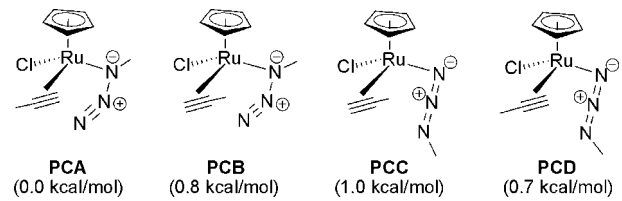



***Figure 1.*** Structures and computed energies of the activated complexes.

(54) Kirchner, K.; Calhorda, M. J.; Schmid, R.; Veiros, L. F. *J. Am. Chem. Soc.* **2003**, *125*, 11721.

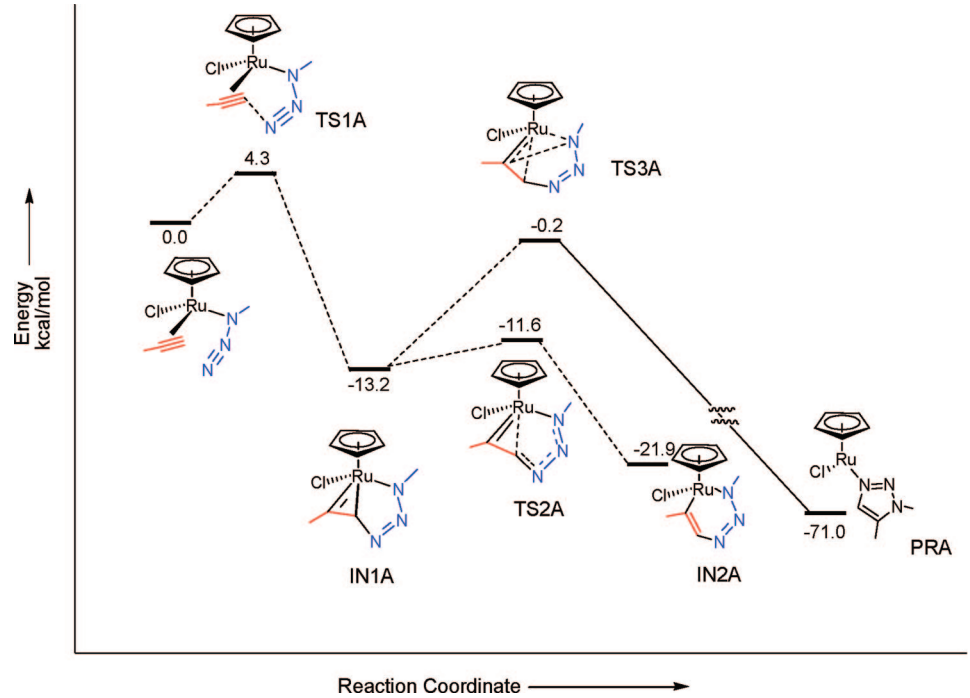



***Figure 2.*** Schematic representation (energy vs reaction coordinate) of the reaction of organic azides and alkynes catalyzed by [CpRuCl].

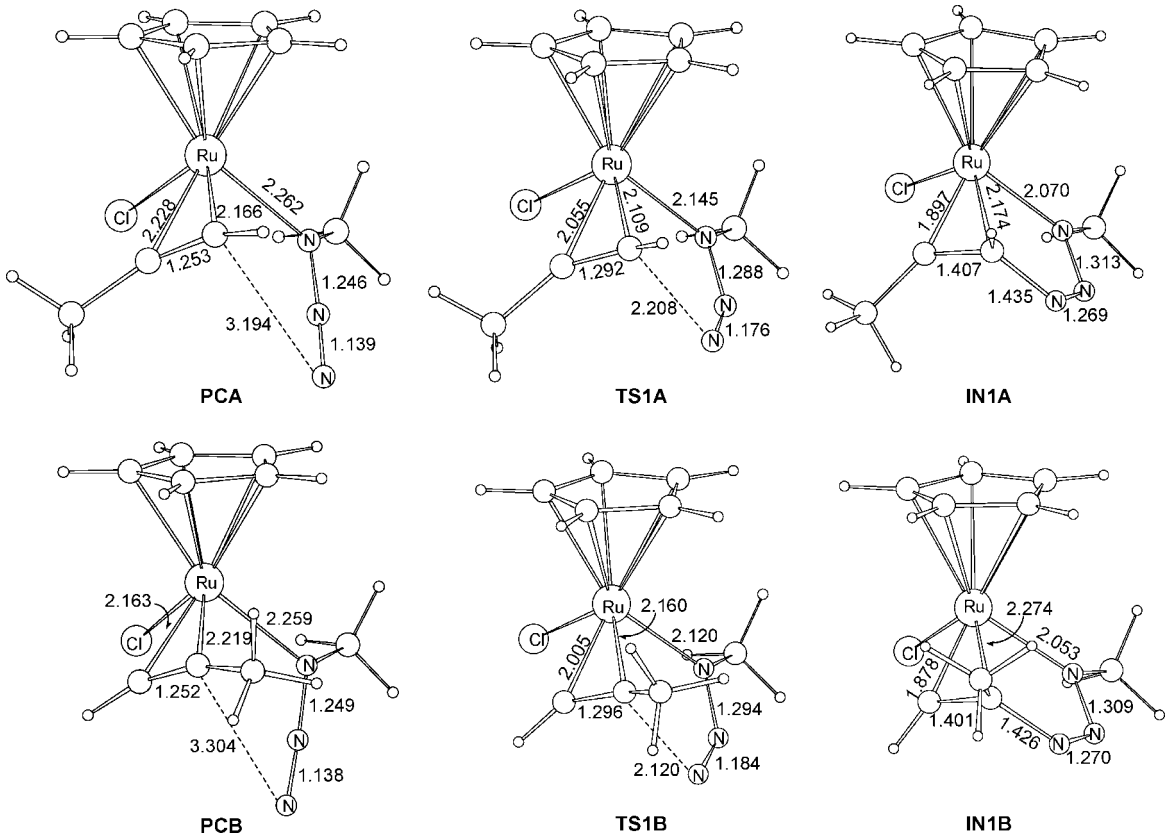



***Figure 3.*** Selected structural parameters (Å) calculated for species involved in the oxidative coupling steps of pathways A and B (from **PCA** and **PCB**, respectively).

reduced from 24 kcal/mol for the uncatalyzed process[6] to 13 kcal/mol, accounting for the observed rate acceleration. Pathway B, leading to the 1,4-regioisomer (see Supporting Information for complete details) is disfavored by ca. 3 kcal/mol in the oxidative coupling step. Further examination of the structural features of the species involved in the oxidative coupling steps (Figure 3) reveals the steric repulsion between the methyl substituent of the propyne and the hydrogens on the Cp ring in the metallacycle intermediate **IN1B**, whereas it is avoided in the intermediate **IN1A**. The Ru−$C_\beta$ bond distance in the intermediate **IN1B** is 2.274 Å, longer than the Ru−$C_\beta$ distance in **IN1A**, supporting the steric repulsion argument. Clearly, these

steric interactions are amplified in the [Cp*RuCl] complexes, explaining the high regioselectivity of those catalytic systems. Pathways beginning from the azide coordinated to ruthenium via the terminal nitrogen (starting from **PCC** and **PCD**) were also evaluated, revealing much higher activation barriers for the formation of even the first intermediate, 20.9 and 17.8 kcal/mol, respectively.

The computational results are in general agreement with the observed performance of the $CpRuCl(PPh_3)_2$ catalyst: the reactions are much slower than those with the Cp* analogue, the regioselectivity does not exceed ca. 85:15 (in favor of the 1,5-regioisomer), and the yields are modest at best. Higher sensitivity of the catalysis to the steric demands of the azide substituent are also explained by this model: $\sigma$-coordination of the azide to the ruthenium atom via its N-1 nitrogen is a required event for the subsequent oxidative addition step, and the stability of the complex **PCA** (and the strength of this interaction) is directly affected by the size of the azide substituent.

Based on these results, we propose that the mechanism of the Ru(II)-catalyzed cycloaddition reactions of azides with alkynes involves an irreversible oxidative coupling, followed by a rate-determining reductive elimination. The DFT calculations demonstrate that the oxidative coupling step is, in essence, a nucleophilic attack of the coordinated alkyne on the terminal, electrophilic nitrogen of the coordinated azide. Both steric and electronic factors favor the pathway starting from the **PCA** activated complex species which leads to the 1,5-regioselectivity observed experimentally.

## Conclusion

A general catalytic system for the cycloaddition of azides with both internal and terminal alkynes is now available. After investigation of the catalytic activities of a series of ruthenium complexes, [Cp*RuCl] compounds emerged as the most efficient and regioselective catalysts. In the presence of the readily synthesized and air stable $Cp*RuCl(PPh_3)_2$ catalyst, a range of organic azides react with terminal alkynes containing a variety of functionalities, usually at elevated temperature, to give selectively 1,5-disubstituted triazole products. The Cp*RuCl(COD) catalyst exhibits higher activity and is particularly suitable for ambient temperature cycloadditions involving internal alkynes, aryl azides, and generally thermally labile reactants. Nevertheless, both catalysts exhibit excellent activity as well as chemo- and regioselectivity. Together with the CuAAC reaction, the new RuAAC process provides ready access to all $^1$H-1,2,3-triazole regioisomers.

Computational studies indicate that the [Cp*RuCl]-catalyzed reactions of azides with alkynes involve an irreversible oxidative coupling of azide and alkyne to give ruthenacycles, followed by a rate-determining reductive elimination. The regioselectivity is determined by the oxidative coupling step, which can also be viewed as a nucleophilic attack of the activated alkyne at the electrophilic terminal nitrogen of the azide.

**Acknowledgment.** This work was supported by the Skaggs Institute for Chemical Biology, the Scripps Research Institute, and Pfizer, Inc. (V.V.F.), and the Hong Kong Research Grant Council (G.J.; Z.L). We are grateful to Dr. J. C. Loren and Prof. K. B. Sharpless for stimulating discussions and advice.

**Supporting Information Available:** Experimental procedures, compound characterization data, X-ray crystallographic data, and details of computational studies. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0749993

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(56) Zhou, Y. B.; Ke, Z. F.; Zhao, C. Y. *Acta Chim. Sinica* **2006**, *64*, 2071.