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Selective Formation of 1,4-Disubstituted Triazoles from Ruthenium-Catalyzed Cycloaddition of Terminal Alkynes and Organic Azides: Scope and Reaction Mechanism

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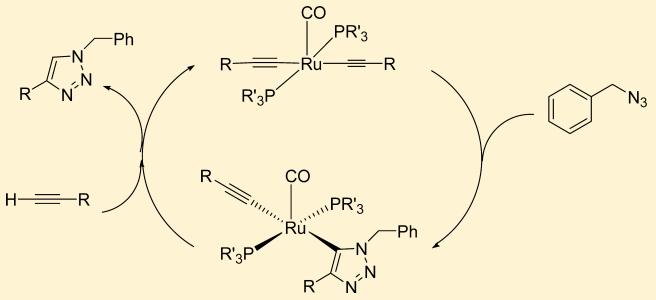
Supporting Information

ABSTRACT: The catalytic activity of a series of ruthenium complexes lacking cyclopentadienyl ligands has been evaluated for the cycloaddition of terminal alkynes and azides to give selectively 1,4-disubstituted 1,2,3-triazoles. The complex $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ was found to be an effective catalyst for the cycloaddition reactions. In the presence of $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$, primary and secondary azides reacted with a range of terminal alkynes containing various functionalities to selectively produce 1,4-disubstituted 1,2,3-triazoles. The ruthenium-catalyzed azide−alkyne cycloaddition appears to proceed via a Ru−acetylide species as the key intermediate, which undergoes formal cycloaddition with an azide to give a ruthenium triazolide complex. The 1,4-disubstituted 1,2,3-triazole product is generated by metathesis of the triazolide complex with a terminal alkyne. In support of the reaction mechanism, the acetylide complex $Ru(C{\equiv}CCMe_3)_2(CO)(PPh_3)_3$ reacts cleanly with benzyl azide to give a ruthenium triazolide complex, which reacts with excess *tert*-butylacetylene in the presence of PPh_3 to give 4-*tert*-butyl-1-benzyl-1,2,3-triazole and the diacetylide complex $Ru(C{\equiv}CCMe_3)_2(CO)(PPh_3)_3$. The mechanism is also supported by DFT calculations.



INTRODUCTION

1,3-Dipolar cycloaddition of azides and alkynes represents the most direct route to 1,2,3-triazoles.[1] The thermal cycloaddition reaction has been known for more than a century and was thoroughly studied by Huisgen and co-workers in the 1950s−1970s.[2] Although the reaction is highly exothermic, the cycloaddition involving unactivated substrates is often very slow, even at elevated temperature (80−120 °C for 12−24 h),[3] due to the high activation barrier (ca. 25−26 kcal/mol for reaction of methyl azide with propyne).[4] Moreover, a mixture of regioisomers is usually formed when an unsymmetrically substituted alkyne is involved.

The reaction rate and regiochemistry of the cycloaddition reaction can be drastically altered by metal catalysts. In 2002, the Meldal[5] and Fokin and Sharpless[6] groups independently reported Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC) to yield selectively 1,4-disubstituted 1,2,3-triazoles under mild conditions. As perhaps the most powerful click reaction to date, a wide range of applications of this reaction have been described in recent years, especially in the areas of organic synthesis, chemical biology, drug development, and materials sciences.[7] More recently, we[8] and others[9] have disclosed that (pentamethylcyclopentadienyl)ruthenium chloride complexes can effectively catalyze the facile cycloaddition of a wide range of azides and terminal alkynes (RuAAC) to afford regioselectively the complementary 1,5-disubstituted 1,2,3-triazoles. The system can also promote cycloaddition reactions of internal alkynes and azides. Applications of RuAAC, although not as widely as those of CuAAC, have also appeared in the literature.[10]

It is generally accepted that CuAAC involves copper−acetylide species as the key intermediates.[4,11,12] Since many transition-metal complexes can react with terminal alkynes to give acetylide complexes, one might expect that metal complexes other than those of copper could also catalyze azide−alkyne cycloaddition to yield selectively 1,4-disubstituted 1,2,3-triazoles. However, previous efforts in searching for efficient catalytic systems of noncopper metal complexes for the transformation have so far met with unsatisfactory results.[11] Recently, Meng et al. reported that charcoal impregnated with zinc was able to promote the cycloaddition of aryl azides and

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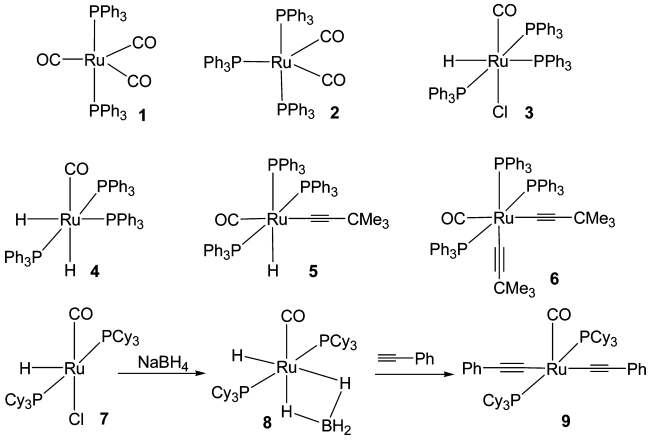
alkynes to give the corresponding 1,4-disubstituted 1,2,3-triazoles.[13]

During the course of our effort to develop ruthenium-mediated cycloaddition of azides and alkynes, we interestingly found that ruthenium(II) complexes lacking cyclopentadienyl ligands, such as $RuH_2(CO)(PPh_3)_3$, can catalyze the cycloaddition of terminal acetylenes and azides to give selectively 1,4-substituted triazole regioisomers,[14] rather than 1,5-disubstituted 1,2,3-triazoles as in the case of the Cp*RuCl system. In this paper, we will report the results of our detailed study on the reactions catalyzed by a variety of ruthenium(II) complexes lacking cyclopentadienyl ligands, including the scope of the catalytic reactions and mechanistic aspects. Through isolation and characterization of active reaction intermediates and DFT studies, we have been able to elucidate the reaction mechanism of the click reaction.

RESULTS AND DISCUSSION

Selection of Catalysts. In our effort to find efficient ruthenium catalysts for the cycloaddition of azides and terminal alkynes to give selectively 1,4-disubstituted 1,2,3-triazoles, the catalytic properties of several ruthenium complexes lacking cyclopentadienyl ligands were examined. The structures of these ruthenium complexes are shown in Scheme 1. Most of the complexes (**1**−**7**) are known. The new complexes $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ (**8**) and $Ru(C{\equiv}CPh)_2(CO)(PCy_3)_2$ (**9**) can be readily prepared from $RuHCl(CO)(PCy_3)_2$ (**7**). Treatment of **7** with $NaBH_4$ produced **8**, which was converted to **9** upon treatment with 5 equiv of HC≡CPh. It is possible that the reaction of **8** with $NaBH_4$ to give **9** may give boron-containing coproducts, although our attempts to identify boron-containing coproducts were unsuccessful. Excess HC≡CPh is crucial for the success in the preparation of complex **9**. For example, the reaction of $RuH(BH_4)(CO)(PCy_3)_2$ with 3 equiv of HC≡CPh produced a complicated mixture, including unreacted **8**, and complex **9** could not be detected by in situ NMR in this case.

Scheme 1. Structures of Complexes 1−9



The catalytic properties of these ruthenium complexes were investigated using the cycloaddition of benzyl azide and phenylacetylene as the prototypical reaction. In the screening experiments, a mixture of benzyl azide (**10a**) and phenylacetylene (**11a**) (1/1.5 or 1/2 equiv) in THF was heated at 80 °C for a period of time in the presence of 5 mol % of a ruthenium complex (with respect to the limiting reagent benzyl azide). The resulting reaction mixture or the isolated product was then analyzed by ^1H NMR. Results of the catalytic reactions are given in Table 1.

The tricarbonyl Ru(0) complex $Ru(CO)_3(PPh_3)_2$ (**1**) is completely inactive (entry 1). Other complexes show varied activities, depending on the ligand environment around the metal center, all giving selectively 1,4-disubstituted triazole **12a**. The catalytic activity of the dicarbonyl Ru(0) complex $Ru(CO)_2(PPh_3)_3$ (**2**) is very poor, and the reaction only has a conversion of the azide at ca. 26% after the reaction mixture was refluxed in THF for 4 h (entry 2). The Ru(II) chloro complex $RuHCl(CO)(PPh_3)_3$ (**3**) is marginally active (entry 3). The dihydride complex $RuH_2(CO)(PPh_3)_3$ (**4**) is more active; 99% conversion of the azide was achieved in 2 h, and the expected triazole **12a** was obtained in 79% yield (entry 4).[14] The acetylide complexes $RuH(C{\equiv}CCMe_3)(CO)(PPh_3)_3$ (**5**) and $Ru(C{\equiv}CCMe_3)_2(CO)(PPh_3)_3$ (**6**) have catalytic activity similar to that of $RuH_2(CO)(PPh_3)_3$ (entries 5 and 6), giving 1,4-disubstituted 1,2,3-triazole in ca. 63% yield after the reaction mixture was refluxed in THF for 1.5 h.

Interestingly, when PPh_3 in $RuHCl(CO)(PPh_3)_3$ is replaced with the bulkier and more electron-rich ligand PCy_3, the catalytic reactivity increased significantly. Thus, $RuHCl(CO)(PCy_3)_2$ (**7**) is much more effective than $RuHCl(CO)(PPh_3)_3$, giving 1,4-disubstituted 1,2,3-triazole in ca. 51% yield after the reaction mixture was refluxed in THF for 1 h (entry 7). The most effective catalytic precursor found in this study is the hydride complex $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ (**8**). In the presence of 5 mol % of the complex, the reaction is completed within 1 h to give product **12a** in 89% yield (entry 8). Reduction in the loading of **8** from 5 to 2 mol % does not affect the yield of the product (entry 10). The reaction works well in aprotic solvents such as THF, benzene, CH_3CN, and dioxane and the protic solvent CH_3OH (entries 10−14). When the ratio of **10a** to **11a** was changed from 2 to 1.5, the reaction yield was affected negatively (entry 15). It is noted that the catalytic reaction could not proceed at room temperature, however. The diacetylide complex $Ru(C{\equiv}CPh)_2(CO)(PCy_3)_2$ (**9**) has a catalytic activity similar to that of $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ (**8**) (entries 9 and 16). The result is expected, because $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ (**8**) can react with terminal alkyne to give the diacetylide complex $Ru(C{\equiv}CPh)_2(CO)(PCy_3)_2$ (**9**), as described in Scheme 1.

Scope of Catalytic Reactions. The most active catalysts are $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ (**8**) and $Ru(C{\equiv}CPh)_2(CO)(PCy_3)_2$ (**9**). The hydride complex **8** has an activity similar to that of **9** and can be prepared more conveniently. Moreover, the reactions of the various alkynes and azides catalyzed by complex **9** will inevitably produce the byproduct triazole **12a**. Therefore, complex **8** was used in our subsequent investigations on the scope of the cycloaddition reactions. These reactions were carried out in THF using 2 mol % of the hydride complex **8** as the catalytic precursor. The products were isolated after a mixture of an azide and an alkyne was heated at 80 °C (oil bath temperature) for 1.5 h. The structures of the triazole products are fully consistent with their ^1H and $^{13}C\{^1H\}$ NMR and HRMS data. In addition, the structure of **12l** has been confirmed by single-crystal X-ray diffraction studies (see the Supporting Information).

The results of the catalytic reactions are shown in Table 2. The hydride complex **8** efficiently catalyzed the cycloaddition of benzyl azide (**10a**) with aryl- and heteroarylacetylenes (entries 1−5). The presence of a coordinating amine or pyridyl

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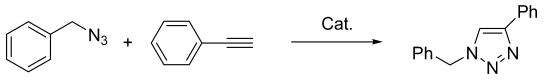
Table 1. Cycloaddition of Benzyl Azide and Phenylacetylene Catalyzed by Ruthenium Complexes[a]



10a 11a 12a

entry	cat.	solvent	S/C	time (h)	conversn (%)[b]	yield (%)[c]
1	$Ru(CO)_3(PPh_3)_2$ (**1**)	THF	20[d]	4	0	0
2	$Ru(CO)_2(PPh_3)_3$ (**2**)	THF	20[d]	4	26	ND[e]
3	$RuHCl(CO)(PPh_3)_3$ (**3**)	THF	20	2	51	31
4	$RuH_2(CO)(PPh_3)_3$ (**4**)	THF	20	2	99	79[f]
5	$RuH(C{\equiv}CCMe_3)(CO)(PPh_3)_3$ (**5**)	THF	20	1.5	100	63
6	$Ru(C{\equiv}CCMe_3)_2(CO)(PPh_3)_3$ (**6**)	THF	20	1.5	100	63
7	$RuHCl(CO)(PCy_3)_2$ (**7**)	THF	20	1	100	51
8	$RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$) (**8**)	THF	20	1	100	89
9	$Ru(C{\equiv}CPh)_2(CO)(PCy_3)_2$ (**9**)	THF	20[d]	1	100	92
10	**8**	THF	50	1.5	100	89
11	**8**	CH_3CN	50	1.5	100	87
12	**8**	dioxane	50	1.5	100	83
13	**8**	CH_3OH	50	1.5	100	88
14	**8**	benzene	50	1.5	100	88
15	**8**	THF	50[d]	1.5	97	81
16	$Ru(C{\equiv}CPh)_2(CO)(PCy_3)_2$ (**9**)	THF	50	1.5	100	95

[a]General reaction conditions: **10a** (0.5 mmol), **11a** (1.0 mmol), 80 °C, 0.5 mL of solvent was added unless otherwise noted. [b]The conversions were estimated on the basis of the integration of triazole and unreacted azide in ^{1}H NMR spectra. [c]On the basis of azide (**10a**) used, determined by ^{1}H NMR integration using $PhSiMe_3$ as the internal standard. [d]**10a** (0.5 mmol) and **11a** (0.75 mmol) were used. [e]ND = not determined. [f]A similar result was obtained when the reaction was carried out in 2.5 mL of THF.

group at the meta position does not affect the reactivity appreciably, and the products **12d,e** were obtained in 72% and 86% yields, respectively (entries 4 and 5). However, 2-ethynylpyridine whose N atom is in the position ortho to the alkyne group, could not react with benzyl azide to afford the corresponding product. The cycloaddition of **10a** with polyaromatic alkynes, such as naphthalenylacetylene (**11f**), phenanthrenylacetylene (**11g**), and ferrocenylacetylene (**11h**), proceeded smoothly, giving the corresponding triazoles in 87−93% yields (entries 6−8). The reaction of **10a** with the alkenyl alkyne **11i** gave the product **12i** in 62% yield (entry 9). Aliphatic alkynes containing an OH or CN group also readily reacted with **10a**, and the yields of the products **12j,k** are comparable to those from the reactions of aromatic alkynes (entries 10 and 11). The reaction of benzyl azide with 3-butyn-1-ol, which has a shorter linker between the alkyne and hydroxyl functional groups, afforded the cycloaddition product in 30% yield only.

In all of the above examples, the reactions only produce 1,4-disubstituted triazoles. Interestingly, the reaction of **10a** with the alkynes **11l,m**, substituted with a strong electron-withdrawing sulfonyl or carboxyl group, afforded respectively the 1,4-disubstituted 1,2,3-triazoles **12l,m** in 72% and 71% yields (entries 12 and 13) together with a minor amount of the corresponding 1,5-disubstituted 1,2,3-triazole products (in 24% and 21% isolated yields, respectively). When cyclohexyl azide (**10b**) was allowed to react with phenylacetylene (**11a**), the triazole product **12n** was obtained in excellent yield (92%, entry 14). However, when sterically hindered *tert*-butylacetylene was allowed to react with **10a**, the product 4-*tert*-butyl-1-benzyl-1*H*-1,2,3-triazole (**12o**) was obtained in a low yield of 24% (entry 15). Low yields (less than 15%) were also observed in the cycloaddition reactions of phenyl azide or *p*-tolyl azide with phenylacetylene (entry 16). Finally, the hydride complex **8** failed to catalyze the cycloaddition of azides and internal alkynes under the typical reaction conditions.

The results shown in Table 1 clearly indicate the potential value of the Ru-AAC, even though the advantage of using the ruthenium catalyst in place of a conventional copper catalyst was not demonstrated at this stage.

Mechanism Considerations. It is generally believed that CuAAC involves Cu−acetylide species of varying nuclearity as the key intermediate, which reacts with an azide to give a Cu(triazolyl) intermediate. The 1,4-disubstituted 1,2,3-triazole product is generated by protolysis of the Cu−C(triazolyl) bond. The mechanism is supported by DFT calculations.[15] A mononuclear NHC copper triazolide complex has been isolated from the reaction of azidodi-4-tolylmethane with a copper NHC acetylide in a previous study.[16] The triazolide complex reacts quantitatively with acetic acid to give the expected triazole product. The selectivity of the reactions catalyzed by ruthenium complexes in the present study is the same as that of CuAAC. Therefore, a catalytic cycle involving ruthenium acetylide can be similarly proposed to explain the regioselectivity.

In agreement with the involvement of ruthenium acetylide species in the catalytic reactions, we found that ruthenium acetylide complexes such as $RuH(C{\equiv}CCMe_3)(CO)(PPh_3)_3$ (**5**), $Ru(C{\equiv}CCMe_3)_2(CO)(PPh_3)_3$ (**6**), and $Ru(C{\equiv}CPh)_2(CO)(PCy_3)_2$ (**9**) are all catalytically active. Since reactions of ruthenium hydride complexes with terminal alkynes to give acetylide complexes are well precedented, it is reasonable to assume that acetylide species are generated in situ and involved in reactions using hydride complexes such as $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ (**8**), $RuH_2(CO)(PPh_3)_3$ (**4**), $RuHCl(CO)(PCy_3)_2$ (**7**), and $RuHCl(CO)(PPh_3)_3$ (**3**). In fact, Wakatsuki et al have reported that $RuH_2(CO)(PPh_3)_3$ reacts with excess $HC{\equiv}CCMe_3$ to give first $RuH(C{\equiv}CCMe_3)(CO)(PPh_3)_3$ (**5**) and then $Ru(C{\equiv}CCMe_3)_2(CO)$-

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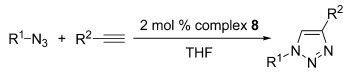
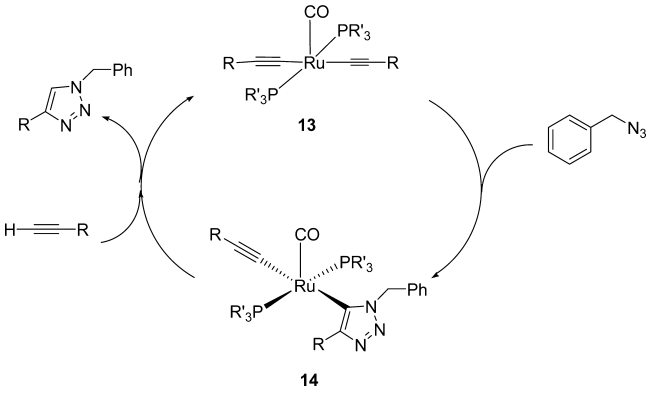
Table 2. Cycloaddition of Azides and Various Alkynes Using Complex 8 as the Catalyst[a]



Entry	Azides	Alkynes	Products	Yields (%)[b]
1	10a	11a	12a	87
2	10a	11b	12b	92
3	10a	11c	12c	95
4	10a	11d	12d	72
5	10a	11e	12e	86
6	10a	11f	12f	87
7	10a	11g	12g	93
8	10a	11h	12h	91
9	10a	11i	12i	62
10[c]	10a	11j	12j	88
11[c]	10a	11k	12k	79
12	10a	11l	12l	72[d]
13	10a	11m	12m	71[e]
14	10b	11a	12n	92
15	10a	11n	12o	24
16	10c	11a	12p	<15

[a]Reaction conditions: azide (0.5 mmol), alkyne (1.0 mmol), catalyst **8** (0.01 mmol), 80 °C, 1.5 h, 0.5 mL of THF unless otherwise noted. [b]Isolated yields. [c]0.025 mmol of catalyst **8** was used. [d]24% yield of 1,5-product was isolated. [e]21% yield of 1,5-product was isolated.

Scheme 2. Proposed Catalytic Cycle of 1,4-RuAAC



$(PPh_3)_3$ (**6**), which can dissociate a PPh_3 ligand readily in solution.[17] We have demonstrated that the five-coordinate bis-alkynyl complex $Ru(C{\equiv}CPh)_2(CO)(PCy_3)_2$ (**9**) was produced from the reaction of $HC{\equiv}CPh$ with $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ (**8**). It has also been reported that the five-coordinate bis-alkynyl complexes $M(C{\equiv}CPh)_2(CO)(P^iPr_3)_2$ (M = Os, Ru) were produced from the reactions of $HC{\equiv}CPh$ with $MH(\eta^2\text{-}BH_4)(CO)(P^iPr_3)_2$.[18] Furthermore, we have found experimentally that $RuH(C{\equiv}CCMe_3)(CO)(PPh_3)_3$ (**5**) and $Ru(C{\equiv}CCMe_3)_2(CO)(PPh_3)_3$ (**6**) have a catalytic activity similar to that of $RuH_2(CO)(PPh_3)_3$, and $Ru(C{\equiv}CPh)_2(CO)(PCy_3)_2$ has a catalytic activity similar to that of $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$.

On the basis of the above observations, we propose that the active species in the reactions catalyzed by $RuH_2(CO)(PPh_3)_3$ (**4**), $RuH(C{\equiv}CCMe_3)(CO)(PPh_3)_3$ (**5**), $Ru(C{\equiv}CCMe_3)_2(CO)(PPh_3)_3$ (**6**), and $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ (**8**) are bis-acetylide complexes of the type $Ru(C{\equiv}CR)_2(CO)(PR'_3)_2$ (**13**). A plausible catalytic cycle is illustrated in Scheme 2 using benzyl azide as the substrate. The diacetylide undergoes a formal cycloaddition reaction with an azide to give the Ru(triazolyl) complex **14**. Metathesis of the Ru−C bond with a terminal alkyne gives the 1,4-disubstituted 1,2,3-triazole product and regenerates the acetylide species **13**.

Model Stoichiometric Reactions. In an effort to detect the active species involved in the reaction catalyzed by $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ (**8**), we have examined the ^{31}P NMR spectrum of the reaction mixture of phenylacetylene and benzyl azide (in 2/1 molar ratio) in benzene-d_6 catalyzed by complex **8** (5 mol %). The in situ $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture (after heating at 80 °C for 30 min) indicates that **8** has been consumed completely and the mixture contains at least four phosphorus-containing species. Unfortunately, it is difficult to separate/isolate or identify these phosphorus-containing species from the mixture. In another approach to get reaction

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Scheme 3. Reaction of Complex 6 with Benzyl Azide To Form Complex 15, Which Further Reacts with *tert*-Butylacetylene To Give Complex 6

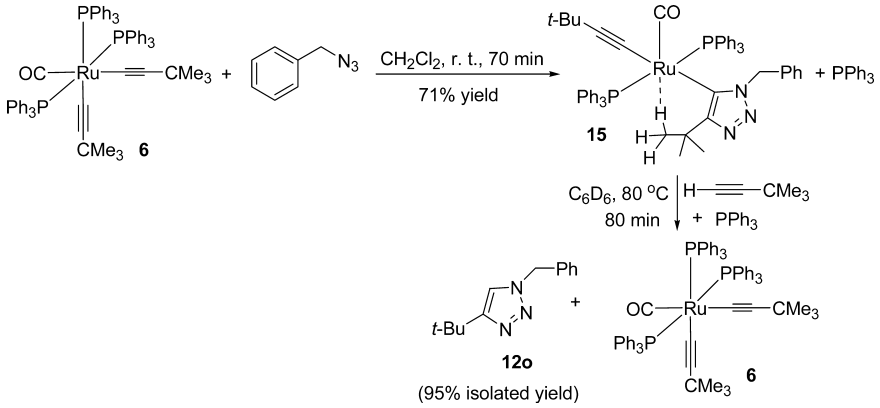

Table 3. Crystal Data and Structure Refinement Details for $15{\cdot}2C_6H_6$

empirical formula	$C_{68}H_{67}N_3OP_2Ru$
formula wt	1105.26
wavelength	0.710 73 Å
cryst syst	triclinic
space group	$P\bar{1}$
unit cell dimens	
a	10.9419(14) Å
b	12.9169(17) Å
c	21.300(3) Å
α	84.167(2)°
β	76.817(2)°
γ	80.056(2)°
V	2881.0(7) Å^3
Z	2
calcd density	1.274 Mg/m^3
cryst size	0.20 × 0.18 × 0.15 mm^3
θ range for data collecn	1.60–26.00°
no. of rflns collected	28 136
no. of indep rflns	11 189 (R(int) = 0.0363)
completeness to θ = 25.00°	99.1%
no. of data/restraints/params	11 189/0/682
goodness of fit on F^2	0.993
final R indices ($I > 2\sigma(I)$)	R1 = 0.0358, wR2 = 0.0716
largest diff peak and hole	0.532 and −0.265 e Å^{-3}

Table 4. Selected Bond Lengths (Å) and Angles (deg) in 15

Bond Distances			
Ru(1)–C(20)	1.790(2)	Ru(1)–C(14)	2.061(2)
Ru(1)–C(1)	2.125(2)	Ru(1)–P(1)	2.3734(6)
Ru(1)–P(2)	2.4146(7)	O(1)–C(20)	1.161(3)
C(1)–C(2)	1.395(3)	N(1)–C(2)	1.362(3)
N(1)–N(2)	1.309(2)	N(2)–N(3)	1.363(2)
N(3)–C(1)	1.367(2)	N(3)–C(7)	1.459(3)
C(2)–C(3)	1.500(3)	C(14)–C(15)	1.196(3)
C(15)–C(16)	1.487(3)		
Bond Angles			
C(20)–Ru(1)–C(14)	97.38(9)	C(20)–Ru(1)–C(1)	98.19(9)
C(14)–Ru(1)–C(1)	164.13(8)	C(20)–Ru(1)–P(1)	86.21(7)
C(14)–Ru(1)–P(1)	87.98(6)	C(1)–Ru(1)–P(1)	89.99(6)
C(20)–Ru(1)–P(2)	92.61(7)	C(14)–Ru(1)–P(2)	85.18(6)
C(1)–Ru(1)–P(2)	97.15(6)	P(1)–Ru(1)–P(2)	172.853(19)
N(3)–C(1)–Ru(1)	135.25(15)	C(2)–C(1)–Ru(1)	123.57(15)
O(1)–C(20)–Ru(1)	178.2(2)	C(15)–C(14)–Ru(1)	175.4(2)
C(14)–C(15)–C(16)	177.9(3)	N(3)–C(1)–C(2)	100.89(17)
N(2)–N(3)–C(1)	113.14(17)	N(1)–N(2)–N(3)	106.46(16)
N(2)–N(1)–C(2)	108.60(17)	N(1)–C(2)–C(1)	110.92(19)

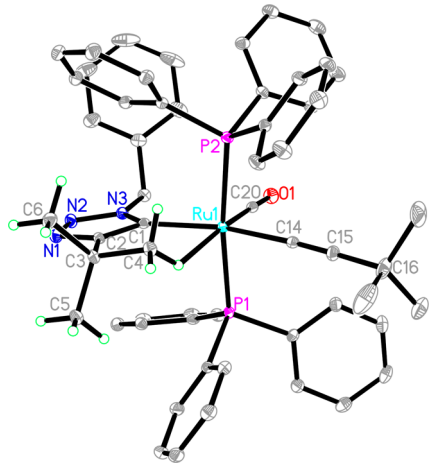

Figure 1. ORTEP diagram of complex **15**. The hydrogen atoms on Ph and C≡CCMe$_3$ are omitted for clarity.

intermediates involved in the catalytic reaction, we have collected the in situ $^{31}P\{^1H\}$ NMR spectra of the reaction of the complex Ru(C≡CPh)$_2$(CO)(PCy$_3$)$_2$ (**9**) with benzyl azide. The ^{31}P NMR showed that the signal of complex **9** disappeared after heating at 80 °C for 30 min, and the mixture contained several phosphorus-containing species, including those with the same ^{31}P chemical shifts as those generated in the catalytic reactions. When a mixture of complex **9** (0.005 mmol) and benzyl azide (0.01 mmol) in benzene (0.2 mL) was stirred at room temperature for 5 min under N_2, the ESI-HRMS of the reaction mixture (diluted with methanol) showed an ion peak at m/z 1026.5156 (see the Supporting Information), which is assignable to the $[M + H]^+$ peak of the expected intermediate, the triazolide complex Ru(C≡CPh)[(C$_2$N$_3$)(CH$_2$Ph)Ph](CO)(PCy$_3$)$_2$ (**14′**).

Solid evidence for the involvement of acetylide and triazolide species in the catalytic reactions comes from the isolation and characterization of the related species from the reaction of the

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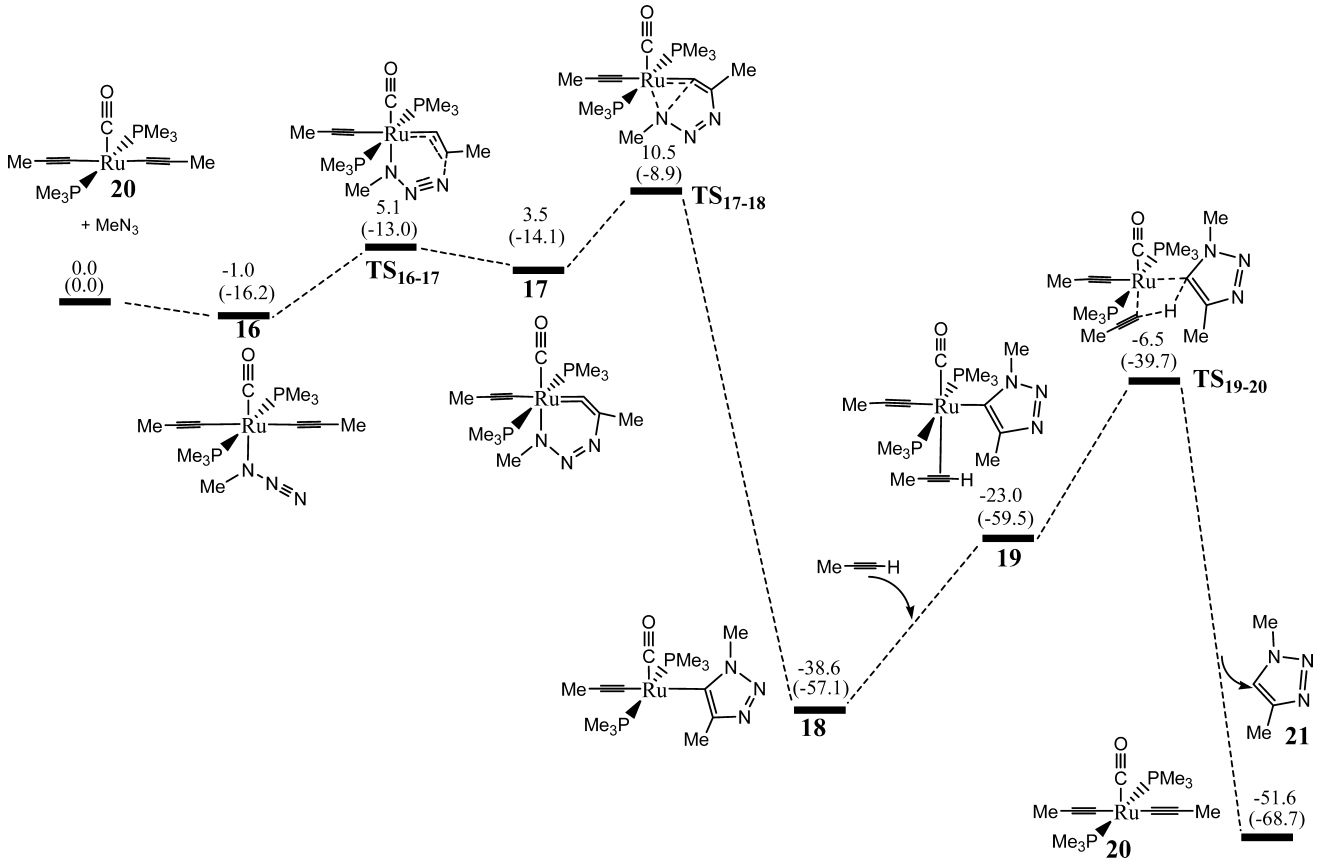

Figure 2. Energy profile calculated for the reaction mechanism proposed in Scheme 2 for the ruthenium-catalyzed cycloaddition of alkynes with azides. The relative free energies and electronic energies (in parentheses) are given in kcal/mol.

acetylide complex $Ru(C{\equiv}CCMe_3)_2(CO)(PPh_3)_3$ (**6**)[17] with benzyl azide. In CH_2Cl_2, benzyl azide reacted readily with the complex $Ru(C{\equiv}CCMe_3)_2(CO)(PPh_3)_3$ (**6**) to afford the ruthenium triazolide complex **15**. The reaction is essentially complete at room temperature in 70 min (Scheme 3). Further reaction of complex **15** with benzyl azide to afford a ditriazolide complex was not observed. It is noted that triazolide complexes have been previously isolated from reactions of azides with NHC copper(I)[16] and gold(I) (Cu-catalyzed)[19] acetylide complexes.

The structure of complex **15** has been confirmed by X-ray diffraction. A brown single crystal suitable for a single-crystal X-ray diffraction study was obtained by slow diffusion of hexane into the benzene solution of complex **15**. The crystal data and refinement details are given in Table 3, and selected bond lengths and bond angles of complex **15** are shown in Table 4. Figure 1 shows the X-ray structure of complex **15**. The coordination geometry of **15** is a distorted octahedron with two *trans*-disposed PPh_3 ligands. The triazolyl ligand and the alkynyl ligand are *trans* to each other. The Ru−C(triazolyl) bond length (2.125(2) Å) is slightly longer than the Ru−C(vinyl) bond in $RuCl(PhC{=}CHPh)(CO)(PPh_3)_2$ (2.03 (1) Å).[20] Another interesting feature of the structure is that it contains an agostic Ru···H−C interaction involving one of the hydrogens of the CMe_3 group of the triazolyl ligand with a Ru···H distance of 2.0998 Å.

The ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR and MS spectroscopic data are in agreement with the solid-state structure. The ^1H NMR spectrum of complex **15** shows the ^{t}Bu resonances at 1.13 and 0.63 ppm and the methylene resonance of the benzyl group at 4.38 ppm, all as singlets. The $^{13}C\{^1H\}$ spectrum exhibited resonances of the tertiary carbons of ^{t}Bu at 31.5 and 30.1 ppm and resonances of the methyl groups at 32.0 and 28.4 ppm. The methylene resonance of the benzyl group of the triazolyl ligand was observed at 53.6 ppm, and the resonances of the two carbon atoms of the alkynyl group appear at 67.8 (singlet) and 101.9 ppm (triplet). A triplet signal of the CO ligand was observed at 208.3 ppm. The $^{31}P\{^1H\}$ NMR spectrum displayed only a singlet at 33.8 ppm, as expected. The mass spectrum of complex **15** showed an ion peak of the cation (**15** + H^+) at m/z 950.2937 (calcd 950.3055).

The triazole product could be generated by a metathesis reaction of the triazolide complex with a terminal alkyne. To test this idea, we have treated complexes **15** with excess of *tert*-butylacetylene in the presence of PPh_3. When complex **15** was allowed to react with *tert*-butylacetylene and PPh_3 in deuterated benzene at 80 °C for 80 min, complex **6** was produced along with the triazole product **12o**, which was isolated in 95% yield (Scheme 3). The reaction of complex **15** with excessive *tert*-butylacetylene and PPh_3 became complicated when the reaction time was prolonged, likely due to further reaction of complex **6** with *tert*-butylacetylene. If PPh_3 was not added to the reaction mixture, the reaction gave a mixture of phosphorus-containing products, which could not be separated and identified, and complex **6** was not produced, as indicated by in situ NMR.

The triazolide complex **15** was found to be an active catalyst for cycloaddition of **10a** with **11a**, giving 99% of conversion of the azide and 67% yield of **12a** after a reaction mixture in the presence of 2 mol % of the complex was refluxed in THF for

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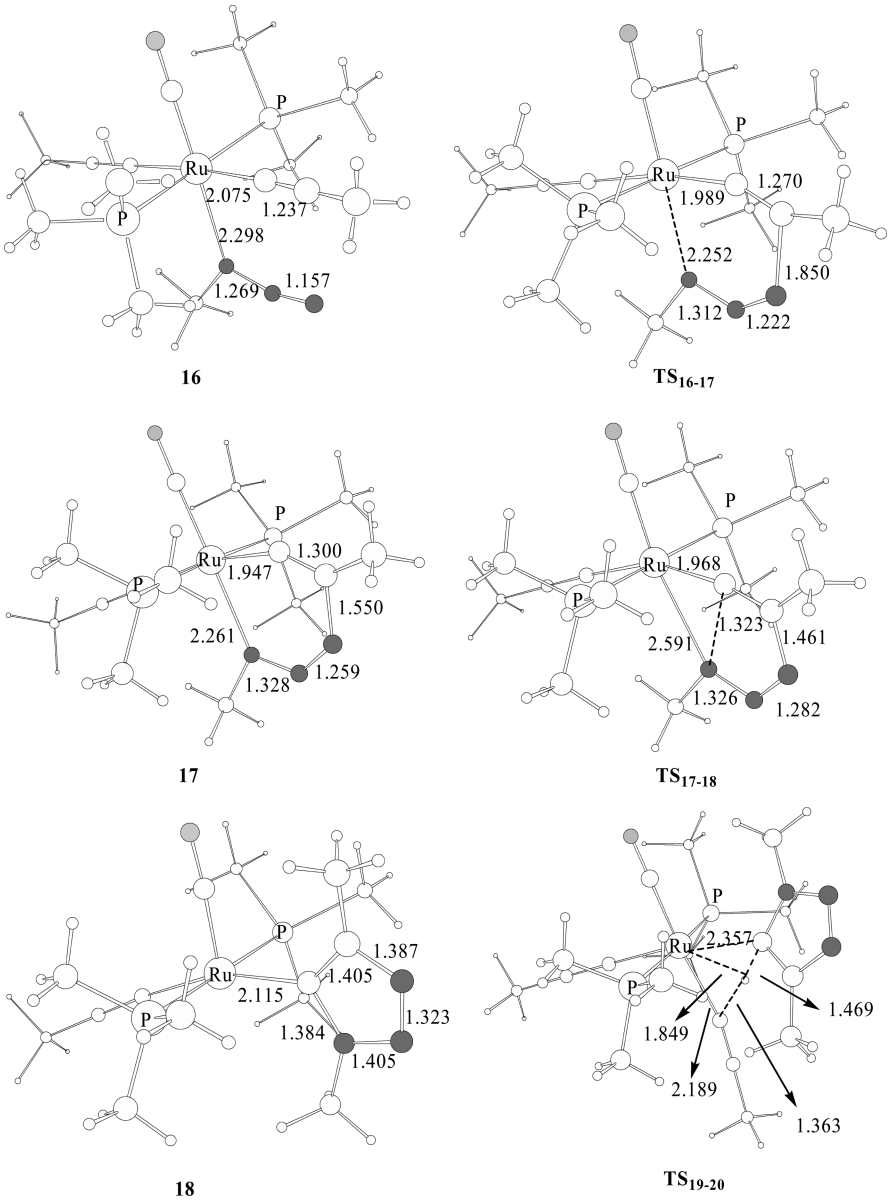

Figure 3. Selected structural parameters (Å) calculated for important species shown in Figure 2.

1.5 h. The observation confirms the intermediacy of triazolide complexes in the catalytic cycle.

DFT Studies. The experimental observations strongly suggest that ruthenium acetylide intermediates are involved in the catalytic cycles. However, several questions could not be easily defined experimentally. For example, does the coupling of an acetylide ligand and an azide involve coordinated azide or free azide? Is triazole released through direct metathesis or oxidation addition of C−H bond of alkynes? Why is 1,4-disubstituted triazole formed preferentially? To answer these questions, density functional theory (DFT) calculations were carried out.

We first examined the energetics associated with the mechanism proposed in Scheme 2, which gives the 1,4-disubstituted triazole products observed experimentally. In the theoretical study, PMe_3 was used as the model phosphine and methyl azide and propyne were used as the model organic substrates. We first studied the reaction pathway starting with the reaction of the model complex $Ru(C{\equiv}CMe)_2(CO)(PMe_3)_2$ (**20**) with methyl azide to give azide-coordinated complex **16**, in which the azide coordinates to the metal center via the alkylated nitrogen atom. Figure 2 gives the energy profile calculated for the proposed mechanism. Figure 3 gives the structures calculated for those species involved. The reaction of $Ru(C{\equiv}CMe)_2(CO)(PMe_3)_2$ (**20**) with methyl azide to give **16** was calculated to be thermodynamically favorable by 1.0 kcal/mol. From **16**, oxidative coupling of the coordinated methyl azide and one of the acetylide ligands leads to the formation of the six-membered ruthenium vinylidene intermediate **17**. An amide migration in **17** can then occur to give the ruthenium triazolide complex **18** via the transition state $\mathbf{TS_{17\text{-}18}}$. The overall barrier leading to the formation of **18** via **16** is 10.5 kcal/mol. Finally, the ruthenium triazolide complex **18** undergoes a metathesis reaction with propyne via the four-centered transition state $\mathbf{TS_{19\text{-}20}}$ (Figure 3) to give the 1,4-dimethyl-1,2,3-triazole product and to regenerate the catalyst precursor complex. Four-centered transition states were also found in metathesis reactions of many other late-transition-

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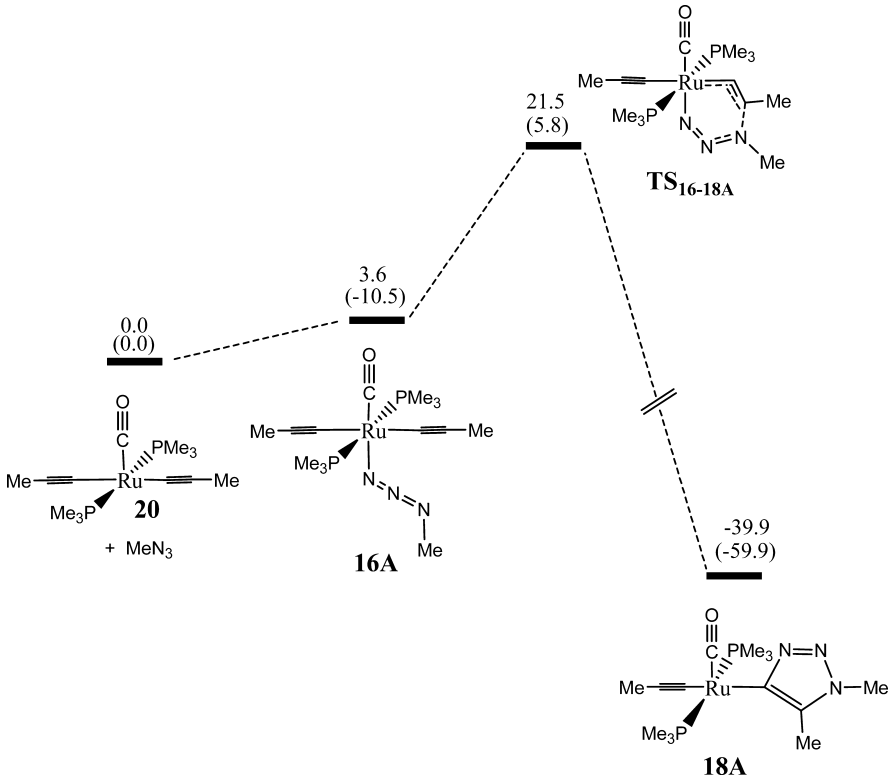

Figure 4. Energy profile calculated for the path that can lead to the formation of 1,5-dimethyl-1,2,3-triazole. The relative free energies and electronic energies (in parentheses) are given in kcal/mol.

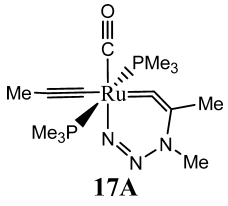

Figure 5. Structure of **17A**.

metal complexes.[21] The rate-determining step is the metathesis reaction, consistent with the experimental result that complex **15**, theoretically modeled by **18**, can be isolated.

We then studied the reaction pathway involving complex **16A**, in which the azide coordinates to the metal center via the terminal nitrogen atom. When methyl azide coordinates to the metal center via the terminal nitrogen atom, one would expect that the reactions would afford the 1,5-disubstituted triazole products. Figure 4 gives the energy profile calculated for the coupling between the terminal N coordinated methyl azide ligand and one of the acetylide ligands in **16A**. The terminal N coordinated complex **16A** is less stable than the methyl bonded N coordinated complex **16** by 4.6 kcal/mol. The overall barrier leading to the formation of **18A** via **16A** is 21.5 kcal/mol, significantly higher than that leading to the formation of **18** via **16** (10.5 kcal/mol). These results are consistent with the experimental observation that 1,5-disubstituted triazole products were not observed.

Two factors contribute to the preference for the acetylide−methyl azide coupling from **16** over from **16A**. **16** is more stable than **16A**, since the methyl-bonded nitrogen in the methyl azide binds better with the metal center than the terminal nitrogen does. The acetylide−methyl azide coupling from **16** initially gives the metal-containing six-membered-ring intermediate **17** (Figures 2 and 3). The Lewis structure drawn for **17** shown in Figure 2 indicates that the N═N bond conjugates well with the C═C bond. The existence of such an intermediate lends stability to the immediately followed transition state $\mathbf{TS_{17\text{-}18}}$. When the acetylide−methyl azide coupling from **16A** is considered, no corresponding intermediate can be located. If it existed, the corresponding intermediate would have the Lewis structure **17A** shown in Figure 5. One can see that the N═N bond in **17A** does not conjugate with the C═C bond, explaining its instability found in the calculations.

We also calculated the paths involving direct coupling (cycloaddition) between one of the acetylide ligands and free methyl azide. The calculation results are shown in Figures 6 and 7. As expected, the two direct coupling paths have similar reaction barriers (ca. 29.6 kcal/mol). However, they are all higher than those calculated via methyl azide coordinated intermediates (10.5 kcal/mol in Figure 2 and 21.5 kcal/mol in Figure 4). The results clearly indicated that the two direct coupling paths to give triazolide intermediates are much more difficult than the paths via methyl azide coordinated intermediates and that the reaction pathway shown in Figure 2 is the most favorable one.

Overall, the reaction pathway shown in Figure 2 is similar to that proposed for the Cu catalysis. However, there are subtle differences in the computed reaction profiles of the two systems. The reaction barrier (6.1 kcal/mol) for the formation of the six-membered ruthenium vinylidene intermediate **17** from acetylide complex **16** is significantly lower than that for the corresponding step in the copper system (17 kcal/mol for mononuclear copper acetylide and 10.5−12.9 kcal/mol for dinuclear copper complexes).[15a] The reaction barrier (7.0 kcal/mol) for the formation of ruthenium triazolide complex **18**

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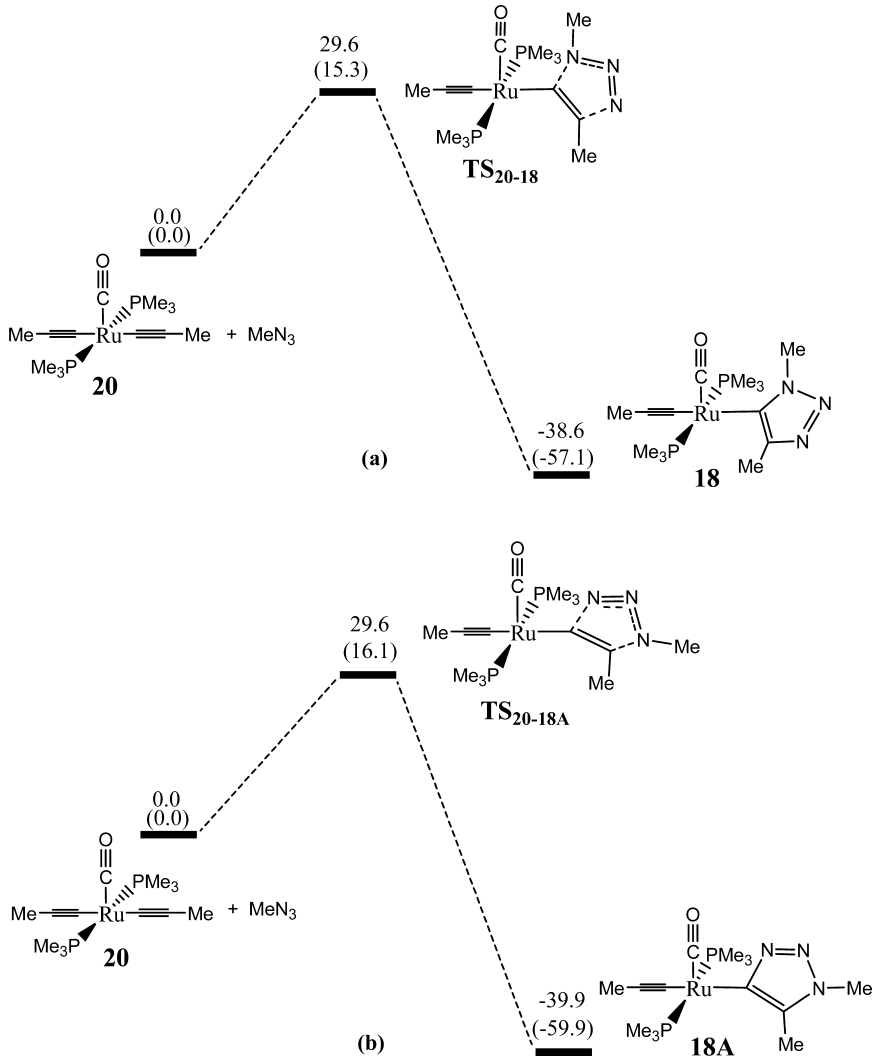

Figure 6. Energy profiles calculated for direct coupling between the acetylide ligand and methyl azide that can lead to the formation of 1,4-dimethyl-1,2,3-triazole (a) and 1,5-dimethyl-1,2,3-triazole (b). The relative free energies and electronic energies (in parentheses) are given in kcal/mol.

from **17** is significantly higher than that for the corresponding step in the copper system (3.2 kcal/mol for mononuclear copper acetylide).[15a] Furthermore, we propose that the triazole product is formed from the metathesis reaction of the ruthenium triazolide complex **18** with alkyne, while the 1,2,3-triazole product was thought to be generated by protolysis of cupper triazolide complexes.[4,11,12]

■ CONCLUSION

The catalytic activity of a series of ruthenium complexes lacking cyclopentadienyl ligands has been evaluated for the cycloaddition of terminal alkynes and azides to give selectively 1,4-disubstituted 1,2,3-triazoles. Complexes such as RuH(η^2-BH_4)(CO)(PCy_3)$_2$ and Ru(C≡CPh)$_2$(CO)(PCy_3)$_2$ were found to be the most effective catalysts for the cycloaddition reactions. In the presence of RuH(η^2-BH_4)(CO)(PCy_3)$_2$, primary and secondary azides reacted with a range of terminal alkynes to produce selectively 1,4-disubstituted 1,2,3-triazoles. Both experimental and computational studies indicate that the Ru-catalyzed reactions of azides with terminal alkynes involve Ru−acetylide species as the key intermediate, which undergoes formal cycloaddition with azide to give a Ru(triazolyl) complex through an alkyne/azide species in which the azide coordinates to the metal center via the internal nitrogen atom. The ruthenium triazolide complex undergoes a metathesis reaction with a terminal alkyne via a four-centered transition state to give the 1,4-disubstituted 1,2,3-triazole product and to regenerate the catalyst precursor complex. The metathesis reaction appears to be the rate-determining step.

■ EXPERIMENTAL SECTION

All manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques, unless otherwise stated. Solvents were distilled under nitrogen from sodium−benzophenone (hexane, diethyl ether, THF, benzene) or calcium hydride (dichloromethane). The organic azides **10a,b**,[22] Ru(CO)$_3$(PPh_3)$_2$ (**1**),[23] Ru(CO)$_2$(PPh_3)$_3$ (**2**),[24] RuHCl(CO)(PPh_3)$_3$ (**3**),[25] RuH$_2$(CO)(PPh_3)$_3$ (**4**),[25] RuH(CO)(C≡CBu-*t*)(PPh_3)$_3$ (**5**),[17] Ru(CO)(C≡CBu-*t*)$_2$(PPh_3)$_3$ (**6**),[17] and RuHCl(CO)(PCy_3)$_2$ (**7**)[26] were prepared according to literature methods. Alkynes **11a−m** and other chemicals were purchased from Aldrich. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ). Mass spectra were collected on a MALDI Micro MX mass spectrometer (MALDI) or an API QSTAR XLSystem (ESI) or GCT Premier mass spectrometer (CI). ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra were collected on a Bruker AV 400 MHz NMR spectrometer or a Bruker ARX 300 MHz NMR spectrometer. ^{1}H and ^{13}C NMR chemical shifts are relative to TMS or residue of deuterium solvents, and ^{13}P NMR chemical shifts are relative to 85% H_3PO_4.

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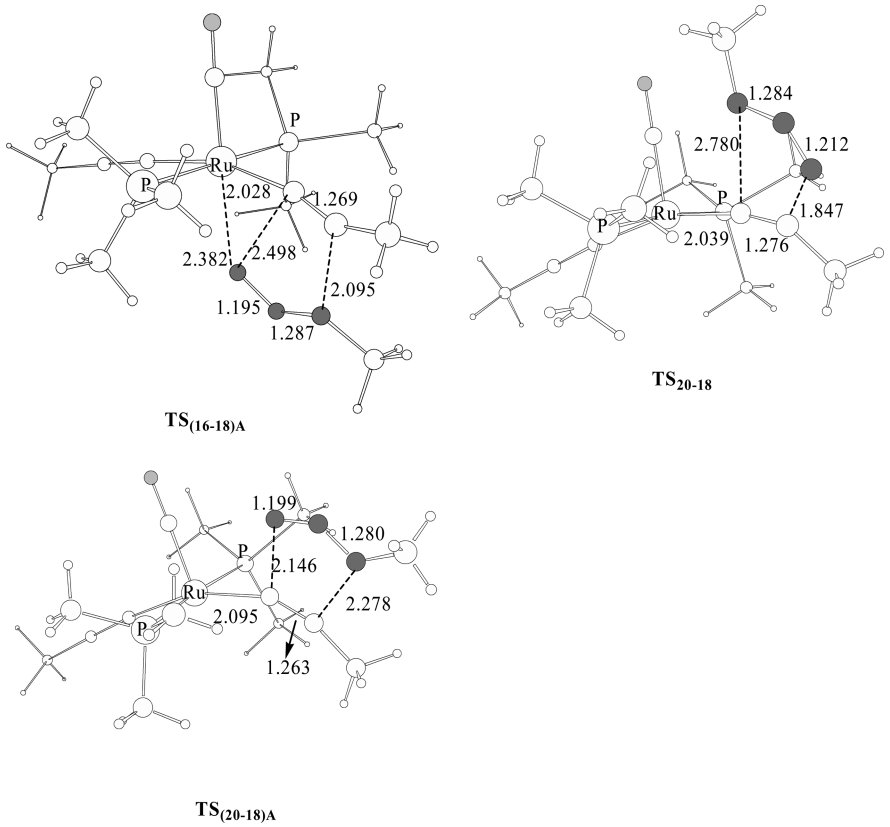

Figure 7. Selected structural parameters (Å) calculated for the transition states shown in Figures 4 and 6.

Single-crystal X-ray analysis was performed on an Oxford Xcalibur PD X-ray diffractometer.

Preparation of RuH(CO)(PCy_3)$_2$(η^2-H_2BH_2) (8). To a solution of RuHCl(CO)(PCy_3)$_2$ (7; 0.200 g, 0.27 mmol) in benzene (10 mL) was added $NaBH_4$ (0.100 g, 2.7 mmol). The mixture was stirred at room temperature for 48 h and then filtered. The volume of the filtrate was reduced to ca. 1 mL, and then Et_2O (1 mL) and hexane (2 mL) were added to give a precipitate. The solid was collected by filtration and washed with THF (1 mL) and hexane (2 mL). The resulting solid was recrystallized using a mixed solvent of CH_2Cl_2 and hexane. The yellow solid was dried under vacuum. Yield: 0.120 g, 63%. $^{31}P\{^1H\}$ NMR (162.0 MHz, CD_2Cl_2, 25 °C): δ 50.2 (s). ^1H NMR (400.1 MHz, CD_2Cl_2, 25 °C): δ −14.8 (t, J = 18.0 Hz, 1H, Ru-*H*), −7.99 (br, 1H, Ru-η^2-H_2BH_2), −5.06 (br, 1H, Ru-η^2-H_2BH_2), 1.25−2.12 (m, 66H, Cy-H), 3.65 (br, 2H, Ru-η^2-H_2BH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, CD_2Cl_2, 25 °C): δ 27.2, 28.3, 30.3, 30.9, 36.4, 205.3. HRMS (MALDI, CHCA): calcd for $C_{37}H_{70}BOP_2Ru^+$ 705.4033, found 705.4844 [M − H^-]$^+$. Anal. Calcd for $C_{37}H_{71}BOP_2Ru{\cdot}0.3CH_2Cl_2$: C, 61.26; H, 9.87. Found: C, 61.21; H, 9.52.

Preparation of Ru(CO)(C≡CPh)$_2$(PCy_3)$_2$ (9). HC≡CPh (0.144 g, 1.41 mmol) was added to a suspension of RuH(CO)(η^2-H_2BH_2)(PCy_3)$_2$ (0.200 g, 0.28 mmol) in 10 mL of benzene. The mixture was refluxed for 15 h. The resulting suspension was cooled to room temperature, the volume of the reaction mixture was reduced to ca. 1 mL, and then methanol (1 mL) was added to give a precipitate. The solid was collected by filtration, washed with methanol, and dried under vacuum to give a dark red microcrystalline solid. Yield: 200 mg, 79%. $^{31}P\{^1H\}$ NMR (162.0 MHz, CD_2Cl_2): δ 43.3 (s). ^1H NMR (400.1 MHz, CD_2Cl_2): δ 1.19−1.31 (m, 20H), 1.48−1.57 (m, 16H), 1.78−1.81 (m, 12H), 2.05−2.09 (m, 12H), 2.84−2.91 (m, 6H), 7.07 (t, J = 7.2 Hz, 2H), 7.21 (t, J = 7.6 Hz, 4H), 7.29 (d, J = 7.6 Hz, 4H). $^{13}C\{^1H\}$ NMR (100.6 MHz, CD_2Cl_2, 25 °C): δ 26.9, 28.4, 30.4, 35.7, 121.7, 124.7, 128.3, 129.8, 130.4, 207.1. HRMS (+ESI): calcd for $C_{53}H_{77}OP_2Ru^+$ 893.4493, found 893.4495 [M + H]$^+$. Anal. Calcd for $C_{53}H_{76}OP_2Ru$: C, 71.35; H, 8.59. Found: C, 71.27; H, 8.62.

Preparation of 15. To a solution of complex **6** (200 mg, 0.186 mmol) in CH_2Cl_2 (15 mL) was added benzyl azide (148 mg, 1.12 mmol). The mixture was stirred at room temperature for 70 min. The solution was concentrated to 1 mL, and hexane (10 mL) was added to give a precipitate. After filtration, the solid was washed with hexane and dried under vacuum to afford a brown solid. Yield: 113 mg, 64%. $^{31}P\{^1H\}$ NMR (162.0 MHz, C_6D_6, 25 °C): δ 33.8 (s). ^1H NMR (400.1 MHz, C_6D_6, 25 °C): δ 0.63 (s, 9H), 1.13 (s, 9H), 4.38 (s, 2H), 7.00−7.06 (m, 22H), 7.60−7.66 (m, 13H). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6, 25 °C): δ 28.4, 30.1, 31.5, 32.0, 53.6, 67.8, 101.9, 127.3, 127.8, 128.1, 128.3, 130.2, 131.6, 132.4, 132.5, 133.2, 133.4, 133.6, 133.8, 134.9, 135.0, 137.6, 152.4, 159.2, 208.3. HRMS (+ESI): calcd for $C_{56}H_{56}N_3OP_2Ru^+$ 950.2937, found 950.3055 [M + H]$^+$. Anal. Calcd for $C_{56}H_{55}N_3OP_2Ru$ + H_2O: C, 69.55; H, 5.94; N, 4.35. Found: C, 69.14; H, 5.66; N, 4.31.

Typical Procedure for the Cycloaddition of Alkyne with Azide. To a mixture of azide (0.5 mmol), alkyne (1.0 mmol), and THF (0.5 mL) was added the catalyst **8** (0.01 mmol). The resulting solution was stirred at 80 °C for 1.5 h. The solvent was evaporated under reduced pressure, and the residue was passed through a flash column of silica gel to afford the desired product. The products **12a−f,h−k,m−p** are known compounds;[27] **12g,l** are new compounds, and their spectroscopic data are listed as follows.

1-Benzyl-4-(phenanthren-1-yl)-1H-1,2,3-triazole (12g). ^1H NMR (400.1 MHz, $CDCl_3$, 25 °C): δ 5.63 (s, PhCH_2, 2H), 7.34−7.42 (m, 5H), 7.55−7.59 (m, 2H), 7.62−7.67 (m, 2H), 7.74 (s, 1H), 7.85 (d, J = 6.8 Hz, 1H), 7.93 (s, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.72 (d, J = 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 54.3, 122.5, 122.7, 122.9, 126.1, 126.6, 126.8, 126.9, 127.1, 128.1, 128.3, 128.8, 129.2, 130.0, 130.3, 130.6, 131.2, 134.6, 147.2. HRMS (+CI): calcd for $C_{23}H_{18}N_3^+$ 336.1495, found 336.1447 [M + H]$^+$.

1-Benzyl-4-tosyl-1H-1,2,3-triazole (12l). ^1H NMR (400.1 MHz, $CDCl_3$, 25 °C): δ 2.39 (s, Ar-CH_3, 3H), 5.52 (s, PhCH_2, 2H), 7.27−7.32 (m, 4H), 7.37 (t, J = 2.8 Hz, 3H), 7.92 (d, J = 8.4 Hz, 2H), 8.04 (s, triazole-*H*, 1H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ

21.5, 54.7, 125.6, 128.0, 128.5, 129.2, 129.3, 129.9, 133.0, 137.0, 145.0, 149.4. HRMS (+CI): calcd for $C_{16}H_{16}N_3O_2S^+$ 314.0958, found 314.0965 $[M + H]^+$.

Crystallographic Details. Crystals of complex **15** suitable for an X-ray analysis were obtained by slow diffusion of hexane into a benzene solution of the complex. The crystal was mounted on a glass fiber, and the diffraction intensity data were collected with a Bruker CCD diffractometer with monochromated Mo Kα radiation (λ = 0.710 73 Å) at 173 K. Lattice determination and data collection were carried out using SMART v.5.625 software. Data reduction and absorption correction were performed using SAINT v 6.26 and SADABS v 2.03. Structure solution and refinement were performed using the SHELXTL v.6.10 software package. The structure was solved by direct methods and refined by full-matrix least squares on F^2. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were introduced at their geometric positions and refined as riding atoms.

Computational Details. Density functional theory calculations at the Becke3LYP (B3LYP)[28] level have been used to perform the geometry optimizations for all species studied here. Frequency calculations at the same level of theory have also been performed to identify all stationary points as minima (zero imaginary frequency) or transition states (one imaginary frequency). An intrinsic reaction coordinate (IRC)[29] analysis was carried out to confirm that all stationary points are smoothly connected to each other. The Gibbs free energy at 298.15 K was obtained on the basis of frequency calculations. The Ru and P atoms were described using the LANL2DZ basis set including a double-valence basis set with the Hay and Wadt effective core potential (ECP).[30] An additional f polarization shell was added for Ru, with an exponent of 1.235.[31] In the case of P, a d polarization shell was added, with an exponent of 0.387.[32] The 6-31G[33] basis set was used for other atoms. All calculations were performed with the use of the Gaussian 03 packages.[34]

The B3LYP method has been known to neglect dispersion effects that are likely to play a key role in weakly bound complexes.[35] Therefore, we used single-point B3LYP-D3 energies,[36] which include a dispersion energy correction, for the energy curve shown in Figure 2. A detailed comparison of the B3LYP and B3LYP-D3 results is given in the Supporting Information.

The results presented were obtained with a basis set of a double-ζ quality described above. To test the basis set dependence of the results, we carried out single-point energy calculations for selected species shown in Figure 2 using a better basis set having a triple-ζ quality for all atoms. On the basis of the LanL2DZ basis set, we split the d-type valence orbitals to get a triple-ζ representation of the 4d electrons for Ru. Similarly, we split the p-type valence orbitals to get a triple-ζ representation of the 3p electrons for P. f and d polarization shells were also added for Ru and P, respectively, as described above. The 6-311G basis set was used for other atoms. The results of these additional single-point calculations show that the use of the better basis set does not change the shape of the potential energy curve given in Figure 2 and that both basis sets give the same conclusion. For example, the electronic energies of **16**, $\mathbf{TS}_{16\text{-}17}$, **17**, $\mathbf{TS}_{17\text{-}18}$, **18**, and $\mathbf{TS}_{19\text{-}20}$ relative to **20** + MeN_3 are −16.2, −13.0, −14.1, −8.9, −57.1, and −39.7 kcal/mol, respectively, using the double-ζ quality basis set. Using the triple-ζ quality basis set, the relative electronic energies are −15.4, −9.5, −10.2, −4.6, −52.4, and −32.7 kcal/mol, respectively.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, tables, and CIF files giving 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.

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Notes

The authors declare no competing financial interest.

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