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Electronic effects of ruthenium-catalyzed [3+2]-cycloaddition of alkynes and azides

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ABSTRACT

A combined experimental and theoretical study of ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) reactions is presented and various electronic analyses were conducted to provide a basis in understanding the observed regioselectivity of the 1,2,3-triazole products. Computational studies using density functional theory (DFT) and atoms in molecules quantum theory (AIM) further yield fresh details on the electronic factors that determine the regioselectivity in the RuAAC. It is found that the formation of 1,2,3-triazole products is irreversible and from the Hammett study, the pathway involving a vinyl cationic intermediate is ruled out. The electronic effect favors the formation of 5-electron-donating-group substituted-1,2,3-trizoles.

1. Introduction

Synthesis of 1,2,3-triazoles has recently attracted much attention mainly due to the development of the copper(I) catalyzed azide/alkyne cycloaddition (CuAAC) and for valuable applications in medicinal chemistry, biological systems, and materials sciences.[1–7] The CuAAC methodology, however, is only feasible with terminal alkynes, potentially limiting its scope. The Fokin and Jia groups have demonstrated that ruthenium based catalysts, such as CpRuCl$(PPh_3)_2$ and Cp*RuCl$(PPh_3)_2$, are capable of promoting the cycloaddition of azides and alkynes.[8] In contrast to the Cu-catalyzed systems, both terminal and internal alkynes are good substrates for the Ru-catalyzed azide-alkyne cycloaddition (RuAAC). Weinreb et al. further explored these reactions with unsymmetrical internal alkynes and found interesting regioselectivity.[9,10] Recently, Lin et al. published their further findings on these reactions together with DFT calculations that rationalized the selectivity circumstantially and suggested that the 'Cp(*)RuCl' core is the catalytically active center and the reductive elimination of the triazole product is rate-determining.[11] Since RuAAC offers the most direct synthetic methodology to prepare 1,4,5-trisubstituted 1,2,3-triazoles, a better understanding of the factors that influence the regioselectivity would lead to the design and development of useful synthetic routes to prepare highly attractive trisubstituted triazoles.[12–15] Herein, we report experimental and computational studies to elucidate the electronic contribution from the alkyne moiety on the regioselectivity of RuAAC reactions.

2. Results and discussion

2.1. Effect of the substituent

The Hammett equation has been recognized as one of the most useful methodologies to study and explain the mechanisms of a wide range of different reactions.[6] In order to analyze the electronic effects in the RuAAC reactions, we prepared a number of *para*-substituted diarylacetylenes by one-pot Sonogashira coupling reactions to compare their reactivities.[16] The competition experiments between diphenylacetylene and its disubstituted analogues in the RuAAC reactions were performed by heating the reaction mixture of benzyl azide, 5 equiv of diphenylacetylene, 5 equiv of the bis-*para*-substituted diaryl alkynes, and 5 mol% of CpRuCl$(PPh_3)_2$ at 80 °C for 3 h. The results of relative reactivities are summarized in Table 1. It was observed that the electron-rich alkynes are more reactive than the electron-deficient species. The Hammett plot of log k_{rel} versus σ generates a reaction constant of −0.79 (Fig. 1) with a slightly lower correlation coefficient (R^2=0.79), which could be attributed to the fact that both *para*-substituents can contribute to influence the stability of the reaction intermediate, albeit unequally. Even so, the relatively small reaction constant unequivocally rules out the pathway involving a vinyl cation intermediate.[17] This observation is consistent with the reported

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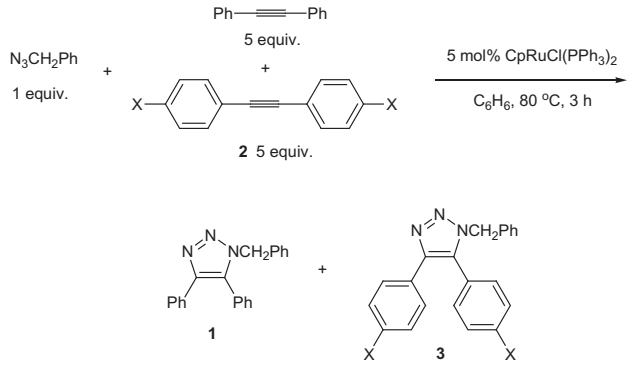
Table 1
Electronic influence of X substituent on relative activity



Entry	Alkyne	X	Product	Relative activity[a,b]	σ
1	**2a**	F	**3a**	1.50	0.06
2	**2b**	Cl	**3b**	1.22	0.23
3	**2c**	Br	**3c**	1.12	0.23
4	**2d**	OMe	**3d**	2.00	−0.27
5	**2e**	CO_2Me	**3e**	0.38	0.45
6	**2f**	CN	**3f**	0.48	0.66

[a] The ratio of **3**/**1**; determined from the integration of the ^{1}H NMR (500 MHz) spectrum of the crude product.
[b] Average of two runs.

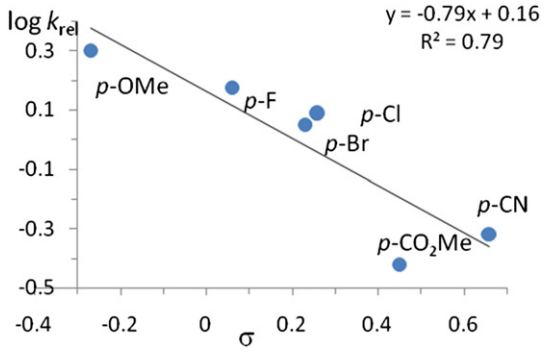
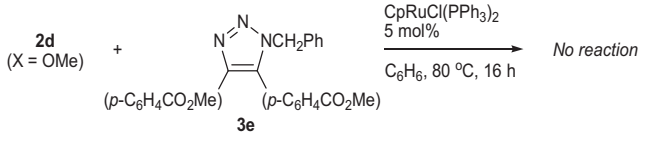


Fig. 1. Hammett plot of log k_{rel} versus σ.

properties of 'Cp*Ru$^+$' cationic complexes, which are totally inactive to catalyze the cycloaddition reactions of alkynes and azides.[11]

The reversibility of RuAAC was examined by heating the solution of the alkyne **2d** (X=OMe), triazole **3e**, and $CpRuCl(PPh_3)_2$ in benzene at reflux for 16 h. No apparent reaction was observed as the starting materials were recovered and the formation of the cycloadduct **3d** was not detected (Scheme 1). These results indicate



Scheme 1. Reversibility of RuAAC of **3e** to **3d**.

that the formation of 1,2,3-triazole is irreversible under the reaction conditions of these RuAAC reactions.

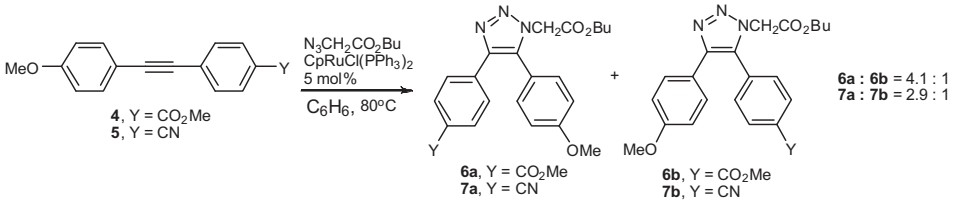
Diaryl alkynes **4** and **5**, both with electronically opposite, *para*-substituents, provide an excellent platform to examine and elucidate the electronic effect on the regiochemistry of the RuAAC reactions by minimizing steric considerations (Scheme 2). Indeed, it was found that two sets of the regioisomers of triazole (**6a**, **6b**, and **7a**, **7b**) were generated with moderate ratios (4.1:1 and 2.9:1, respectively). The triazoles **6a** and **7a**, with the 4-electron deficient and 5-electron rich aryls, were identified as the major isomers according to a series of H,H-COSY and NOE spectroscopic analyses. Since the observed regioselectivity in these two RuAAC reactions is mainly due to the electronic factors,[10,11] the results suggest that the formation of 5-electron-donating-group substituted-1,2,3-trizoles is more favorable.

2.2. Density functional theory studies

Informative DFT calculations on the RuAAC reaction using methylazide and propyne as model reactants with the 'CpRuCl' core have been previously reported by Lin et al.[11] In this work, we focused on the RuAAC reaction of alkyne **4** with ethyl 2-azidoacetate (for modeling butyl 2-azidoacetate) to understand the electronic interactions in the transition states that could result in the observed regioselectivity. Triazole products **6a** and **6b** were found to be more stable than the starting materials by 44.8 and 43.6 kcal/mol, respectively, with **6a** more favorable than **6b** by 1.2 kcal/mol. These data are in good agreement with the observation that the RuAAC reaction is irreversible under the above-mentioned reaction conditions, and thus suggest that the observed regioselectivity is a result of kinetic preference.

All transition states and intermediates located have similar geometries to the structures reported in the literature.[11] It was found that the relative energy of the transition state for the C—N bond formation of the major product **6a** is 0.6 kcal/mol lower than that of **6b** ($\Delta G^{\ddagger}$=18.4 vs 19.0 kcal/mol, see Supporting information), and the calculated overall activation barrier for the formation of **6a** is 1.0 kcal/mol lower than that for **6b**. As the DFT calculation results are consistent with the experimental findings, we further analyzed the molecular orbital of the transition state to identify the interactions in the C—N bond formation process. It was found that the electronic interactions mainly involve the electron donation from one of the alkynyl carbons to the π^* orbital of the terminal N=N group of the azide moiety (Fig. 2).[10] This observation provides a plausible explanation for the lower overall activation energy barrier for the cyclization leading to triazole **6a**, since the carbon at the β carbon of the C≡C moiety (referenced to the 4-methoxyphenyl ring) is more electron-donating than the α carbon due to the electron-donation from the methoxy group.

This bond formation process was further probed with Bader's atom in molecule (AIM) quantum theory by using AIM2000 software for the topological analysis.[18,19] The AIM-based theory analyzes interactions between atoms via the topological mapping of electron density. The relief of the electron density displays different characteristic points called critical points, which are important for the understanding of the interactions that transpire within the



Scheme 2. Electronic factors influencing regiochemistry of RuACC.

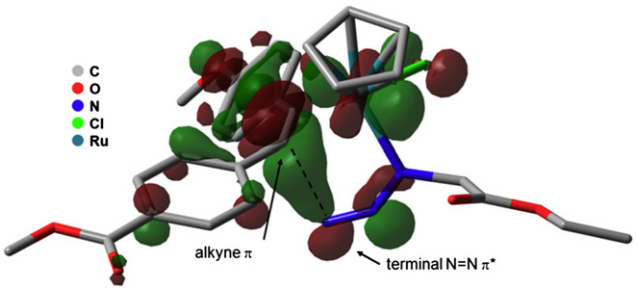


Fig. 2. HOMO of the transition state for the cyclization of **6a** formation.

molecule. Herein, we mainly focus on the bond critical points (BCPs) and ring critical points (RCPs). BCP is a point of maximum charge density found between a pair of nuclei while RCP is a point of minimum density found within a ring surface.[9] AIM analysis of the transition state for the cyclization shows a BCP between the β carbon and terminal N of the azide, indicating a C–N bond is being formed. The β carbon and azide form a nearly planar geometry with a C–N–N–N dihedral angle of −3.4°. Enclosed within the transition state is an RCP. As reported by Palusiak and Krygowski, an RCP can be treated as an indicator of aromaticity and the estimation of π-electron delocalization.[20] The generation of an RCP at the cyclization reaction site in this transition state structure therefore implies the delocalization of π-electrons within this transient cyclic structure from the alkynyl to azido-group (Fig. 3). Both the BCP and RCP descriptors confirm the observed orbital interaction between the alkyne and azide groups in the transition state.

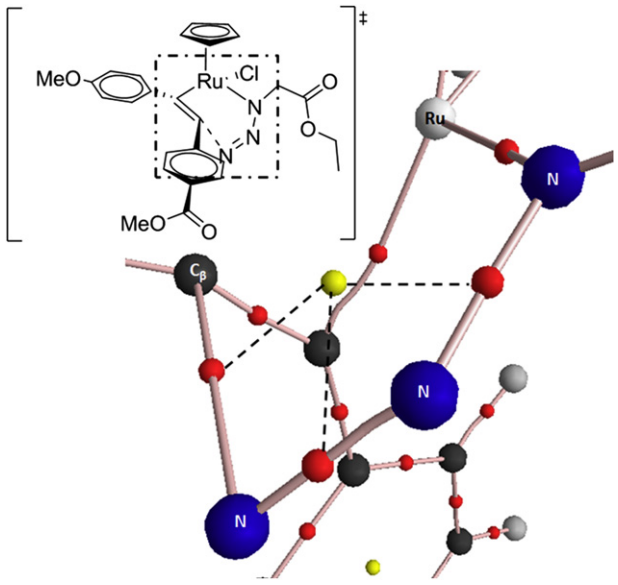


Fig. 3. Inset showing the zoom-in area of AIM analysis of the cyclization transition state. BCPs are red dots with bond path drawn through connecting a pair of nuclei. RCPs are yellow dots. The dotted line connects BCP associated with the RCP. For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.

3. Conclusion

In summary, our combined experimental and theoretical studies on the RuAAC reactions with internal alkynes provide clear evidence of electronic factors influencing regioselectivity. The RuAAC reactions for the formation of 1,2,3-triazole are irreversible under these experimental conditions and the Hammett studies reveal that the involvement of vinyl cation intermediates is not plausible. Our calculations suggest that the C–N bond formation is a process of nucleophilic attack by the alkynyl carbon onto nitrogen. As a result, the electron-rich alkynes are more reactive and the formation of 5-electron-donating-group substituted 1,2,3-trizoles is also more favorable. These insightful findings will be helpful for the development of the next generation of catalysts with enhanced selectivities and substrate scope.

4. Experimental section

4.1. Materials

All purchased chemicals were used without further purification. THF was distilled from sodium benzophenone ketyl. ^{1}H and ^{13}C NMR spectra were obtained on 200, 300 or 500 MHz spectrometers and referenced to TMS or residual $CHCl_3$. Analytical TLC was carried out using aluminum-backed 0.2 mm silica gel 60 F_{254} plates. Purification or separation of product was carried out with flash column chromatography using 230–400 mesh silica gel. Microwave-assisted reactions were performed in a CEM Discover single mode microwave reactor, equipped with vertically-focused IR temperature sensor. Controlled temperature, power and time setting was used in all reactions. Synthesis of benzyl azide and **2f**,[21] **1**,[8] **2a** to **2e**,[16] **4**,[16] and **5**,[22] followed literature protocols.

4.1.1. Benzyl azide. A solution of benzyl bromide (500.0 mg, 2.92 mmol), sodium azide (285.0 mg, 4.38 mmol), water (4 mL), and acetone (6 mL) was heated to reflux for 14 h. The acetone was removed under vacuum and the remaining mixture was extracted with ether (20 mL×2). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to give the title compound (311.0 mg, 2.34 mmol, 80%) as a light yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.33 (s, 2H), 7.29–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 54.8, 128.2, 128.3, 128.8, 135.3.

4.1.2. Butyl 2-azidoacetate[15]. A solution of butyl 2-bromoacetate (941.0 mg, 4.87 mmol), sodium azide (475.0 mg, 7.31 mmol), water (6.4 mL), and acetone (9.6 mL) was heated to reflux for 14 h. The acetone was removed under vacuum and the remaining mixture was extracted with ether (20 mL×2). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to give the title compound (708.4 mg, 4.51 mmol, 92%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, J=4.7 Hz, 3H), 1.35–1.39 (m, 2H), 1.60–1.66 (m, 2H), 3.84 (s, 2H), 4.18 (t, J=6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.4, 18.8, 30.3, 50.1, 65.5, 168.2.

*4.1.3. 1,2-Bis(4-fluorophenyl)ethyne (**2a**).* 4-Fluoro-1-iodobenzene (177.6 mg, 0.8 mmol), dichlorobis(triphenylphosphine)palladium (II) (33.7 mg, 0.048 mmol), and copper(I) iodide (15.2 mg, 0.08 mmol) were charged into a reaction tube. DMF (4 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 731 mg, 718 μL, 4.8 mmol), water (5.8 μL, 0.3 mmol), and trimethylsilylacetylene (57 μL, 0.4 mmol) were added to the tube sequentially. The reaction tube was sealed, heated to 120 °C in the microwave for 45 min. After cooling to room temperature, water was added (50 mL) and extracted with ether (50 mL). The organic layer was neutralized with hydrochloric acid (1 N), washed with satd $NaCl_{(aq)}$ (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was further purified by column chromatography (SiO_2, hexanes; R_f 0.20) to give **2a** (58 mg, 0.27 mmol, 68%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99–7.07 (m, 4H), 7.45–7.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 87.9, 115.8, 119.1, 133.5, 160.8.

*4.1.4. 1,2-Bis(4-chlorophenyl)ethyne (**2b**).* Starting with 4-chloro-1-iodobenzene (131 mg, 0.55 mmol), dichlorobis(triphenylphosphine) palladium(II) (23.2 mg, 0.033 mmol), CuI (10.5 mg, 0.055 mmol), DBU (494 μL, 3.3 mmol), and trimethylsilylacetylene (39 μL, 0.275 mmol), compound **2b** (34 mg, 0.14 mmol, 50%) was produced

as a light yellow solid. (SiO_2, hexanes; R_f 0.30) ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, J=8.7 Hz, 4H), 7.43 (d, J=8.7 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 89.2, 121.4, 128.8, 132.8, 134.5.

*4.1.5. 1,2-Bis(4-bromophenyl)ethyne (**2c**).* Starting with 4-bromo-1-iodobenzene (1.13 g, 4.0 mmol), dichlorobis(triphenylphosphine) palladium(II) (168.5 mg, 0.24 mmol), CuI (76 mg, 0.40 mmol), DBU (3.6 mL, 24 mmol), and trimethylsilylacetylene (285 μL, 2.0 mmol), compound **2c** (378 mg, 1.12 mmol, 57%) was produced as a colorless solid. (SiO_2, hexanes; R_f 0.30). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, J=8.1 Hz, 4H), 7.47 (d, J=8.1 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 89.4, 121.9, 122.8, 131.7, 133.0.

*4.1.6. 1,2-Bis(4-methoxyphenyl)ethyne (**2d**).* Starting with 4-iodoanisole (187.2 mg, 0.8 mmol), dichlorobis(triphenylphosphine)palladium(II) (33.7 mg, 0.048 mmol), CuI (15.2 mg, 0.08 mmol), DBU (718 μL, 4.8 mmol), and trimethylsilylacetylene (57 mL, 0.40 mmol), compound **2d** (66.6 mg, 0.28 mmol, 70%) was produced as a light yellow solid. (SiO_2, EtOAc/hexanes, 1:20; R_f 0.33). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.86 (d, J=8.4 Hz, 4H), 7.45 (d, J=8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.2, 87.9, 113.9, 115.6, 132.8, 159.3.

*4.1.7. Dimethyl 4,4′-(1,2-ethyndiyl)bisbenzoate (**2e**).* Methyl 4-iodobenzoate (124.7 mg, 0.476 mmol), dichlorobis(triphenylphosphine)palladium(II) (20 mg, 0.029 mmol), and copper(I) iodide (9.0 mg, 0.048 mmol) were put into a reaction tube. DMF (2.4 mL), triethylamine (0.4 mL, 2.85 mmol), and trimethylsilylacetylene (71.2 μL, 0.5 mmol) were added to the tube sequentially. The reaction tube was sealed, heated to 120 °C in the microwave oven, and held for 5 min. Another equivalent of methyl 4-iodobenzoate (125.0 mg, 0.476 mmol), DBU (854 μL, 5.7 mmol), and water (3.4 μL, 0.19 mmol) were added to the reaction. The reaction mixture was reheated to 120 °C and held for another 15 min. After cooling to room temperature, the reaction mixture was added to water (30 mL) and extracted with diethyl ether (50 mL). The organic layer was neutralized with hydrochloric acid (1 N), washed with satd $NaCl_{(aq)}$ (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc/hexanes, 1:9; R_f 0.50) to give **2e** (28 mg, 0.095 mmol, 19%) as a light yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.91 (s, 6H), 7.58 (d, J=8.4 Hz, 4H), 8.02 (d, J=8.1 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.3, 91.3, 127.2, 129.5, 130.2, 131.6, 166.3.

*4.1.8. 4,4′-(1,2-Ethynediyl)bisbenzonitrile (**2f**).* Trimethylsilylacetylene (137 μL, 0.96 mmol) was added to a solution of 4-bromobenzonitrile (145.6 mg, 0.8 mmol), dichlorobis(triphenylphosphine)palladium(II) (28 mg, 0.04 mmol), copper(I) iodide (15.2 mg, 0.08 mmol), and triethylamine (333 μL, 2.4 mmol) in benzene (4 mL). The reaction mixture was heated to reflux (70 °C) for 16 h, quenched with water (20 mL) and extracted with ether (50 mL). The organic layer was washed with satd $NH_4Cl_{(aq)}$ (20 mL), hydrochloric acid (1 N, 20 mL), satd $NaCl_{(aq)}$ (20 mL) dried over Na_2SO_4, filtered, and concentrated. The crude intermediate was redissolved in CH_2Cl_2 (5 mL) and methanol (5 mL), and potassium carbonate (1.1 g, 8 mmol) was added to the solution. After stirring at room temperature for 1 h, the reaction mixture was added to water (20 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:7; R_f 0.70) to give 4-ethynylbenzonitrile (52.6 mg, 0.413 mmol, 52%). Dichlorobis(triphenylphosphine)palladium(II) (14.5 mg, 0.02 mmol), CuI (7.9 mg, 0.041 mmol), triethylamine (172 μL, 1.24 mmol), and 4-bromobenzonitrile (75.3 mg, 0.413 mmol) were added to the solution of 4-ethynylbenzonitrile in benzene (2 mL). The reaction mixture was heated to reflux for 16 h and diluted with ether (50 mL). The organic solution was washed with water (20 mL), hydrochloric acid (1 N, 20 mL), satd $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:7; R_f 0.55) to give **2e** (22.3 mg, 0.098 mmol, 24%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.59–7.67 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 91.5, 112.3, 118.2, 127.0, 132.1, 132.2.

*4.1.9. Methyl 4-[2-(4-methoxyphenyl)ethynyl]benzoate (**4**).* Methyl 4-iodobenzoate (200 mg, 0.763 mmol), dichlorobis(triphenylphosphine)palladium(II) (32.1 mg, 0.046 mmol) and copper(I) iodide (14.5 mg, 0.076 mmol) were put into a reaction tube. DMF (3.0 mL), triethylamine (0.64 mL, 4.6 mmol), and trimethylsilylacetylene (54.3 μL, 0.76 mmol) were added to the tube sequentially. The reaction tube was sealed, heated to 120 °C in the microwave oven and held for 5 min. 4-Iodoanisole (178 mg, 0.763 mmol), DBU (1.36 mL, 9.2 mmol), and water (5.5 μL, 0.3 mmol) were added to the reaction. The reaction mixture was reheated to 120 °C and held for another 15 min. After cooling to room temperature, the reaction mixture was added to water (30 mL) and extracted with diethyl ether (50 mL). The organic layer was neutralized with hydrochloric acid (1 N), washed with satd $NaCl_{(aq)}$ (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was further purified by column chromatography (SiO_2, hexanes; R_f 0.30) to give **4** (68.7 mg, 0.26 mmol, 34%). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.81 (s, 3H), δ3.90 (s, 3H), 6.85–6.88 (m, 2H), 7.44–7.47 (m, 2H), 7.52–7.55 (m, 2H), 7.97–7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.1, 55.3, 87.8, 92.6, 114.1, 114.8, 128.4, 129.1, 129.5, 131.3, 133.2, 156.0.166.6.

*4.1.10. 4-(4-Methoxyphenylethynyl)benzonitrile (**5**).* 4-Iodoanisole (200 mg, 0.85 mmol), dichlorobis(triphenylphosphine)palladium (II) (35.9 mg, 0.051 mmol) and copper(I) iodide (16.0 mg, 0.085 mmol) were put into a reaction tube. DMF (3.0 mL), triethylamine (360 μL, 2.56 mmol), and trimethylsilylacetylene (133 μL, 0.94 mmol) were added to the tube sequentially. The reaction tube was sealed, heated to 120 °C in the microwave oven and held for 5 min. 4-Bromobenzonitrile (155 mg, 0.85 mmol), DBU (1.52 mL, 10.2 mmol), and water (6.0 μL, 0.34 mmol) were added to the reaction. The reaction mixture was reheated to 120 °C and held for another 15 min. After cooling to room temperature, the reaction mixture was added to water (30 mL) and extracted with diethyl ether (50 mL). The organic layer was neutralized with hydrochloric acid (1 N), washed with satd $NaCl_{(aq)}$ (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was further purified by column chromatography (SiO_2, hexanes; R_f 0.30) to give **5** (30.0 mg, 0.13 mmol, 15%). ^1H NMR($CDCl_3$, 300 MHz) δ 3.82 (s, 3H), 6.87 (d, J=9.0 Hz, 2H), 7.46 (d, J=8.7 Hz, 2H), 7.53–7.60 (m, 4H); ^{13}C NMR($CDCl_3$, 75 MHz) δ 55.3, 86.7, 94.1, 111.0, 114.2, 118.6, 128.6, 130.4, 131.8, 132.0, 133.3, 160.3.

*4.1.11. 1-Benzyl-4,5-diphenyl-1H-1,2,3-triazole (**1**).* A solution of benzyl azide (30 mg, 0.23 mmol), diphenylacetylene (48.2 mg, 0.27 mmol), and $CpRuCl(PPh_3)_2$ (8.2 mg, 0.011 mmol) in anhydrous benzene (10 mL) was refluxed under nitrogen for 3 h. The reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:4) to give **1** (53.7 mg, 0.17 mmol, 77%) as a light yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.39 (s, 2H), 7.00–7.26 (m, 10H), 7.37–7.55 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.0, 126.7, 127.4, 127.6, 127.8, 128.0, 128.4, 128.6, 129.1, 129.6, 130.0, 130.9, 133.8, 135.3, 144.5.

*4.1.12. 1-Benzyl-4,5-bis(4-fluorophenyl)-1H-1,2,3-triazole (**3a**).* A solution of benzyl azide (10.0 mg, 0.075 mmol), **2a** (17.6 mg, 0.083 mmol), and $CpRuCl(PPh_3)_2$ (2.7 mg, 0.004 mmol) in anhydrous benzene (2 mL) was refluxed under nitrogen for 3 h. The reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5, R_f 0.51) to give **3a** (15.0 mg, 0.043 mmol,

57%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.38 (s, 2H), 6.91–7.10 (m, 8H), 7.25–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.2, 115.6, 116.6, 123.6, 126.9, 127.4, 128.3, 128.4, 128.5, 128.9, 132.0, 135.1, 144.0, 162.5, 163.4; HRMS-FAB (m/z): $[M+H]^+$ calcd for ($C_{21}H_{16}N_3F_2$), 348.1312; found 348.1317.

*4.1.13. 1-Benzyl-4,5-bis(4-chlorophenyl)-1H-1,2,3-triazole (**3b**).* A solution of benzyl azide (10 mg, 0.075 mmol), **2b** (20.0 mg, 0.083 mmol), and $CpRuCl(PPh_3)_2$ (2.7 mg, 0.004 mmol) in anhydrous benzene (2 mL) was refluxed under nitrogen for 3 h. The reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3, R_f 0.45) to give **3b** (16.7 mg, 0.044 mmol, 58%) as a light yellow oil. ^{1}H NMR($CDCl_3$, 500 MHz) δ 5.38 (s, 2H), 6.99–7.05 (m, 4H), 7.20–7.27 (m, 5H), 7.36–7.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.2, 125.9, 127.3, 127.9, 128.3, 128.7, 128.8, 129.1, 129.6, 131.3, 132.8, 133.8, 135.0, 136.2, 143.8; HRMS-FAB (m/z): $[M+H]^+$ calcd for ($C_{21}H_{16}N_3Cl_2$), 380.0721; found 380.0719.

*4.1.14. 1-Benzyl-4,5-bis(4-bromophenyl)-1H-1,2,3-triazole (**3c**).* A solution of benzyl azide (10.5 mg, 0.079 mmol), **2c** (29.0 mg, 0.087 mmol), and $CpRuCl(PPh_3)_2$ (2.9 mg, 0.004 mmol) in anhydrous benzene (2 mL) was refluxed under nitrogen for 3 h. The reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5, R_f 0.46) to give **3c** (17.6 mg, 0.038 mmol, 50%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.38 (s, 2H), 6.94–7.02 (m, 4H), 7.25–7.38 (m, 7H), 7.52–7.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.2, 122.0, 124.4, 126.4, 127.4, 128.2, 128.4, 128.8, 129.5, 131.5, 131.7, 132.6, 132.7, 135.0, 143.8; HRMS-FAB (m/z): $[M+H]^+$ calcd for ($C_{21}H_{16}N_3Br_2$), 467.9711; found 467.9704.

*4.1.15. 1-Benzyl-4,5-bis(4-methoxyphenyl)-1H-1,2,3-triazole (**3d**).* A solution of benzyl azide (10.0 mg, 0.075 mmol), **2d** (19.7 mg, 0.083 mmol), and $CpRuCl(PPh_3)_2$ (2.7 mg, 0.004 mmol) in anhydrous benzene (2 mL) was refluxed under nitrogen for 3 h. The reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3 R_f 0.40) to give **3d** (27.3 mg, 0.073 mmol, 97%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 3H), 3.84 (s, 3H), 5.36 (s, 2H), 6.77–6.92 (m, 4H), 7.01–7.49 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.8, 55.2, 55.3, 113.8, 114.6, 119.7, 123.7, 127.4, 127.9, 128.0, 128.6, 131.4, 132.9, 135.6, 144.3, 159.1, 160.4; HRMS-FAB (m/z): $[M+H]^+$ calcd for ($C_{23}H_{22}N_3O_2$), 372.1712; found 372.1708.

*4.1.16. 1-Benzyl-4,5-bis[4-(methylcarboxylate)phenyl]-1H-1,2,3-triazole (**3e**).* A solution of benzyl azide (4.0 mg, 0.031 mmol), **2e** (9.0 mg, 0.031 mmol), and $CpRuCl(PPh_3)_2$ (1.1 mg, 0.002 mmol) in anhydrous benzene (2 mL) was refluxed under nitrogen for 3 h. The reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5 R_f 0.23) to give **3e** (8.0 mg, 0.019 mmol, 62%) as a light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.92 (s, 3H), 3.94 (s, 3H), 5.68 (s, 2H), 7.25–7.38 (m, 5H), 7.51–7.54 (m, 2H), 8.05–8.13 (m, 4H), 8.22–8.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.1, 52.4, 53.2, 125.4, 125.9, 127.9, 128.6, 128.9, 129.5, 129.7, 129.8, 130.0, 131.1, 131.4, 134.2134.3, 147.5, 165.0, 166.6; HRMS-FAB (m/z): $[M]^+$ calcd for ($C_{25}H_{21}N_3O_4$), 427.1532; found 427.1532.

*4.1.17. 1-Benzyl-4,5-bis[4-cyanophenyl]-1H-1,2,3-triazole (**3f**).* A solution of benzyl azide (10.0 mg, 0.075 mmol), **2f** (18.9 mg, 0.083 mmol), and $CpRuCl(PPh_3)_2$ (2.7 mg, 0.004 mmol) in anhydrous benzene (2 mL) was refluxed under nitrogen for 3 h. The reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.25) to give **3e** (17.5 mg, 0.049 mmol, 61%) as a light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.42 (s, 2H), 6.94–7.27 (m, 7H), 7.52–7.73 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.7, 111.7, 114.3, 127.0, 127.3, 128.7, 129.0, 130.7, 132.0, 132.5, 133.0, 134.4, 134.6, 143.4; HRMS-FAB (m/z): $[M+H]^+$ calcd for ($C_{23}H_{16}N_5$), 362.1406; found 362.1400.

4.2. Reversibility of RuAAC

A solution of alkyne **2d** (7.9 mg, 0.033 mmol), triazole **3e** (15 mg, 0.033 mmol), and $CpRuCl(PPh_3)_2$ (1.2 mg, 0.0017 mmol) in benzene (2.0 mL) was refluxed for 16 h under nitrogen. The solvent was removed under vacuum and analyzed with ^{1}H NMR spectroscopy. Only the starting materials remain.

4.3. Competition studies between diphenylacetylene and 1,2-bis(4-substituted phenyl)ethyne (2)

$CpRuCl(PPh_3)_2$ (1.5 mg, 0.002 mmol), benzyl azide (5.3 mg, 0.04 mmol), diphenylacetylene (35.6 mg, 0.2 mmol), and **2** (0.2 mmol) were added into benzene (2 mL). The mixture was refluxed under nitrogen for 3 h, and concentrated. The crude mixture was analyzed by ^{1}H NMR, and the ratio of the two products was determined by the integration of their benzylic hydrogens. Two independent reactions were performed to obtain the ratio.

4.4. Studies on the regioselectivity of RuAAC

A solution of butyl 2-azidoacetate (10.0 mg, 0.063 mmol), **4** (18.6 mg, 0.07 mmol), and $CpRuCl(PPh_3)_2$ (2.3 mg, 0.003 mmol) in anhydrous benzene (2 mL) was refluxed under nitrogen for 3 h. Solvent was removed under vacuum, and the reaction mixture was filtered with a short silica gel plug (eluted with 1:1 ethyl acetate/hexanes) and concentrated to give the mixture (20.0 mg, 74%) of **6a** and **6b**. The ratio of **6a** and **6b** and their identity was determined by ^{1}H NMR ($CDCl_3$, 300 MHz), H,H-COSY and NOESY. Compound **6a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84–0.89 (t, J=7.5 Hz, 3H), 1.20–1.33 (m, 2H), 1.49–1.59 (m, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.09–4.13 (t, J=6.9 Hz, 2H), 4.96 (s, 2H), 6.97–7.00 (d, J=9.0 Hz, 2H), 7.20–7.23 (d, J=8.7 Hz, 2H), 7.62–7.65 (d, J=8.7 Hz, 2H), 7.90–7.99 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.1, 18.9, 30.4, 49.1, 52.0, 55.4, 66.0.114.0, 115.0, 118.5, 126.4, 128.2, 129.8, 130.4, 131.1, 135.3, 143.2, 161.0, 166.8. Compound **6b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84–0.89 (t, J=7.5 Hz, 3H), 1.20–1.33 (m, 2H), 1.49–1.59 (m, 2H), 3.75 (s, 3H), 3.93 (s, 3H), 4.09–4.13 (t, J=6.9 Hz, 2H), 4.97 (s, 2H), 6.77–6.80 (d, J=9.0 Hz, 2H), 7.39–7.43 (m, 4H), 8.10–8.13 (d, J=8.4 Hz, 2H); HRMS-APCI (m/z): $[M+H]^+$ calcd for ($C_{23}H_{25}N_3O_5$) 424.1872; found 424.1865.

A solution of butyl 2-azidoacetate (10.6 mg, 0.068 mmol), **5** (17.5 mg, 0.075 mmol), and $CpRuCl(PPh_3)_2$ (2.4 mg, 0.003 mmol) in anhydrous benzene (2 mL) was refluxed under nitrogen for 3 h. The solvent was removed under vacuum, and the reaction mixture was filtered with a short silica gel plug (eluted with 1:3 ethyl acetate/hexanes) and concentrated to give the mixture (20.4 mg, 79%) of **7a** and **7b**. The ratio of **7a** and **7b** and their identity was determined with ^{1}H NMR ($CDCl_3$, 300 MHz), H,H-COSY and NOESY. Compound **7a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J=7.2 Hz, 3H), 1.21–1.33 (m, 2H), 1.50–1.59 (m, 2H), 3.86 (s, 3H), 4.11–4.14 (m, 2H), 4.95 (s, 2H), 7.00 (d, J=8.7 Hz, 2H), 7.22 (d, J=11.1 Hz, 2H), 7.52 (d, J=8.4 Hz, 2H), 7.68 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 18.9, 30.3, 49.1, 55.4, 66.1, 111.0, 115.2, 118.1, 126.8, 128.4, 130.8, 131.0, 132.9, 133.1, 135.7, 142.4, 166.4. Compound **7b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84–0.89 (t, J=7.2 Hz, 3H), 1.21–1.33 (m, 2H), 1.50–1.59 (m, 2H), 3.76 (s, 3H), 4.11–4.14 (m, 2H), 4.98 (s, 2H), 6.80 (d, J=8.7 Hz, 2H), 7.36–7.38 (d, J=8.4 Hz, 2H), 7.46 (d, J=8.1 Hz, 2H), 7.74 (d, J=7.8 Hz, 2H); HRMS-APCI (m/z): $[M+H]^+$ calcd for ($C_{22}H_{23}N_4O_3$), 390.1692; found 390.1691.

4.5. Computational details

Density functional theory (DFT) calculations were performed by employing the Gaussian 03 program.[23] B3LYP theory was applied,[24,25] LANL2DZ ECP basis set was used for Ru atom,[26-28] and a 6-31G(d) Pople basis set for the rest of the atoms.[29–31] See the Supporting information for a summary of Cartesian coordinates and thermodynamic data. For atoms in molecules quantum theory (AIM), the wavefunction was generated with a Gaussian 09 package.[32] B3LYP theory was applied, all electron Well-tempered basis set (WTBS) was used for Ru,[33,34] and a 6-31G(d) Pople basis set was used for the rest of the atoms. The wavefunction output was analyzed with AIM2000 software for topological interpretation. WTBS was obtained from an EMSL basis set library.[35]

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Supplementary data

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