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Steric Parameterization Delivers a Reciprocally Predictive Model for Substrate Reactivity and Catalyst Turnover in Rh-Catalyzed Diyne-Alkyne [2 + 2 + 2] Cycloadditions

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Cite This: *ACS Catal.* 2023, 13, 3463−3470 Read Online

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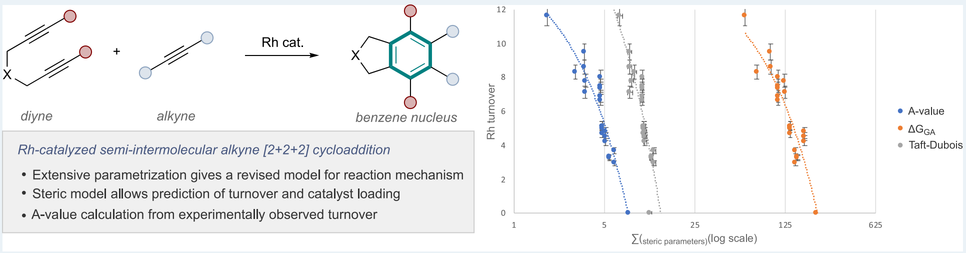


ABSTRACT: The Rh-catalyzed [2 + 2 + 2] cycloaddition of diynes and alkynes is a synthetically useful transformation that rapidly constructs complex scaffolds and has been used extensively for >70 years. Despite this utility, substrate reactivity issues persist, which are not mechanistically defined. Here, we provide a general predictive model for reactivity and turnover for this reaction. Contrary to the proposed electronic model, this is a predominately sterically driven process where productive turnover is proportional to alkyne steric parameters. This model allows for a priori prediction of catalyst loading, turnover, and reaction yield based on a simple assessment of the steric parameter (e.g., A-value) of the alkyne. The relationship is reciprocal, allowing A-values to be calculated from observed turnover.

KEYWORDS: *catalysis, cycloaddition, mechanism, parameterization, rhodium*

Transition-metal-catalyzed alkyne [2 + 2 + 2] cycloadditions are broadly used to yield densely functionalized benzenes.[1−12] Significant contributions have been made in the implementation of [2 + 2 + 2] cycloaddition using several metal catalysts including cobalt, iridium, rhodium, and ruthenium.[2−11] The reaction has three general categories: [2 + 2 + 2] cyclo(homo)trimerization of a single alkyne, intramolecular [2 + 2 + 2] of a triyne, and the semi-intermolecular [2 + 2 + 2] of a diyne and an alkyne (Scheme 1a). Completely intermolecular cycloadditions using three different alkynes are very difficult, due to issues with simultaneous control of both chemo- and regioselectivity;[13] however, tethering methods have offered a specific solution to this problem.[14,15] The diyne-alkyne process offers the most modular approach and has therefore seen significant interest in methodological development. The related [2 + 2 + 2] cycloadditions involving nitriles (to yield pyridines) and alkenes (to yield cyclohexadienes) expand this overall area and enable access to an increased diversity of scaffolds.[16,17] Overall this general reaction class has been extensively deployed within the synthetic strategy, including natural product and pharmaceutical synthesis, and polymerization.[2−12]

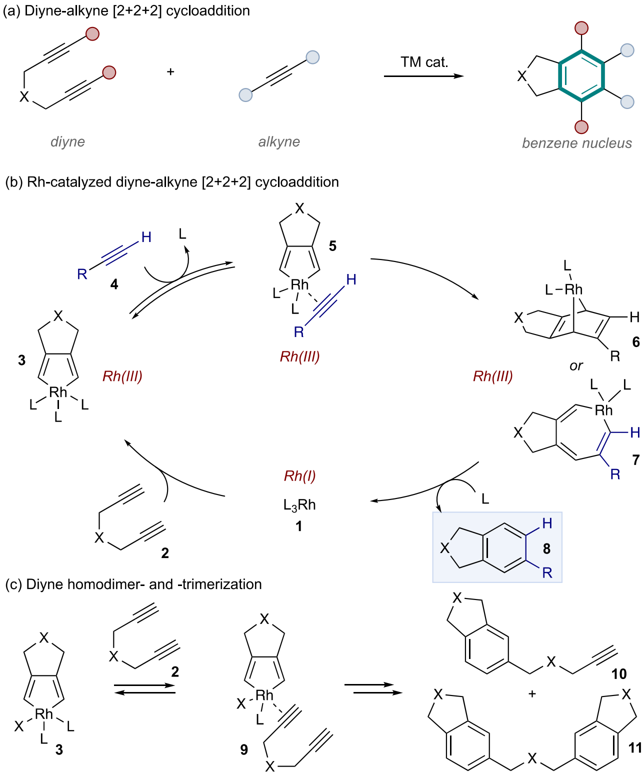
The Rh-catalyzed diyne-alkyne process, in particular, has seen the significant application.[8] The mechanism of this reaction has been difficult to study due to the inherent reactivity of the intermediates (Scheme 1b);[18] however, it is generally agreed that the first step is the rate-determining coordination of the Rh(I) catalyst **1** to the diyne **2**. Subsequent coordination of the alkyne **4** gives complex **5**, which rapidly gives a new intermediate, possibly the norbornadiene derivative **6** or metallocycloheptatriene species **7**.[18−20] These intermediates are then proposed to undergo reductive elimination to return the active catalyst **1** and the benzene product **8**.

The seemingly trivial coordination of the monoalkyne (i.e., Scheme 1b **3** → **5**) is a key event. If this is ineffective, competing processes can result. Specifically, coordination (**9**) and insertion of the diyne lead to undesired products, such as homodimer **10** and homotrimer **11** (Scheme 1c). Accordingly, alkyne coordination is product-determining.

The most broadly used alkynes are either terminal or internal with electron-withdrawing groups—propiolate ester

Received: December 21, 2022
Revised: February 14, 2023

Scheme 1. (a) General Description of the Diyne-Alkyne [2 + 2 + 2] Cycloaddition Processes; (b) Outline Mechanism of the Rh-Catalyzed Diyne-Alkyne [2 + 2 + 2] Cycloaddition (Counteranion Not Shown); and (c) Competing Pathways[a]



[a]X = linker, e.g., CH_2, NTs, O, etc.

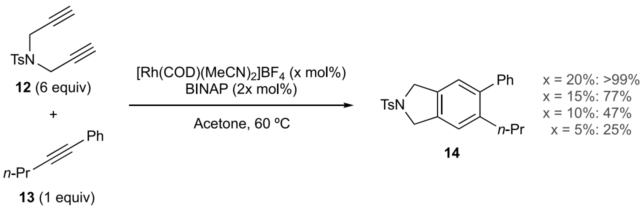
derivatives are very common.[2−12] Comparatively fewer examples exist of Rh-catalyzed diyne-alkyne cycloadditions using unactivated internal alkynes (i.e., those that do not use electron-deficient alkynes or highly activated diynes).[21−28] Based on this observed reactivity, electronic arguments dominate the current understanding of this reaction: an electronic-deficient alkyne is often accepted to be essential for reaction efficiency but with little mechanistic data to underpin this argument.[29−32] Indeed, two observations indicate that the present understanding might require refinement: (1) terminal alkynes without electron-withdrawing groups are highly effective in general;[2−12] (2) Rh(III) species **3** is electrophilic; thus, a preference for an electron-deficient alkyne seems counterintuitive.[33−35] Based on this, ambiguity remains over the determinants for reactivity in this otherwise very well-studied reaction.

Here, we report a parameterization of the Rh-catalyzed diyne-alkyne [2 + 2 + 2] cycloaddition using a broad internal alkyne dataset. This has led to a redefinition of the key reactivity descriptors, which, in contrast to current understanding, are principally driven by sterics. In addition, we decouple the alkyne electronic activation argument from observed reactivity and show that rate enhancement is in fact due to improved alkyne insertion arising from chelation to the electron-withdrawing group. These data provide a rubric for a priori prediction of catalyst loading and catalytic turnover for untested substrates. Finally, the relationship between steric parameters and turnover allows each to be calculated from the other.

■ DISCUSSION

Terminal alkynes are ubiquitous in this area, with internal alkynes comparatively under-represented. Despite the prevalence of an electronic model for reactivity, we hypothesized that steric parameters were possibly more significant due to what we considered as an unlikely preference of Rh(III) for an electron-deficient alkyne.[33−35] To explore this, we undertook a holistic and impartial assessment of reaction variables using several unactivated internal alkynes and common diynes to ensure representative sampling of the reaction space (variables for parametrization in Tables S1−7). This led to a benchmark system—an example is in Scheme 2. Note that the objective of this variable assessment was not to re-engineer/reoptimize toward new reaction conditions but rather to understand general reactivity trends.

Scheme 2. Rh-Loading Issues in a Benchmark System



To wit, a survey of rhodium catalysts identified $[Rh(COD)(MeCN)_2]BF_4$ as the most effective. Assessment of reaction conditions concluded that acetone as solvent at 60 °C was optimal.

The reaction was tolerant to an ambient atmosphere, experiencing little change in conversion from air to N_2 or Ar; however, N_2 was used as standard. In principle, oxygen can react with the intermediate rhodacycle (**3**, Scheme 1) to generate furan derivatives; however, these were not observed here.[36]

Evaluation of alkyne, diyne, and rhodium loading revealed little change when alkyne stoichiometry was altered; however, large changes in yield were observed as diyne and rhodium loadings were varied, consistent with previous conclusions that formation of the rhodacycle (**3**) is rate-determining.[18] Our own analysis of reaction orders for the reaction in Scheme 2 (see Tables S12−16) was consistent with these previous studies.[37] Increasing the equivalents of rhodium and diyne became detrimental, likely due to heterogeneity (observed).

Bidentate phosphine ligands were essential—no reaction was observed with monodentate ligands (Table S6).[38] A clear relationship between bite angle and conversion was observed yielding a parabolic graph, suggesting maximum yield could be achieved at 97°, this closely corresponded with dppb (96°) and BINAP (93°) (Figure S1). Reactions based on dppb gave zero conversion (Table S6) and subsequent NMR analysis of the dppb system revealed that the complex did not appear to form readily in solution (Figure S2). Formation of the dppb complex prior to reaction delivered moderate yield; however, this remained inferior to BINAP.

All of the above observations were consistent with and generally representative of the prior art in this area with two key differences noted:

(1) Product formation was only possible with the slow addition of the diyne, clearly indicating that the terminal alkyne of diyne **12** was more reactive than the internal

alkyne **13**. Homodimer and trimerization byproducts were observed in all cases (the diyne was fully consumed).

(2) High catalyst loadings (20 mol %) were necessary to obtain reasonable conversion to desired product **14**. Data for variation of Rh loading using alkyne **13** are shown in Scheme 2 ("reasonable conversion" defined here as 80%). Approximately five (productive) turnovers were observed for this substrate regardless of Rh loading. Literature processes using terminal or electronically activated alkynes operate effectively with 5 mol % Rh or lower;[2−12] however, alkyne **13** is not electronically activated, which either indicated a requirement for electronic activation or a significant steric contribution or a combination of both as the cause of the observed low product yield.

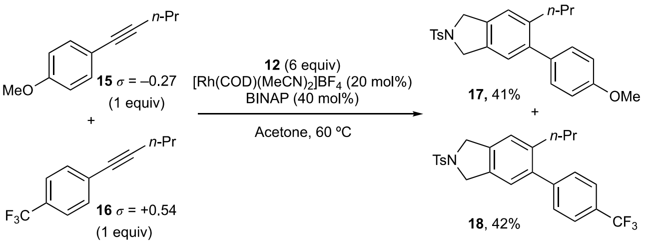
Analysis of Electronic Parameters. As noted above, the current understanding is that this reaction is governed by electronics, with electron-deficient alkynes proposed to be more reactive than electron-rich alkynes. This model has clear outliers, with examples of unactivated alkynes shown to be successful in the literature,[2−12] and contrasts with the electronic requirements of the Rh(III) intermediate.

Competition experiments suggested that an entirely electronic mechanistic framework was potentially misleading. For example, the competition experiment between electronically opposing alkynes **15** and **16** revealed no selectivity (Scheme 3a). The product ratio remained consistent over the duration of the reaction (Figure S14).

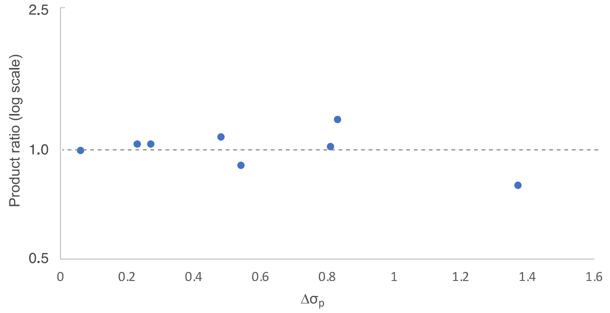
A series of similar competition experiments using a range of alkynes with different Hammett parameters was performed where the ratio of products was measured against the difference in Hammett parameters of the competing alkynes.

Scheme 3. (a) Example Competition Experiment; (b) Competition Reactions Exploring Electronic Influence and Graph of the Ratio of Competition Products vs $\Delta\sigma_p$[a]

(a) Example competition experiment between electron-rich and electron-deficient alkyne



(b) Aggregate view of competition experiments



[a] The chart indicates the product ratio on $\log_5$ scale vs Hammett parameter where the dotted line indicates a 1:1 ratio of products (no selectivity). See the ESI for full details.

An aggregate view of the data is shown in Scheme 3b: differences in electronics were statistically insignificant overall (see Table S11 for full details).

Alkyne electronic influence was subsequently assessed based on the Hammett parameters of the alkyne in reactions with a series of diynes (Scheme 4; Table S8, Figure S4).[45,46]

Alkyne **12** was first assessed under the same reaction conditions with a series of 16 *para*-substituted arylpentynes; these alkynes were selected to have the same steric parameters but a range of electronic parameters ($-0.8 \leq \sigma \leq 0.8$; Scheme 4a). The resulting plot revealed that alkyne electronics appears to have no clear impact on the reaction ($R^2 < 1\%$). Indeed, in contrast to the electronic model, the most electronically rich alkyne (p-NMe$_2$) performed comparably to neutral (H) and significantly better than those that are electron-deficient (e.g., p-CO$_2$H, p-NO$_2$). Performing the same analysis using mono-methyl substituted alkyne **19** and dimethyl derivative **20** using five representative alkynes, gave the same trend with respect to alkyne electronics (i.e., no strong correlation). An interesting observation was a general reactivity decrease on moving from **12** → **19** → **20**, consistent with an increase in steric demand around the respective rhodacycle intermediates.

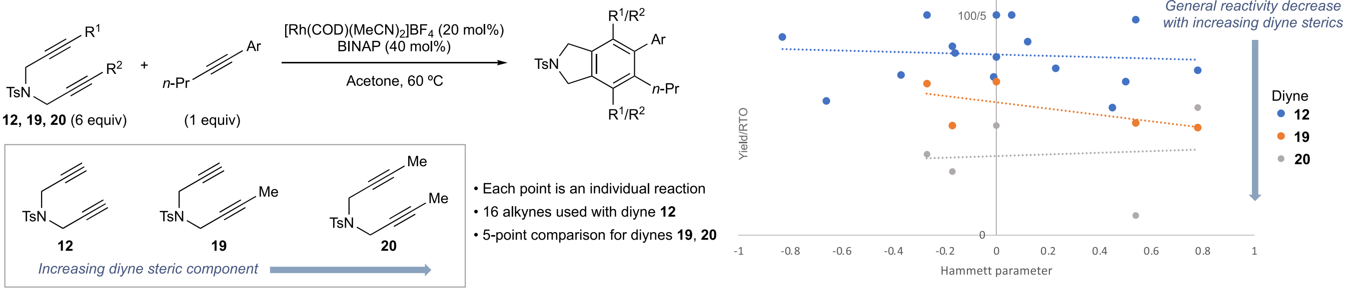
A subsequent analysis of three different terminal diynes **12**, **21**, and **22** provided similar observations (Scheme 4b). Comparison of the data of diynes **12** and **21**, which proceed via a 5-membered rhodacycle, indicated a generally lower reactivity of malonate-derived diyne **21**; however, no correlation to alkyne electronics was observed. Diyne **22**, which proceeds via a 6-membered rhodacycle, was less reactive in general, but did indicate a stronger influence by alkyne electronics; however, the generally poorer reactivity of **22** possibly assists in explaining the lower frequency of products derived from 6-membered rhodacycles in this area.[39−44]

Note that mono-methyl alkyne **19** generates a 3:1 mixture of regioisomeric products, regardless of reaction conditions (see Table S8). In addition, there is a pronounced solvent effect: acetone was optimal with a general decrease in reaction efficiency when using DCE or PhMe (Table S8, Figure S4). Solubility issues may contribute to these observations as reactions were clearly heterogeneous. While acetone was optimal, only trace evidence of [2 + 2 + 2] with acetone was observed throughout.[47−49] This solvent effect is poorly understood, we hypothesize that acetone may help stabilize Rh(III) species **3** − progressive addition of acetone to reactions in DCE led to a steady increase in product yield despite all reactions remaining homogenous (see Table S7).

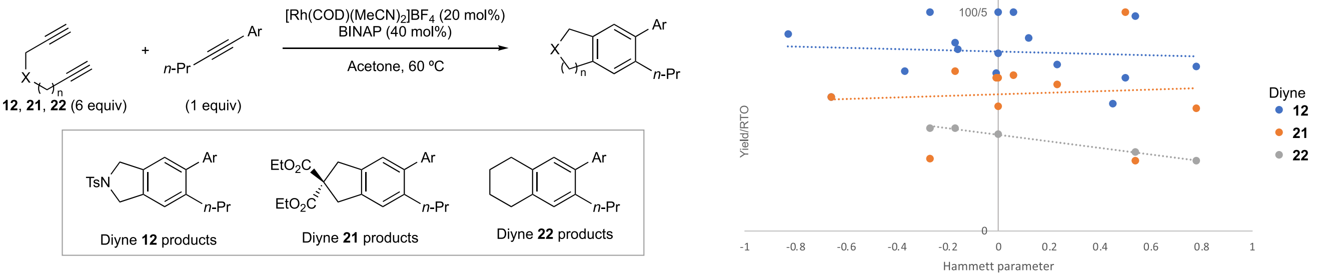
Analysis of Steric Parameters. With no strong relationship to electronics observed across a substantial dataset, and an indication of steric contribution in the data for alkynes **12**, **19**, and **20** (Scheme 5a), alkyne steric parameters were therefore examined. We selected the well-known A-value and Taft-Dubois (TD) parameter, as well as the recently described computational descriptor ΔG_{GA} value[50] for a holistic and impartial analysis. These data were extracted and initially analyzed in comparison to reaction yield. A clear relationship was observed (Table S9, Figures S5 and S6), which implied that when steric demands are low, productive catalyst turnover is high, and, conversely, where steric demand is high, turnover is low. This was consistent with observations of lower product output with increasing steric demand of the diyne (Scheme 4a). Importantly, rate data using electronically similar but sterically different alkynes also showed that reaction orders

Scheme 4. (a) Comparative Relationship between the Hammett Parameter and Observed Yield for Diynes 12, 19, and 20; (b) Comparative Relationship between Hammett Parameter/RTO (Rhodium Turnover Numbers) and Observed Yield for Diynes 12, 21, and 22[a]

(a) Electronic influence across a larger dataset using Hammett parameter



(b) Electronic influence with variation of terminal diyne linker



[a] See the ESI for full details.

remain the same; however, the larger alkyne had a slower overall rate (Pages S341–343).

Based on this, a more informative fundamental relationship could be extracted that allows yield, turnover, and catalyst loading to be more accurately understood (Scheme 5a). Correlation of turnover with steric parameter indicates a clear relationship. These data implied that RTO (rhodium turnover numbers) was inversely proportional to the steric parameters of the substituents of the alkyne. These data have two main implications:

> (1) When using internal alkynes for the diyne-alkyne [2 + 2 + 2] reaction, high rhodium loadings will be required for alkynes possessing substituents with a large cumulative steric footprint, thus decreasing possible turnover. For example, when the alkyne is significantly bulky, e.g., when the cumulative A-value is 5, one can only expect ca. 5 productive catalyst turnovers during the reaction, and a high catalyst loading (i.e., 15–20 mol %) will be required for useful yields. While this limitation is inescapable as the sterics of the substrate cannot be changed (vide infra for an exception), this allows prediction of turnover and therefore catalyst loading a priori by a routine assessment of the alkyne substituent A-values. There is, of course, a limit. When the substrate was exceptionally bulky, for example, *tert*-butyl-substituted internal alkynes (cumulative A-values > 8), no desired product was observed.

Indeed, if "synthetically useful" is defined as 80% yield, based on heterogeneity issues associated with catalyst loadings above 20 mol % (as noted above), this defines a useful approximation of a maximum value for cumulative A-values of the internal alkyne substrates as ~5.6. These data can be summarized graphically, providing a simple visual guide to predicting turnover based on cumulative A-value. This therefore allows prediction of catalyst loading required to obtain a useful chemical yield based on specific substrate classes (Scheme 5b).

Note that turnover here refers to productive turnover, i.e., leading to the desired product. Overall Rh turnover will be greater since the catalyst will engage in dimer- and trimerization of the diyne in the competing unproductive pathways shown in Scheme 1c—diyne is fully consumed in these reactions.

> (2) The reciprocal relationship is also valid, and one can approximate the A-value of a functional group based on productive catalyst turnover (Scheme 6).

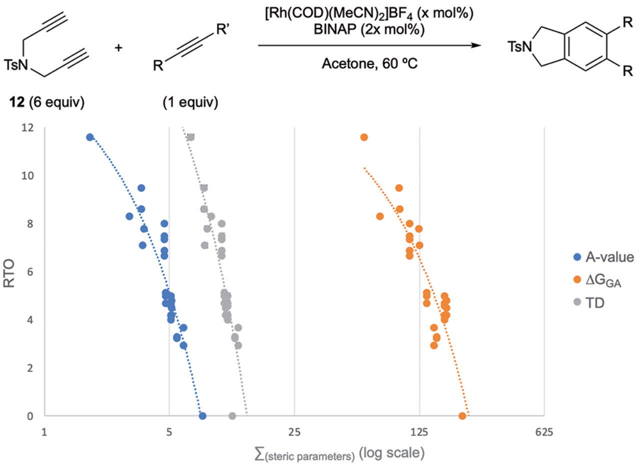
To ensure validity, the A-values were calculated from RTO for reactions with several alkynes-bearing motifs with known A-values (Scheme 6a). The calculated A-values based on RTO were found to be in good agreement. As far as the authors are aware, this is the first example of this type of analysis. Based on this, the same approach could be used to calculate the A-value of a motif for which it is currently unknown. For instance, MIDA boronates are a useful class of boron reagents;[51,52] however, their steric parameters are unknown. The cycloaddition using 1-pentyne BMIDA and propyne BMIDA gave the desired products in 68%, (ca. 3.40 RTO) and 73% (ca. 3.65 RTO), respectively (Scheme 6b).

This allows the A-value of a BMIDA to be calculated as ca. 4.03, consistent with predictions based on X-ray data, which indicate an approximate A-value for BMIDA ca. 3.90.[53,54] This demonstrates the applicability of this steric parameterization as a new method to approximate the steric demands of an unknown functional group.

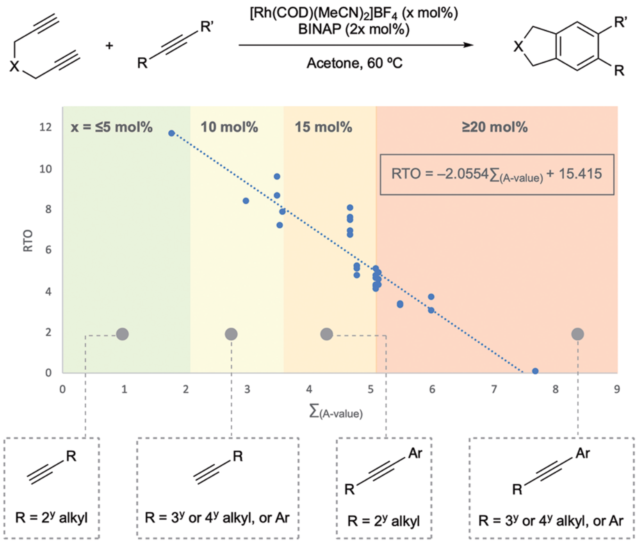
To further ensure reliability, the same analysis was performed for two additional diynes, each with six alkynes, and the same trend was observed (Table S10 and Figure S7). A key point to note is that physical effects, specifically solubility, can be difficult to predict, as noted in the solvent effects above, and this can significantly affect reaction outcomes.

Scheme 5. (a) Steric Parameterization Showing the Correlation between the Steric Footprint of Internal Alkyne Substituents and Productive RTO; (b) Simple Model for Predicting Turnover/Catalyst Loading based on A-Value Approximation[a]

(a) Steric influence in the model system using three common descriptors



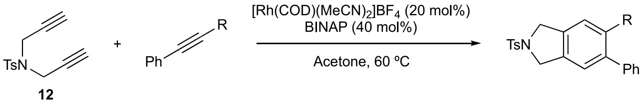
(b) A user-friendly rubric for *a priori* determination of catalyst loading/reaction efficiency



[a] See the ESI for full details.

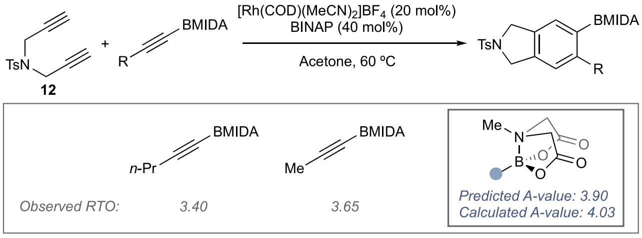
Scheme 6. (a) Reciprocal Correlation between RTO and the Steric Parameter; Calculation of A-Value from Observed RTO and Comparison to Known Values; (b) Use of the Approach To Calculate an Unknown A-Value

(a) Calculation of A-value from RTO – correlation to known A-values



R	CF$_3$	*i*-Pr	SiMe$_3$	Ph
Observed RTO:	*4.44*	*4.50*	*3.28*	*2.95*
Predicted A-value:	*2.34*	*2.31*	*2.91*	*3.07*
Literature A-value:	*2.10*	*2.15*	*2.50*	*3.00*

(b) Calculation of A-value from RTO – unknown A-value

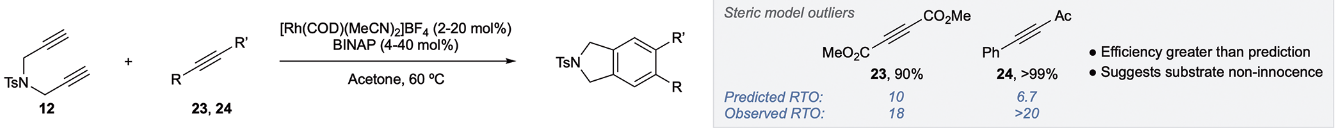


The above analysis using steric parameters also allowed the identification of important outliers (Scheme 7). The steric parameters of alkynes **23** and **24** predict 10 and 6.7 RTOs, respectively; however, in an apparent breach of the steric model, the experimentally determined RTOs were 18 and >20, respectively (Scheme 7a). Since **23** and **24** have electron-withdrawing functional groups, it may be tempting to attribute this increased RTO to an electronic phenomenon—this is not the case. Analysis of control reactions using alkynes **25**−**30** showed a clear trend that can be represented by the relationship between Rh loading and yield (Scheme 7b chart (i), and Figure S8). Alkynes **27**−**30** demonstrate some resilience when Rh loading is decreased from 20 mol % to 2 mol %. Importantly, electron-deficient alkyne **27** shows the same behavior as **28**−**30** despite exhibiting considerably different electronics. The common feature is that these alkynes contain Lewis basic functional groups. Conversely, alkyne **25** lacks a Lewis basic group and reaction yield is significantly affected by changes in Rh loading. The same trend is observed with electron-deficient alkyne **26**—the lower yield for this alkyne is clearly attributable to sterics (Me vs CF$_3$). This is intrinsically linked to the turnover (Scheme 7b chart (ii)): Alkyne **25** has no coordinating group and achieves ca. 7 turnovers regardless of Rh loading. This leads to a quantitative yield at ≥15 mol % Rh but 14% yield at 2 mol %. Likewise, alkyne **26** has an electron-withdrawing group but does not have a ligating motif and has static RTO (ca. 5). Conversely, as Rh loading decreases, RTO increases for **27**−**30**, which have Lewis basic groups. While the overall trend holds, increasing the steric environment around the chelating group (i.e., moving from **28** to **29** to **30**), clearly affects reaction efficiency. These data therefore suggest that Rh-catalyzed [2 + 2 + 2] cycloaddition reactions are not more effective to electron-deficient alkynes by virtue of alkyne electronics. Instead, increased reaction efficiency arises from enhanced productive turnover enabled by improved alkyne coordination to catalyst through Lewis basic functional groups.[55,56] This helps mitigate the steric impact and allows the reaction to move forward more productively. Chelation has been proposed and exploited as a control vector by Tanaka and coworkers for asymmetric processes;[25,32] however, the general and fundamental correlation not previously been established, despite the broad utility of this reaction in chemical synthesis for >70 years.

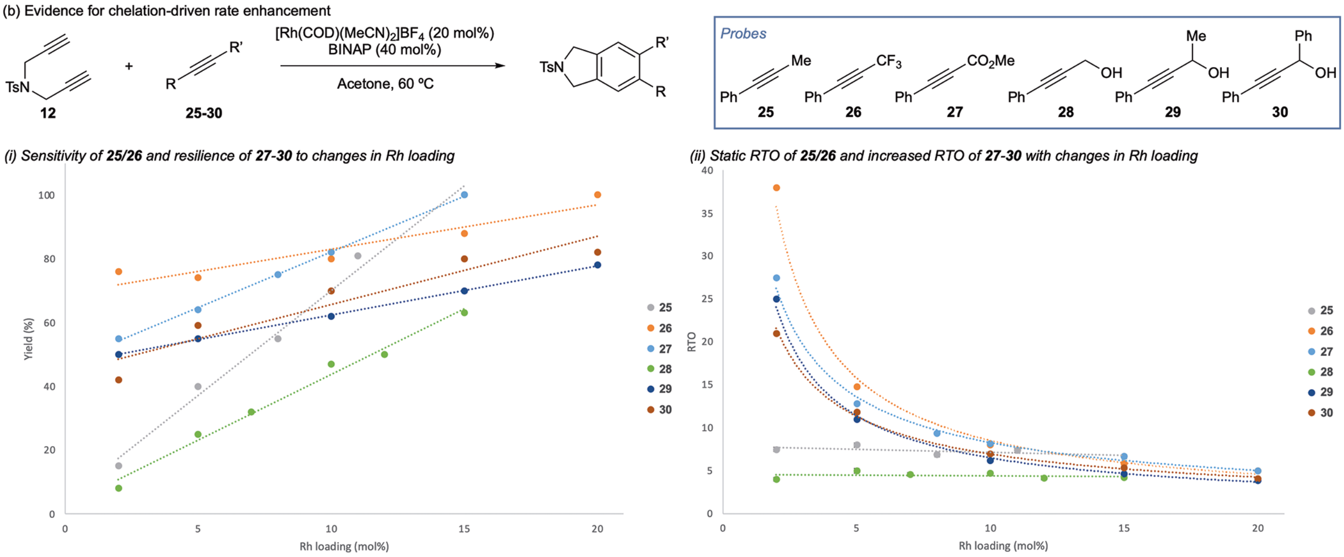
In summary, this work defines the origin of substrate effects in Rh-catalyzed [2 + 2 + 2] alkyne-diyne cycloadditions. Parameterization of an extensive dataset has indicated that this reaction is unlikely to be strongly electronically influenced, and instead, reactivity is principally under steric control, where the steric parameters of the alkyne govern turnover and yield. From these data, it is possible to determine the likelihood of success of a given reaction as well as the expected turnover and, therefore, optimal catalyst loading a priori by evaluation of common steric descriptors for alkyne functional groups. Moreover, the inverse relationship exists where an A-value can be extracted from turnover. Finally, the origin of the enhanced reactivity of electronically activated substrates has been determined as a Lewis base effect that promotes alkyne insertion.

Scheme 7. (a) Steric Model Outliers and Predicted vs Observed RTO; (b) Yield vs Rh Loading and RTO vs Rh Loading for Alkynes 25−30[a]

(a) Substrates that deviate from steric parameterization



(b) Evidence for chelation-driven rate enhancement



(i) Sensitivity of **25/26** and resilience of **27-30** to changes in Rh loading

(ii) Static RTO of **25/26** and increased RTO of **27-30** with changes in Rh loading

[a] See the ESI for full details.

■ ASSOCIATED CONTENT

Data Availability Statement

Analytical data generated during the current study are also available in the University of St Andrews repository as of date of publication, https://doi.org/10.17630/bf157aaa-a79b-457c-976d-d273313b0e7a. Crystallographic data for compound **64** is available from the Cambridge Crystallographic Data Centre (CCDC) under Deposition Number 2164403.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c06300.

Optimization data; complexation using BINAP and dppb; general procedures; characterization and crystal structure data; Hammett parameter analysis; steric parameterization data; and kinetic data (PDF)

Crystallographic data for compound 72 (CIF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Funding

University of St Andrews and Leverhulme Trust (RF-2022-014).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.M.H.-M. thanks the EaSI-CAT CDT and the University of St Andrews for a PhD studentship. A.J.B.W. thanks the Leverhulme Trust for a Research Fellowship. We thank the reviewers for helpful suggestions during the review process.

■ REFERENCES

(1) Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. Cyclisierende polymerisation von acetylen I über cyclooctatetraen. *Justus Liebigs Ann. Chem.* **1948**, *560*, 1−92.

(2) Vollhardt, K. P. C. Cobalt-mediated [2+2+2]-cycloadditions: A maturing synthetic strategy [new synthetic methods (43)]. *Angew. Chem., Int. Ed.* **1984**, *23*, 539−556.

(3) Kotha, S.; Brahmachary, E.; Lahiri, K. Transition metal catalyzed [2+2+2] cycloaddition and applications in organic synthesis. *Eur. J. Org. Chem.* **2005**, *2005*, 4741−4767.

(4) Gandon, V.; Aubert, C.; Malacria, M. Recent progress in cobalt-mediated [2+2+2] cycloaddition reactions. *Chem. Commun.* **2006**, *2006*, 2209−2217.

(5) Chopade, P. R.; Louie, J. [2+2+2] Cycloadditions reactions catalyzed by transition metal complexes. *Adv. Synth. Catal.* **2006**, *348*, 2307−2327.

(6) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. Cotrimerizations of acetylenic compounds. In *Organic Reactions*, RajanBabu, T. V, Ed.; Wiley: Hoboken, 2007; Vol. *68*, pp 1−302.

(7) Domínguez, G.; Pérez-Castells, J. Recent advances in [2+2+2] cycloaddition reactions. *Chem. Soc. Rev.* **2011**, *40*, 3430−3444.

(8) Shibata, Y.; Tanaka, K. Rhodium-catalyzed [2+2+2] cycloaddition of alkynes for the synthesis of substituted benzenes: Catalysts, reaction scope, and synthetic applications. *Synthesis* **2012**, *44*, 323−350.

(9) *Transition-Metal-Mediated Aromatic Ring Construction*, Tanaka, K., Ed., Wiley: Hoboken, 2013; pp 3−298

(10) Kotha, S.; Lahiri, K.; Sreevani, G. Design and synthesis of aromatics through [2+2+2] cyclotrimerization. *Synlett* **2018**, *29*, 2342−2361.

(11) Matton, P.; Huvelle, S.; Haddad, M.; Phansavath, P.; Ratovelomanana-Vidal, V. Recent progress in metal-catalyzed [2+2+2] cycloaddition reactions. *Synthesis* **2022**, *54*, 4−32.

(12) Galan, B. R.; Rovis, T. Beyond Reppe: Building substituted arenes by [2+2+2] cycloadditions of alkynes. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830−2834.

(13) Torres, Ò.; Fernàndez, M.; Díaz-Jiménez, À.; Pla-Quintana, A.; Roglans, A.; Solà, M. Examining the factors that govern the regioselectivity in rhodium-catalyzed alkyne cyclotrimerization. *Organometallics* **2019**, *38*, 2853−2862.

(14) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. Ru(II)-Catalyzed chemo- and regioselective cyclotrimerization of three unsymmetrical alkynes through boron temporary tether. One-pot four-component coupling via cyclotrimerization/Suzuki−Miyaura coupling. *J. Am. Chem. Soc.* **2004**, *126*, 3712−3713.

(15) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. Cp*RuCl-catalyzed formal intermolecular cyclotrimerization of three unsymmetrical alkynes through a boron temporary tether: Regioselective four-component coupling synthesis of phthalides. *J. Am. Chem. Soc.* **2005**, *127*, 9625−9631.

(16) Varela, J. A.; Saá, C. Construction of pyridine rings by metal-mediated [2+2+2] cycloaddition. *Chem. Rev.* **2003**, *103*, 3787−3802.

(17) Fujii, K.; Nagashima, Y.; Shimokawa, T.; Kanazawa, J.; Sugiyama, H.; Masutomi, K.; Uekusa, H.; Uchiyama, M.; Tanaka, K. Stereoselective cyclohexadienylamine synthesis through rhodium-catalysed [2+2+2] cyclotrimerization. *Nat. Synth.* **2022**, *1*, 365−375.

(18) Roglans, A.; Pla-Quintana, A.; Solà, M. Mechanistic studies of transition-metal-catalyzed [2+2+2] cycloaddition reactions. *Chem. Rev.* **2021**, *121*, 1894−1979.

(19) Parera, M.; Dachs, A.; Solà, M.; Pla-Quintana, A.; Roglans, A. Direct detection of key intermediates in rhodium(I)-catalyzed [2+2+2] cycloadditions of alkynes by ESI-MS. *Chem. − Eur. J.* **2012**, *18*, 13097−13107.

(20) Dachs, A.; Osuna, S.; Roglans, A.; Solà, M. Density functional study of the [2+2+2] cyclotrimerization of acetylene catalyzed by Wilkinson's catalyst, $RhCl(PPh_3)_3$. *Organometallics* **2010**, *29*, 562−569.

(21) Yoshida, K.; Morimoto, I.; Mitsudo, K.; Tanaka, H. $RhCl_3$/amine-catalyzed [2+2+2] cyclization of alkynes. *Tetrahedron* **2008**, *64*, 5800−5807.

(22) Wang, Y.-H.; Huang, S.-H.; Lin, T.-C.; Tsai, F.-Y. Rhodium(I)/cationic 2,2′-bipyridyl-catalyzed [2+2+2] cycloaddition of α,ω-diynes with alkynes in water under air. *Tetrahedron* **2010**, *66*, 7136−7141.

(23) Kaiser, R. P.; Hessler, F.; Mosinger, J.; Císarová, I.; Kotora, M. A [2+2+2]-Cyclotrimerization approach to selectively substituted fluorenes and fluorenols, and their conversion to 9,9′- spirobifluorenes. *Chem. − Eur. J.* **2015**, *21*, 13577−13582.

(24) Wu, Y.-T.; Hayama, T.; Baldridge, K. K.; Linden, A.; Siegel, J. S. Synthesis of fluoranthenes and indenocorannulenes: Elucidation of chiral stereoisomers on the basis of static molecular bowls. *J. Am. Chem. Soc.* **2006**, *128*, 6870−6884.

(25) Tanaka, K.; Suda, T.; Noguchi, K.; Hirano, M. Catalytic [2+2+2] and thermal [4+2] cycloaddition of 1,2-bis(arylpropiolyl)-benzenes. *J. Org. Chem.* **2007**, *72*, 2243−2246.

(26) Wu, T.-C.; Hsin, H.-J.; Kuo, M.-Y.; Li, C.-H.; Wu, Y.-T. Synthesis and structural analysis of a highly curved buckybowl containing corannulene and sumanene fragments. *J. Am. Chem. Soc.* **2011**, *133*, 16319−16321.

(27) Chen, M.-K.; Hsin, H.-J.; Wu, T.-C.; Kang, B.-Y.; Lee, Y.-W.; Kuo, M.-Y.; Wu, Y.-T. Highly curved bowl-shaped fragments of fullerenes: Synthesis, structural analysis, and physical properties. *Chem. − Eur. J.* **2014**, *20*, 598−608.

(28) Dutta, A. K.; Linden, A.; Zoppi, L.; Baldridge, K. K.; Siegel, J. S. Extended corannulenes: Aromatic bowl/sheet hybridization. *Angew. Chem., Int. Ed.* **2015**, *54*, 10792−10796.

(29) Nishida, G.; Suzuki, N.; Noguchi, K.; Tanaka, K. Enantioselective synthesis of tetra-*ortho*-substituted axially chiral biaryls through rhodium-catalyzed double [2+2+2] cycloaddition. *Org. Lett.* **2006**, *8*, 3489−3492.

(30) Tanaka, K. Cationic rhodium(I)/BINAP-type bisphosphine complexes: versatile new catalysts for highly chemo-, regio-, and enantioselective [2+2+2] cycloadditions. *Synlett* **2007**, *2007*, 1977−1993.

(31) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. Asymmetric assembly of aromatic rings to produce tetra-*ortho*-substituted axially chiral biaryl phosphorus compounds. *Angew. Chem., Int. Ed.* **2007**, *46*, 3951−3954.

(32) Tanaka, K.; Sawada, Y.; Aida, Y.; Thammathevo, M.; Tanaka, R.; Sagae, H.; Otake, Y. Rhodium-catalyzed convenient synthesis of functionalized tetrahydronaphthalenes. *Tetrahedron* **2010**, *66*, 1563−1569.

(33) Satoh, T.; Miura, M. Oxidative coupling of aromatic substrates with alkynes and alkenes under rhodium catalysis. *Chem. − Eur. J.* **2010**, *16*, 11212−11222.

(34) Song, G.; Wang, F.; Li, X. C−C, C−O and C−N bond formation via rhodium(III)-catalyzed oxidative C−H activation. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678.

(35) Song, G.; Li, X. Substrate activation strategies in rhodium(III)-catalyzed selective functionalization of arenes. *Acc. Chem. Res.* **2015**, *48*, 1007−1020.

(36) Müller, E.; Beißner, C.; Jäkle, H.; Langer, E.; Muhm, H.; Odenigbo, G.; Sauerbier, M.; Segnitz, A.; Streichfu*β*, D.; Thomas, R. Bis-acetylenketone, überhanhsmetallkomplexe und deren reaktives Verhalten, XII Synthesen von Chinonen. *Liebigs Ann. Chem.* **1972**, *754*, 64−89.

(37) Dachs, A.; Torrent, A.; Pla-Quintana, A.; Roglans, A.; Jutand, A. Rates and mechanism of rhodium−catalyzed [2+2+2] cycloaddition of bisalkynes and a monoalkyne. *Organometallics* **2009**, *28*, 6036−6043.

(38) Shibata, T.; Tahara, Y.-K. Enantioselective intramolecular [2+2+2] cycloaddition of 1,4-diene-ynes: A new approach to the construction of quarternary carbon stereocentres. *J. Am. Chem. Soc.* **2006**, *128*, 11766−11767.

(39) A general lower yield is noted when the diyne increases in length to generate larger fused cycles. This is observed in many different systems. See refs 37−42.

(40) Kotha, S.; Khedkar, P. Differential Reactivity Pattern of Hybrid *o*-Quinodimethane Precursors: Strategic Expansion to Annulated Benzocycloalkanes via Rongalite. *J. Org. Chem.* **2009**, *74*, 5667−5670.

(41) Tanaka, K.; Sawada, Y.; Aida, Y.; Thammathevo, M.; Tanaka, R.; Sagae, H.; Otake, Y. Rhodium-catalyzed convenient synthesis of functinalized tetrahydronaphthalenes. *Tetrahedron* **2010**, *66*, 1563−1569.

(42) Tsutomu, K.; Moriyasu, K.; Kinugawa, R.; Ishihara, T. Rhodium-catalyzed [2+2+2] cycloaddition of various fluorine-containing alkynes−novel synthesis of multi-substituted fluoroalkylated aromatic compounds *Org. Biomol. Chem.* **2010**, *8*, 1718−1724.

(43) Iannazzo, L.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C.; Gandon, V. Alkynylboronates and -boramides in Co^{I}- and Rh^{I}-Catalysed [2+2+2] Cycloadditions: Construction of Oligoaryls through Selective Suzuki Couplings. *Eur. J. Org. Chem.* **2011**, *2011*, 3283−3292.

(44) Rassadin, V. A.; Nicolas, E.; Six, Y. Ti(O*i*Pr)$_4$/*n*BuLi; an attractive reagent system for [2+2+2] cyclotrimerization reactions. *Chem. Commun.* **2014**, *50*, 7666−7669.

(45) Sarie, C.; Thiehoff, C.; Neufeld, J.; Daniliuc, C. G.; Gilmour, R. Enantioselecctive Synthesis of 3-Fluorochromanes via Iodine(I)/Iodine(III) Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 15069−15075.

(46) Neufeld, J.; Stünkel, T.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Gilmour, R. Trifluorinated Tatralins via I(I)/I(III)-Catalysed Ring Expansion: Progamming Conformation by [CH$_2$CH$_2$]→[CF$_2$CHF] Isosterism. *Angew. Chem., Int. Ed.* **2021**, *60*, 13647−13651.

(47) Tanaka, K.; Otake, Y.; Wada, A.; Noguchi, K.; Hirano, M. Cationic Rh(I)/modified-BINAP-catalyzed reactions of carbonyl compounds with 1,6-diynes leading to dienones and ortho-functionalized aryl ketones. *Org. Lett.* **2007**, *9*, 2203−2206.

(48) Miyauchi, Y.; Kobayashi, M.; Tanaka, K. Rhodium-catalyzed intermolecular [2+2+2] cross-trimerization of aryl ethynyl ethers and carbonyl compounds to produce dienyl esters. *Angew. Chem., Int. Ed.* **2011**, *50*, 10922−10926.

(49) Otake, Y.; Tanaka, R.; Tanaka, K. Cationic rhodium(I)/H8-binap complex catalyzed [2+2+2] cycloadditions of 1,6- and 1,7-diynes with carbonyl compounds. *Eur. J. Org. Chem.* **2009**, *2009*, 2737−2747.

(50) McFord, A. W.; Butts, C. P.; Fey, N.; Alder, R. W. 3×Axial vs 3×Equatorial: The ΔG_{GA} value is a robust computational measure of substituent steric effects. *J. Am. Chem. Soc.* **2021**, *143*, 13573−13578.

(51) Gillis, E. P.; Burke, M. D. Iterative cross-coupling with MIDA boronates: towards a general platform for small molecule synthesis. *Aldrichimica Acta* **2009**, *42*, 17−27.

(52) Li, J.; Grillo, A. S.; Burke, M. D. From synthesis to function via iterative assembly of *N*-methyliminodiacetic acid boronate building blocks. *Acc. Chem. Res.* **2015**, *48*, 2297−2307.

(53) Bell, G. E.; Fyfe, J. W. B.; Israel, E. M.; Slawin, A. M. Z.; Campbell, M.; Watson, A. J. B. Synthesis of 2-BMIDA indoles via heteroannulation: Applications in drug scaffold and natural product synthesis. *Org. Lett.* **2022**, *24*, 3024−3027.

(54) Schulz, A. On the steric hindrance of bulky substituents − determination of their cone angles. *Z. Anorg. Allg. Chem.* **2014**, *640*, 2183−2192.

(55) Amatore, M.; Lebœuf, D.; Malacria, M.; Gandon, V.; Aubert, C. Highly Enantioselective Rhodium-Catalyzed [2+2+2] Cycloaddition of Diynes to Sulfonimines. *J. Am. Chem. Soc.* **2013**, *135*, 4576−4579.

(56) Manick, A.-D.; Salgues, B.; Parrain, J.-L.; Zaborova, E.; Fages, F.; Amatore, M.; Commeiras, L. Access to Fluorenones Using Benzocyclopentynone Surrogate as Partner for the [2 + 2 + 2] Cycloaddition Reaction. *Org. Lett.* **2020**, *22*, 1894−1898.