Organic LETTERS

Letter

pubs.acs.org/OrgLett

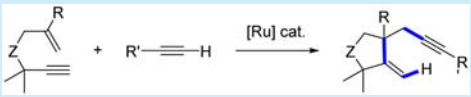
Ruthenium-Catalyzed Hydroalkynylative Cyclization of 1,6-Enynes Induced by Substituent Effects

Rui Liu,[†] Zhenjie Ni,[†] Laurent Giordano, and Alphonse Tenaglia*

Aix Marseille Université, CNRS, Cent Marseille, iSm2, Marseille 13013, France

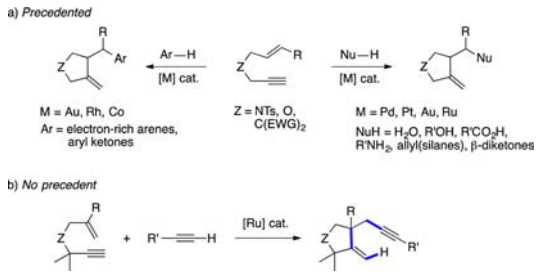
Supporting Information

ABSTRACT: The ruthenium-catalyzed 1,6-enyne cyclization in the presence of bulky substituted terminal alkyne proceeds smoothly at room temperature to afford highly substituted five-membered cyclic compounds featuring a 1,5-enyne motif. Deuterium-labeling experiments showed that the key ruthenacyclopentene intermediate undergoes cleavage of metal−carbon bonds through the metal-assisted σ-bond metathesis reaction, thus leading to the formation of C(sp^2)−H and C(sp^3)−C(sp) bonds.



Incorporation of external pronucleophiles through transition-metal-catalyzed cyclization of enynes is a well-established and efficient route to construct added-value functionalized cyclic systems in an atom-economical manner.[1] Since the pioneering work of Genêt on hydroxycyclization of 1,6-enynes mediated by a water-soluble palladium catalyst (Scheme 1, a, Z = O, Nu = OH),[2] studies involving Pt,[2c,3] Au,[4] and Ru[5]-based complexes or Hg(OTf)$_2$[6] as catalysts have appeared for similar transformations. In this context, major advances have been achieved in increasing the scope of compatible nucleophiles such as alcohols,[2d,3−5,7] acetic acid,[3a,7a] electron-poor anilines or carbamates,[8] as well as β-diketones and allylsilanes as carbon-based nucleophiles.[9] Electron-rich arenes and hetarenes were also efficient as carbon nucleophiles for the Au- and Pt-catalyzed hydroarylative cyclization of enynes providing homoallylic arenes adducts.[9,10] Alternatively, hydroarylative cyclization of enynes involving C−H bond activation of aryl ketones was recently developed by means of Rh[11] and Co[12] catalysts.

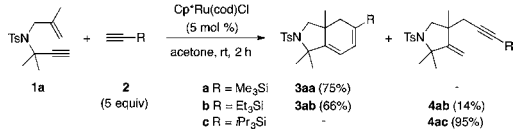
Scheme 1. Cross-Coupling of Enynes with Pronucleophiles



As terminal alkynes are far less nucleophilic in their neutral form compared to heteronucleophiles, use of this substrate class in such a coupling reaction represents a major challenge in many respects. On one hand, such an event requires perfect control of chemoselectivity, and the scarce precedent literature in this regard well demonstrates the difficulty. For instance, the Rh-catalyzed reaction of enynes with terminal alkynes exclusively led to corresponding [2 + 2 + 2] cycloadducts.[13] On the other hand, this prominent substrate class is prone to undergo the metal-catalyzed di-[14] or trimerization[15] reactions. Herein, we present a novel and mild procedure for the ruthenium-catalyzed hydroalkynylative cyclization of enynes and alkynes allowing the formation of 5-membered cyclic compounds featuring the 1,5-enyne motif (Scheme 1, b).

Diverse chemoselective cross-trimerizations involving two[16] or three[17] different alkynes were reported by the Ogata-Fukuzawa group. In addition, three-component cross-addition reactions of two different alkynes with alkenes[18] by combining electron-deficient and electron-rich partners[18c] and/or using alkynes capped with bulky substituents[18a,b] were successfully achieved. These coupling reactions were triggered either by the formation of alkynylmetal hydride[16a,17,18a] and metal alkynilide[16b,18b] species or metalacyclopentadienes.[18c] Based on these observations, we initiated studies on the cross-coupling of **1a** with (trialkylsilyl)ethynes **2** (5 equiv) in acetone in the presence of Cp*Ru(cod)Cl (5 mol %), which might evolve through ruthenacyclopentene intermediates. While (trimethylsilyl)-ethyne **2a** exclusively afforded the [2 + 2 + 2] cycloadduct **3aa** with excellent regioselectivity (97:3), we were pleased to find that (triisopropylsilyl)ethyne **2c** solely led to the desired target **4ac** with 95% yield (Scheme 2). The reaction with (triethylsilyl)-ethyne **2b** was far less chemoselective and gave a mixture of nonseparable adducts **3ab** and **4ab** in a 4.8:1 ratio, *leading to the conclusion that increasing the bulkiness of the substituent of the alkyne had a positive impact on the formation of the cross-coupling cyclized product.*

Scheme 2. Cross-Coupling of Enyne 1a with Alkynes: Initial Experiments



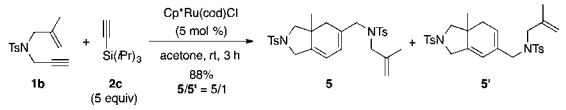
Received: June 30, 2016
Published: August 9, 2016

ACS Publications © 2016 American Chemical Society

DOI: 10.1021/acs.orglett.6b01901
Org. Lett. 2016, 18, 4040−4043

Unfortunately, enynes lacking of substitutents at the propargylic center turned out to be unsuitable for the reaction.[19] Indeed, the coupling reaction of **1b** with alkyne **2c** ignored the latter and led only to homodimers **5**/**5′** (5/1 molar ratio) in 88% overall yield (Scheme 3). Nevertheless, the present hydroalkynylative cross-coupling of enynes provided an entry to highly substituted pyrrolidines containing two quaternary centers.

Scheme 3. Attempted Cross-Coupling of Enyne 1b with 2c



The influence of solvent and ruthenium source was investigated in the reactions of **1a** and **2c** (Table 1). Among the polar, protic, or coordinating solvents (entries 1−8), acetone allowed the formation of **4ac** with the best yield (entry 8). Interestingly, the reaction was easily carried out on a gram scale without alteration of the yield. Structurally close Ru(II) catalysts (entries 11−14) were totally inefficient, except for the cationic complex Cp*Ru(MeCN)$_3$PF$_6$ (entry 9), which exhibited a lower catalytic activity compared to the neutral Cp*Ru(cod)Cl (entry 8). Combining Cp*Ru(MeCN)$_3$PF$_6$ with nBu$_4$NCl to generate neutral ruthenium species[20] restored the performance level at 90% yield (entry 10). Upon decreasing the catalyst loading to 1 mol %, the yield dropped to 78% (instead of 95%) and the reaction time increased to 24 h for complete conversion (not showed in Table 1).

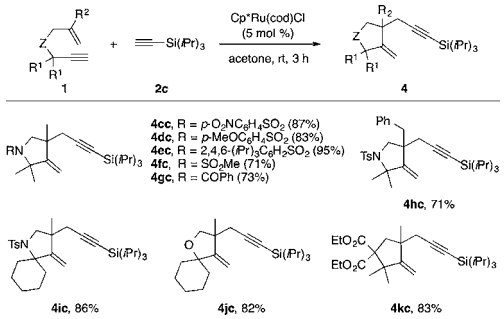
Table 1. Screening of Reaction Conditions[a]

entry	catalyst	solvent	yield of **4ac**[b] (%)
1	Cp*Ru(cod)Cl	THF	61
2	Cp*Ru(cod)Cl	MeCN	85
3	Cp*Ru(cod)Cl	AcOEt	81
4	Cp*Ru(cod)Cl	MeOH	79
5	Cp*Ru(cod)Cl	DCE	51
6	Cp*Ru(cod)Cl	toluene	77
7	Cp*Ru(cod)Cl	H$_2$O/acetone (85/15)	71
8	Cp*Ru(cod)Cl	acetone	95
9	Cp*Ru(MeCN)$_3$PF$_6$	acetone	56
10	Cp*Ru(MeCN)$_3$PF$_6$/*n*-Bu$_4$NCl[c]	acetone	90
11	CpRu(MeCN)$_3$PF$_6$	acetone	NR
12	Cp*Ru(PPh$_3$)$_2$Cl	acetone	NR
13	CpRu(PPh$_3$)$_2$Cl	acetone	NR
14	(η^5-C$_9$H$_7$)Ru(PPh$_3$)$_2$Cl	acetone	NR

[a]Reaction conditions: **1a** (0.2 mmol), **2c** (1.0 mmol), catalyst (0.01 mmol), rt, 3 h. [b]Yields of the isolated product. [c]5/10 mol %. cod = 1,5-cyclooctadiene, Cp* = pentamethylcyclopentadienyl.

Having now the optimized conditions in hand, the scope of this ruthenium-catalyzed hydroalkynylative cyclization of enynes with **2c** was thereafter examined (Scheme 4). A series of nitrogen-tethered enynes featuring variation of substitution at the nitrogen atom as well as at the alkene (R^2) or at the propargyl carbon atom (R^1) could efficiently be involved to provide the expected pyrrolidines **4cc**−**ic** in good to excellent yields. Interestingly, our protocol is not restricted to *N*-containing substrates, as it could delightfully be extended to oxygen-tethered and carbon-linked enynes to give the corresponding cross-adducts **4jc** (82%) and **4kc** (83%), respectively.

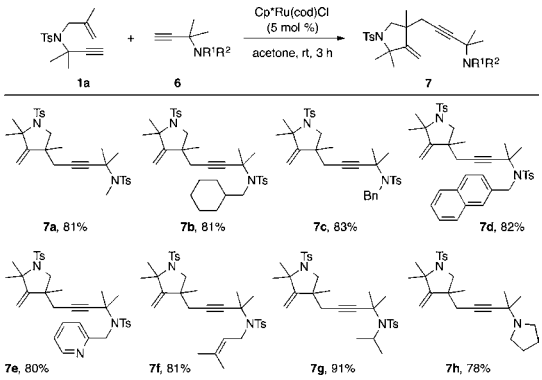
Scheme 4. Hydroalkynylative Cyclization of Enynes 1 with 2c



[a]Reaction conditions: **1** (0.2 mmol), **2c** (1.0 mmol), catalyst (0.01 mmol), rt, 3 h. Isolated yields are indicated.

The hydroalkylnylative cyclization of **1a** was next pursued with other functionalized bulky substituted alkynes. Gratifyingly, tertiary propargylamines proved to be excellent partners for that event (Scheme 5). By way of illustration, *N*-alkyl-, *N*-benzyl-, and *N*-allyl-substituted propargylamines led to the formation of adducts **7a**−**f** in very good yields (80−91%). It is worth noting the chemoselective formation of the cross-adduct **7f** (81%) in the reaction involving two distinct enyne partners. The structural modification of substituents on the nitrogen atom of propargylamine had no influence on the outcome of the reaction as illustrated by the formation of **7h** in 78% yield.

Scheme 5. Cross-Coupling of 1a with Propagylamines[a]



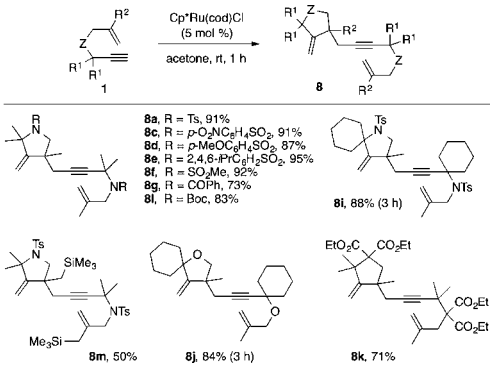
[a]Cp*Ru(cod)Cl (0.01 mmol), **1** (0.20 mmol), **6** (1.00 mmol), rt, 3 h. Yields are those for the isolated products.

Finally, when the reactions were conducted in absence of the bulky alkyne partner, enynes **1** were subjected to the homocoupling cyclization, consequently yielding the dienynes **8** (Scheme 6).[21] Enynes bearing various sulfonyl groups at the nitrogen atom indeed afforded the cyclodimers **8a** and **8c**−**e** in very good yields (87−95%), whereas *N*-benzoyl and *N*-Boc enynes led to **8g** (73%) and **8l** (83%) with slightly lower yields. Enyne featuring the nucleophilic allylsilane motif was moderately tolerated and allowed the formation of **8m** in a fairly 50% yield. Similarly, the homocoupling cyclization was successfully extended to the oxygen-tethered and carbon-linked enynes to give **8j** (84%) and **8k** (71%), respectively.

To gain further insights into the mechanism of the hydroalkynylative cyclization reaction of enynes, deuterium-labeling experiments were conducted in acetone-d_6 (Scheme 7).

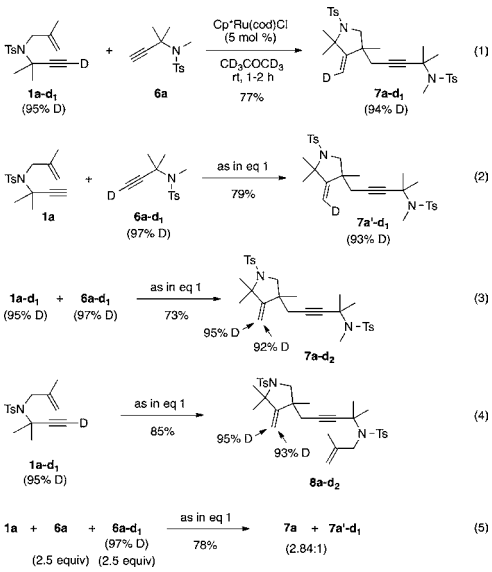
DOI: 10.1021/acs.orglett.6b01901
Org. Lett. 2016, 18, 4040−4043

Scheme 6. Homocoupling Cyclization of Enynes[a]



[a]Cp*Ru(cod)Cl (0.01 mmol), **1** (0.20 mmol), rt, 3 h. Yields are those for the isolated products.

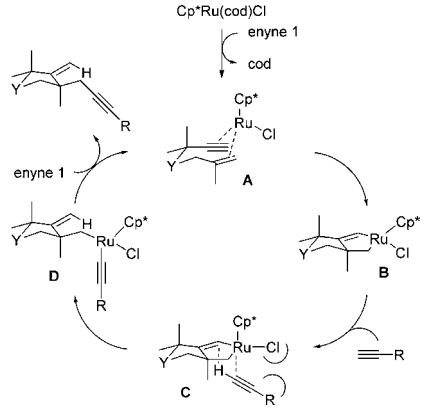
Scheme 7. Deuterium-Labeling Experiments



Labeling either the enyne or the alkyne partner in the cross-coupling reactions allowed location of deuterium in **7a**-d_1 and **7a′**-d_1 (eqs 1 and 2). On the other hand, the cross-coupling of **1a**-d_1 with **6a**-d_1 (eq 3) as well as the dimerization of **1a**-d_1 (eq 4) led excluvively to **7a**-d_2 and **8a**-d_2, respectively, whereas the homocoupling of **1a** carried out in a 9/1 mixture of D_2O/d_6-acetone delivered nondeuterated **8a** (not shown). Furthermore, the kinetic effect (KIE) experiment investigated with the competitive reaction of **1a** with an equimolar mixture of **6a**/**6a**-d_1 (k_H/k_D = 2.84) suggested that the cleavage of the C−H bond of alkyne may have been involved in the rate-determining step. As no deuterium scrambling was observed from these experiments, formation of a ruthenium hydride species followed by subsequent insertions of the triple and double bonds of the enyne was ruled out.

A plausible explanation for this hydroalkynylative cyclization may involve the ruthenacyclopentene **B** formed through oxidative cyclometalation of complex **A** as depicted in Scheme 8. The subsequent reductive elimination would lead to cyclobutene[22] or 1,3-diene products which, however, were not detected by NMR of the crude reaction mixtures. Coordination of a terminal alkyne bearing a small- or medium-sized substituent followed by its insertion and reductive elimination would then deliver the [2 + 2 + 2] cycloadduct (not shown). If alkyne capped

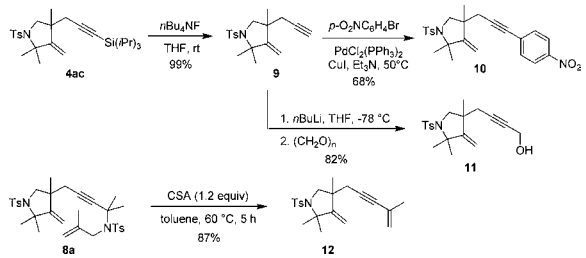
Scheme 8. Proposed Reaction Mechanism



with a bulky substituent were considered instead, its coordination to the metal would presumably be prevented because of the severe steric repulsion with the metal ligands. Accordingly, the cleavage of the ruthenacycle **C** through the metal-assisted σ-bond metathesis reaction[23] leading to the ruthenium acetylide **D**, and subsequent reductive elimination would release the 1,5-enyne adduct with concomitant regeneration of Ru(II) species.

The conversions of the present hydroalkynylative cyclization adducts into more functionalized compounds were briefly examined taking advantage of the (trialkylsilyl)ethyne subunit as the ethyne equivalent (Scheme 9). For instance, proto-

Scheme 9. Synthetic Transformations of 4ac and Dimer 8a



desilylation of **4ac** followed by the Sonogashira cross-coupling with 1-bromo-4-nitrobenzene provided enyne **10**. Treatment of **9** with *n*-butyllithium and subsequent addition of formaldehyde furnished enynol **11**. *In this way, a wide variety of terminal alkynes unsuitable for the coupling reaction can indirectly be used.* Similarly, treatment of the dimer **8a** with camphorsulfonic acid resulted in the elimination of *N*-methallyl-*N*-tosylamine so as to provide the conjugated enyne **12** in 87% yield.

In summary, we have developed an unprecedented ruthenium-catalyzed coupling reaction of enynes and terminal alkynes providing highly substituted five-membered cyclic compounds featuring the 1,5-enyne motif. Unlike the more traditional alkynophilic metal catalysts (Pt, Au) used for the domino enyne cyclization−nucleophile addition reactions, the presented transformation involved the cleavage of a ruthenacyclopentene intermediate through the metal-assisted σ-bond metathesis reaction with a terminal alkyne capped with a bulky substituent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01901.

DOI: 10.1021/acs.orglett.6b01901
Org. Lett. 2016, 18, 4040−4043

Experimental procedures and NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: alphonse.tenaglia@univ-amu.fr.

Author Contributions

†R.L. and Z.N. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the CNRS and MESR for financial support. R.L. and Z.N. are grateful for Ph.D. fellowships from the China Scholarship Council (CSC). We thank Dr. I. DeRiggi (ECM) for help with the NMR spectra analysis and Dr. A. Vasseur (ECM) for fruitful discussions.

DEDICATION

This paper is dedicated to Professor Barry M. Trost (Stanford University) on the occasion of his 75th birthday.

REFERENCES

(1) (a) Genêt, J.-P.; Toullec, P. Y.; Michelet, V. In *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*; Trost, B. M., Li, C.-J., Eds; Wiley-VCH: Weinheim, 2015; pp 27−67. (b) Huguet, N.; Echavarren, A. M. In *Gold Catalysis—An Homogeneous Approach*; Toste, F. D., Michelet, V., Eds.; Imperial College Press: London, 2014; pp 275−330.

(2) (a) Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **1997**, *38*, 8695. (b) Galland, J.-C.; Dias, S.; Savignac, M.; Genêt, J.-P. *Tetrahedron* **2001**, *57*, 5137. (c) Charruault, L.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2002**, *43*, 4757. (d) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M.-N.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, *2003*, 706.

(3) (a) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (b) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J.-P. *Chem. Commun.* **2004**, 850.

(4) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; Lopez, S.; Jimenez-Nuñez, E.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M. *Chem. - Eur. J.* **2006**, *12*, 1677. (c) Genin, E.; Leseurre, L.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Synlett* **2007**, *2007*, 1780.

(5) Faller, J. W.; Fontaine, P. P. *J. Organomet. Chem.* **2006**, *691*, 1912.

(6) Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609.

(7) (a) Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549. (b) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293. (c) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. - Eur. J.* **2003**, *9*, 2627. (d) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

(8) Leseurre, L.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Org. Lett.* **2007**, *9*, 4049.

(9) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721.

(10) Au: (a) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427. (b) Leseurre, L.; Chao, C.-M.; Seki, T.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Tetrahedron* **2009**, *65*, 1911. (c) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698. (d) Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Chem. - Eur. J.* **2009**, *15*, 1319. Pt: (e) Toullec, P. Y.; Chao, C.-M.; Chen, Q.; Gladiali, S.; Genêt, J.-P.; Michelet, V. *Adv. Synth. Catal.* **2008**, *350*, 2401. (f) Pradal, A.; Gladiali, S.; Michelet, V.; Toullec, P. Y. *Chem. - Eur. J.* **2014**, *20*, 7128.

(11) (a) Tanaka, K.; Otake, Y.; Sagae, H.; Noguchi, K.; Hirano, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1312. (b) Tsuchikama, K.; Kuwata, Y.; Tahara, Y.-K.; Yoshinami, Y.; Shibata, T. *Org. Lett.* **2007**, *9*, 3097.

(12) (a) Santhoshkumar, R.; Mannathan, S.; Cheng, C.-H. *Org. Lett.* **2014**, *16*, 4208. (b) Santhoshkumar, R.; Mannathan, S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2015**, *137*, 16116.

(13) (a) Evans, P. A.; Sawyer, J. R.; Lai, K. W.; Huffman, J. C. *Chem. Commun.* **2005**, 3971. (b) Shibata, T.; Arai, Y.; Tahara, Y.-K. *Org. Lett.* **2005**, *7*, 4955.

(14) For selected recent reviews, see: (a) Garcia-Garrido, S. E. In *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*; Trost, B. M., Li, C.-J., Eds.; Wiley-VCH: Weinheim, 2015; p 301. (b) Trost, B. M.; Masters, J. T. *Chem. Soc. Rev.* **2016**, *45*, 2212.

(15) (a) *Transition-Metal-Mediated Aromatic Ring Construction*; Tanaka, K., Ed.; Wiley: Hoboken, 2013. (b) Alexandrovna, M. I.; Ionin, B. I.; Tebby, J. C. *Alkynes in Cycloadditions*; Wiley: Chichester, 2014; pp 5−105.

(16) (a) Ogata, K.; Murayama, H.; Sugasawa, J.; Suzuki, N.; Fukuzawa, S.-i. *J. Am. Chem. Soc.* **2009**, *131*, 3176. (b) Shibata, Y.; Tanaka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 10917.

(17) (a) Ogata, K.; Sugasawa, J.; Atsuumi, Y.; Fukuzawa, S.-i. *Org. Lett.* **2010**, *12*, 148. (b) Ogata, K.; Sugasawa, J.; Fukuzawa, S.-i. *Angew. Chem., Int. Ed.* **2009**, *48*, 6078.

(18) (a) Ogata, K.; Sugasawa, J.; Atsuumi, Y.; Fukuzawa, S.-i. *Org. Lett.* **2010**, *12*, 148. (b) Hoshino, Y.; Shibata, Y.; Tanaka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 9407. (c) Hara, J.; Ishida, M.; Kobayashi, M.; Noguchi, K.; Tanaka, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 2956.

(19) The exact role of the propargylic methyl substituents remains to be established. A working hypothesis rests upon the hyperconjugation in intermediate **B** (Scheme 8), which might favor the σ-bond metathesis step (intermediate **C**).

(20) Varela, J. A.; Rubin, S. G.; Gonzalez-Rodriguez, C.; Castedo, L.; Saa, C. *J. Am. Chem. Soc.* **2006**, *128*, 9262.

(21) For transition-metal-catalyzed dimerization of enynes leading to structurally different compounds, see: (a) Yamamoto, Y.; Kuwabara, S.; Ando, Y.; Nagata, H.; Nishiyama, H.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 6697. (b) Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K.; Han, W.-S.; Kang, S. O. *J. Org. Chem.* **2006**, *71*, 9366. (c) Ez-Zoubir, M.; Le Boucher d'Herouville, F.; Brown, J. A.; Ratovelomanana-Vidal, V.; Michelet, V. *Chem. Commun.* **2010**, *46*, 6332.

(22) Cyclobutene formation through the Ru-catalyzed intermolecular [2 + 2] cycloaddition between alkynes and alkenes is well documented but mainly limited to norbornene derivatives. (a) Parthasarathy, K.; Cheng, C.-H. In *Comprehensive Organic Synthesis II*, 2nd ed.; Knochel, P., Molander, G. A., Eds.; Elsevier: Amsterdam, 2014; Vol. 5, pp 222−272. The intramolecular version of this reaction is quite rare. To the best of our knowledge, there is only one report describing the formation of 1-iodocyclobutene through 1,7-enynes (featuring the iodoalkyne unit) cyclization utilizing a cationic Ru catalyst ($[Cp^*Ru(MeCN)_3]PF_6$). (b) Fürstner, A.; Schlecker, A.; Lehmann, C. W. *Chem. Commun.* **2007**, 4277−4279.

(23) For a rare example of σ-bond metathesis involving a CpRu complex and catecholborane, see: (a) Hartwig, J. F.; Bhandari, S.; Rablen, P. R. *J. Am. Chem. Soc.* **1994**, *116*, 1839. For a review, see: (b) Waterman, R. *Organometallics* **2013**, *32*, 7249.

DOI: 10.1021/acs.orglett.6b01901
Org. Lett. 2016, 18, 4040−4043