J|A|C|S
ARTICLES
Published on Web 07/07/2006

Au- and Pt-Catalyzed Cycloisomerizations of 1,5-Enynes to Cyclohexadienes with a Broad Alkyne Scope

Jianwei Sun, Matthew P. Conley, Liming Zhang, and Sergey A. Kozmin*

Contribution from the University of Chicago, Department of Chemistry, 5735 South Ellis Avenue, Chicago, Illinois 60637

Received May 19, 2006; E-mail: skozmin@uchicago.edu

Abstract: We describe the development of gold- and platinum-catalyzed cycloisomerizations of 1,5-enynes. This catalytic process displays a wide alkyne scope and furnishes a range of highly functionalized 1,4- and 1,3-cyclohexadienes. In the case of 1-siloxy-1-yne-5-enes, the reactions are efficiently catalyzed by AuCl (1 mol %) at ambient temperature to afford siloxy cyclohexadienes or the corresponding 1,2- and 1,3-cyclohexenones upon subsequent protodesilylation. We propose that the reaction proceeds via a novel mechanism involving a series of 1,2-alkyl shifts. Elucidation of this unusual reaction mechanism enabled us, in turn, to significantly expand the scope of the cycloisomerization by incorporation of a quaternary center at the C(3) position of the enyne. Indeed, we established that $PtCl_2$ (5 mol %) efficiently catalyzed the cycloisomerizations of 1,5-enynes containing terminal, internal, and arene-conjugated alkynes. Since a variety of 1,5-enynes are readily accessible, the cycloisomerization provides a rapid approach to a wide range of highy substituted cyclohexadienes for many subsequent synthetic applications.

Introduction

Transition-metal-catalyzed cycloisomerization of 1,6-enynes represents an efficient strategy for the assembly of a variety of five-membered and six-membered alkenes and dienes.[1] The corresponding metal-catalyzed cycloisomerizations of 1,5-enynes have been developed to a much less significant extent. Indeed, the only known mode of reactivity of 1,5-enynes entails the formation of [3.1.0] bicyclohexenes.[2,3] While important from a conceptual viewpoint, the synthetic utility of this process is limited to producing cyclopropane-fused bicyclic alkenes. Herein, we describe the development of gold- and platinum-catalyzed cycloisomerizations of 1,5-enynes to furnish a range of 1,4- and 1,3-cyclohexadienes. This process was enabled by our recent discovery of the gold-catalyzed skeletal rearrangement of 1-siloxy-5-en-1-ynes,[4] which was determined to proceed via a remarkable mechanism involving a series of 1,2-alkyl shifts. Elucidation of this novel reaction mechanism enabled us, in turn, to significantly extend the scope of the initial cycloisomerization precursors, which now includes 1,5-enynes containing terminal, internal, arene-conjugated, and electron-rich alkynes. Since a variety of 1,5-enynes are readily accessible, the cycloisomerization provides a rapid approach to a wide range of highly substituted cyclohexadienes for many subsequent synthetic applications.

Results and Discussion

In the course of our investigation of basic reactivity of siloxy alkynes,[5] we have established that $HNTf_2$ was capable of efficient activation of an electron-rich alkyne moiety toward subsequent intramolecular additions of arenes and alkenes to provide efficient access to substituted tetralone and cyclohexenone derivatives.[5d] While the reaction of siloxy alkynes with arenes proceeded using a catalytic amount of the Brønsted acid promoter, the corresponding enyne cyclizations required the use of a stoichiometric amount of $HNTf_2$. In search of a catalytic enyne cyclization protocol, we examined the effect of a series of transition metal salts on cyclization of siloxy enyne **1** (Table 1). We envisioned that subjection of enyne **1** to an appropriate catalyst capable of chemoselective electrophilic activation of the alkyne moiety should induce the desired 6-endo-cyclization, followed by protodemetalation to give the expected 1-siloxy-1,3-cyclohexadiene. Our selection of metal salts was based on the known alkynophilicity of platinum(II),[6] silver(I),[7] and gold(I)[8] compounds. While $AgNTf_2$ proved to be an excellent catalyst in other reactions involving siloxy alkynes, subjection of enyne **1** to various amounts of either $AgNTf_2$ or AgOTf resulted in formation of multiple reaction products (Table 1, entries 1 and 2). However, treatment of siloxy enyne **1** with 5 mol % AuCl gave a new product that was subsequently

(1) For recent reviews see: (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (b) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (c) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (d) Driver, S. T.; Geissert, A. J. *Chem. Rev.* **2004,** *104*, 1317. (e) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2003**, *9*, 2627. (f) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*, 397.

(2) (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (b) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouries, V.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656. (c) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858.

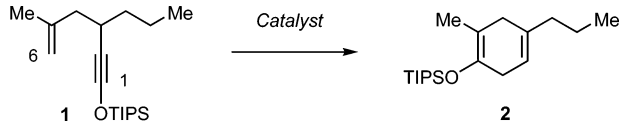
(3) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402.

(4) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806.

(5) (a) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274. (b) Sweis, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 7442. (c) Reddy, D. S.; Kozmin, S. A. *J. Org. Chem.* **2004**, *69*, 4860. (d) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204. (e) Sun, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13512.

10.1021/ja063384n CCC: $33.50

Table 1. Optimization of Cycloisomerization



1 2

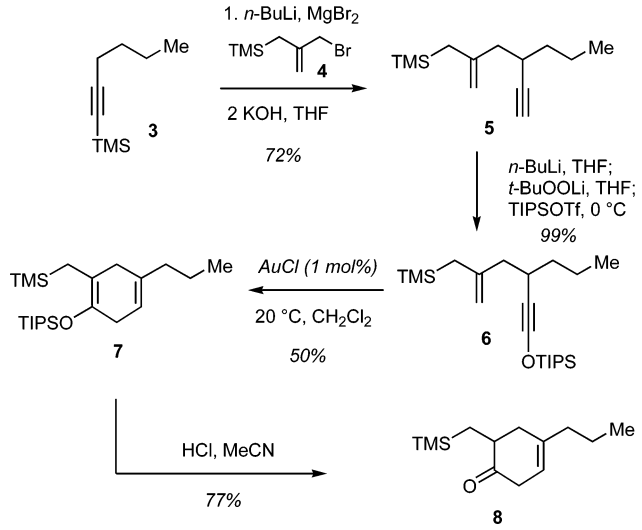
entry	catalyst	solvent	temp, °C	yield,[a] %
1	$AgNTf_2$ (10 mol %)	CH_2Cl_2	20	<5[b]
2	AgOTf (10 mol %)	CH_2Cl_2	20	<5[b]
3	AuCl (5 mol %)	CH_2Cl_2	20	93
4	AuCl (1 mol %)	CH_2Cl_2	20	93
5	PPh_3AuCl (5 mol %)	CH_2Cl_2	20	<5[c]
6	$PPh_3AuCl/AgBF_4$ (5 mol %)	CH_2Cl_2	20	88
7	$PtCl_2$ (10 mol %)	toluene	80	66

[a] Refers to isolated yields of spectroscopically pure products that were full characterized by NMR, IR, and MS. [b] Complex mixture of products was observed. [c] No reaction was observed.

identified as siloxy cyclohexadiene **2** (entry 3). Structural assignment of **2** was based on a series of NMR studies, including COSY, NOESY, HMQC, and HMBC experiments, which unambiguously established the structure of cyclohexadiene **2**, corresponding to a formal and highly unusual migration of a siloxy substituent from the C(1) to the C(6) position. Subsequent experimentation established that the catalytic loading of AuCl can be decreased to 1 mol % with the reaction being complete within 20 min at room temperature, highlighting the remarkable catalytic efficiency of this process. Addition of triphenylphosphine resulted in inhibition of catalytic activity presumably due to the competitive binding of the phosphine ligand to Au(I). The catalytic efficiency, however, can be recovered using Au(PPh_3)Cl in the presence of $AgBF_4$, presumably due to the generation of a cationic gold complex. Among several other metal salts examined, we found that the cycloisomerization can also be catalyzed by $PtCl_2$ (10 mol %) at 80 °C in benzene to give cyclohexadiene **2** in 66% yield (entry 7). These studies revealed that AuCl proved to be the most effective catalyst for the cycloisomerization of siloxy enyne **1**.

Our investigation of the scope of the Au-catalyzed skeletal reorganization of siloxy enynes began with the preparation of enyne **6** (Scheme 1). Propargylic alkylation of alkyne **3** with

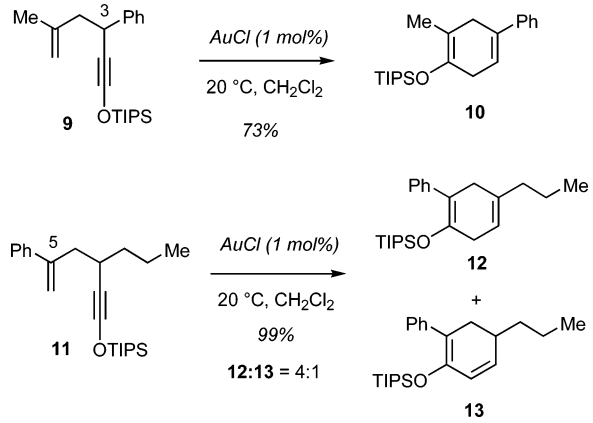
Scheme 1



allyl bromide **4**,[9] followed by desilylation, afforded terminal alkyne **5**. Generation of lithium acetylide, followed by oxidation with *t*-BuOOLi and silylation using TIPSOTf, furnished the required siloxy alkyne **6** in quantitative yield.[10] Subjection of siloxy enyne **3** to AuCl (1 mol %) at 20 °C in CH_2Cl_2 afforded the expected siloxy diene **7** in 50% yield (Scheme 1). The 5-trimethylsilylmethyl group was retained in the cyclization product **4** despite the labile nature of this material. Subsequent treatment of siloxy diene **7** with aq. HCl in MeCN afforded 1,3-cyclohexenone **8** in 77% yield. This experiment demonstrated chemoselective protodesilylation of the silyl enol ether fragment in the presence of the allyl silane moiety, providing efficient synthetic access to a nonconjugated cyclohexenone.

We next examined the outcome of the cycloisimerization upon introduction of the aryl moieties into the cyclization substrates (Scheme 2). To this end, we prepared 3-phenyl and 5-phenyl

Scheme 2



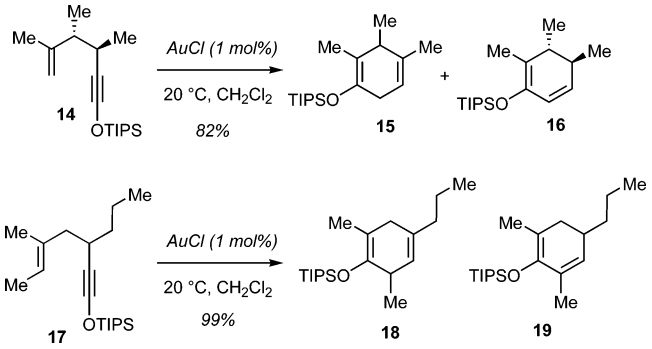
substituted enynes **9** and **11** using a similar alkylation/oxidation tactic as that described above. Subjection of siloxy enyne **9** to the standard cycloisomerization protocol afforded the expected siloxy cyclohexadiene **11** in 73% yield, demonstrating that aryl substitution at the C(3) position was well tolerated. Treatment of enyne **11** with AuCl resulted, however, in the formation of

(6) (a) Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567. (b) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901. (c) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104. (d) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. (e) Fürtsner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (f) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801. (g) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (h) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (i) Mainetti, E.; Mouries, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132. (j) Martin-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757. (k) Cadran, N.; Cariou, K.; Herve, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408.
(7) (a) Ferrara, J. D.; Djebli, A.; Tessier-Youngs, C.; Youngs, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 647. (b) Clark, T. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9522 and references therein.
(8) (a) Hashmi, A. S. K., Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000** *122*, 11553. (b) Hashmi, A. S. K., Schwartz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (c) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 23. (d) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (e) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. (f) He, C.; Shi, Z. *J. Org. Chem.* **2004**, *69*, 3669. (g) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (h) Yao, X.; Li, C. *J. Am. Chem. Soc.* **2004**, *126*, 6884. (i) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (j) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, 126, 11164. (k) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978. (l) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962.
(9) *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1984; Vol. B, pp 107−145.
(10) Julia, M.; Saint-Jalmes, V. P.; Verpeaux, J.-N. *Synlett* **1993**, *3*, 233.

two reactions products, which were identified as the expected 1,4-diene **12** and a conjugated 1,3-diene **13** produced in a 4:1 ratio.

A similar outcome was observed in cycloisomerizations of enynes **14** and **17** (Scheme 3). Subjection of enyne **14** to the

Scheme 3

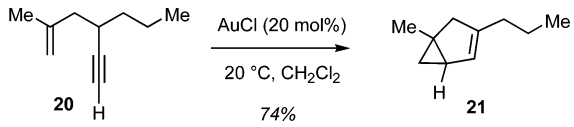


standard cyclization protocol afforded cyclohexadienes **15** and **16** in a 6:1 ratio (82% combined yield). Cycloisomerization of enyne **17** containing a trisubstituted alkene moiety produced dienes **18** and **19** in a 3:1 ratio in quantitative yield. It is noteworthy that skeletal reorganization of enyne **17** resulted in the switching of the C(6)-methyl and the C(1)-siloxy groups, corresponding to the formal metathesis of the alkene and alkyne fragments. Apart from expanding the scope of this novel cycloisomerization reaction, these experiments provided further insight that enabled us to provide a mechanistic rationale of the experimental observations.

Formation of nonconjugated and conjugated cyclohexadienes can be explained using mechanistic analysis presented in Scheme 4. The process begins by activation of siloxy alkyne **B** with π-acidic AuCl toward the intramolecular attack by the proximate alkene (structure **C**), resulting in the cyclization to give cyclopropyl gold carbene **E**. Formation of similar metal carbene intermediates has been proposed in the Pt- and Au-catalyzed cycloisomerizations of 1,5- and 1,6-enynes en route to [3,1,0] and [4,1,0] bicycloalkenes.[2,3] However, instead of the previously observed hydride migration and elimination pathway, the intermediate gold carbene **E** undergoes a highly unusual 1,2-alkyl shift to give oxocarbenium ion **F**. Another 1,2-alkyl shift, followed by fragmentation of the zwitterionic intermediate **G**, affords six-membered gold carbene **H**. Depending on the nature of the R^1 and R^2 substituents of the enyne, gold carbene **H** can participate in two alternative elimination pathways to afford isomeric 1,3- and 1,4-cyclohexadienes (**I** and **J**) with a concomitant regeneration of AuCl.

To further probe the effect of 1-siloxy substitution, we subjected enyne **20** (Scheme 5) to the standard cyclization

Scheme 5



protocol. The reaction produced [3.1.0] bicyclohexene **21** as a single product. Similar observations have been reported by Echavarren,[3] Fürstner,[2a] Malacria,[2b] and Toste.[2c] These results further highlight the crucial role of a siloxy alkyne moiety on the outcome of the enyne cycloisomerization, presumably due to the stabilization of cationic intermediate **E**.

The mechanistic analysis presented in Scheme 4 suggested to us that the introduction of a quaternary center at the C(3) position of the cycloisomerization substrate (Table 2) should favor exclusively the reaction pathway leading to the conjugated diene product (**G** → **I**, Scheme 4) due to the absence of the C(3) hydrogen required for the formation of 1,4-diene. However, the caveat was that the introduction of the quaternary center in the direct proximity to the siloxy alkyne moiety could inhibit the coordination of the AuCl with the alkyne required for initiation of the catalytic cycle. To our delight, subjection of enynes **22** to the general cycloisomerization conditions afforded exclusively a conjugated diene **23** in 88% yield (entry 1, Table 2). Similarly, treatment of phenyl-substituted enyne **24** with AuCl afforded the expected product **25** in 89% yield (entry 2). Finally, cycloisomerization of dienyne **26** proceeded with complete chemoselectivity for the disubstituted alkene to afford **27** as a single reaction product in 84% yield (entry 3). Additional studies revealed that while both di- and trisubstituted alkenes efficiently participated in the cycloisomerization process, ter-

Scheme 4

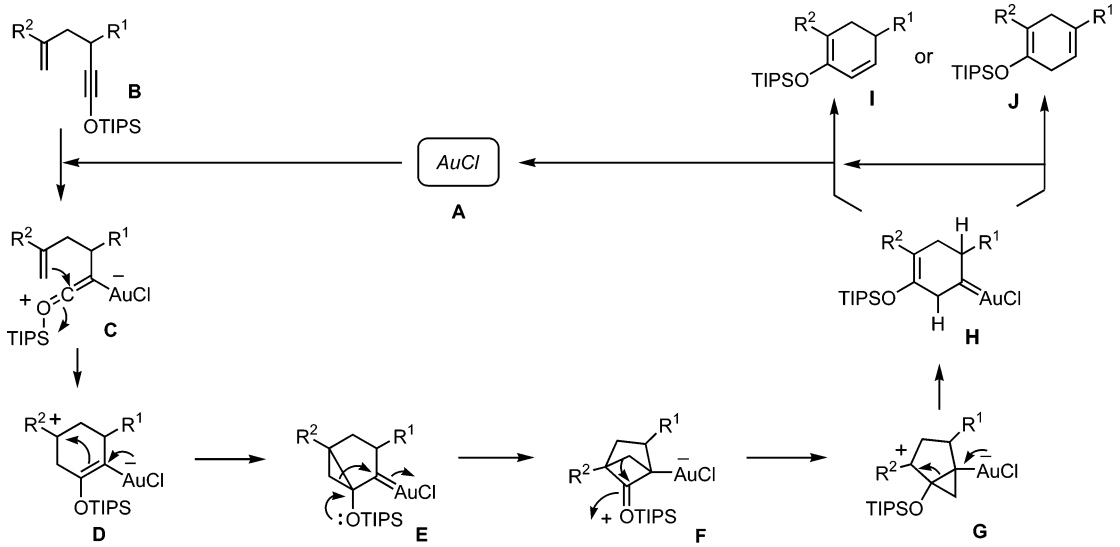
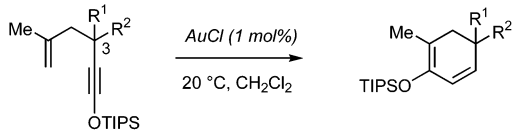
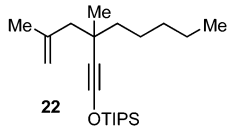
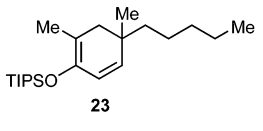
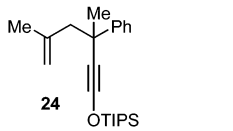
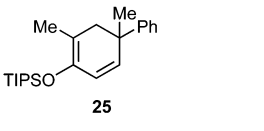
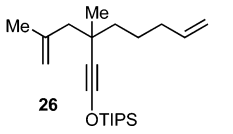
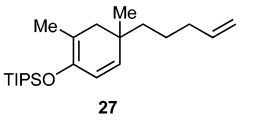


Table 2. Au-Catalyzed Cycloisomerization of Siloxy Enynes



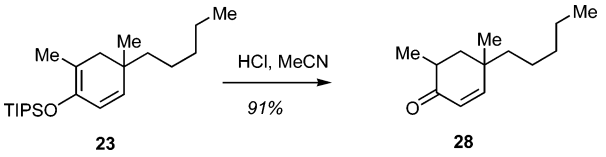
Entry	Siloxy Alkyne	Product	Yield, %[a]
1	 **22**	 **23**	88
2	 **24**	 **25**	89
3	 **26**	 **27**	84

[a] Refers to isolated yields of spectroscopically pure products that were full characterized by NMR, IR, and MS.

minal monosubstituted alkenes proved to be unreactive under the current catalytic protocol.

2-Siloxy-1,3-cyclohexadienes produced by the gold-catalyzed cycloisomerizations can be efficiently converted to 1,2-cyclohexenones, highlighting the general synthetic utility of this process. A representative example is depicted in Scheme 6.

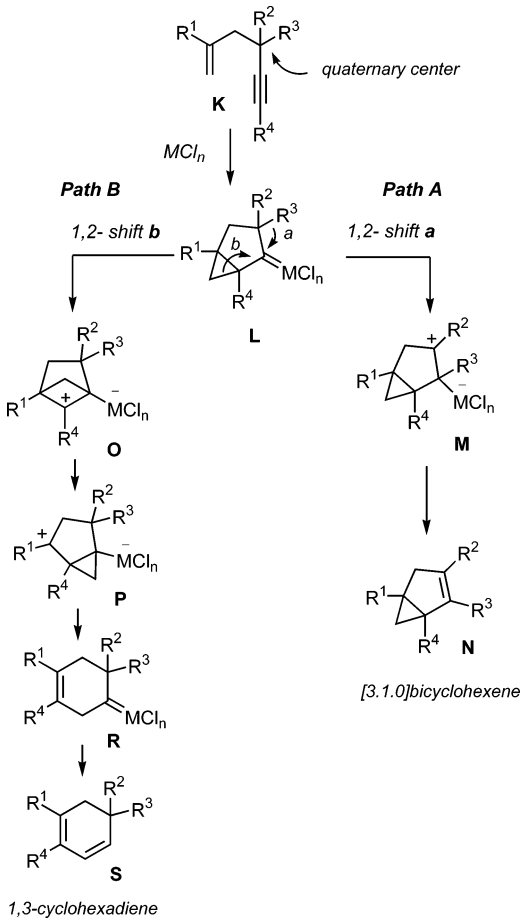
Scheme 6



Treatment of siloxy diene **23** with aqueous HCl in MeCN at ambient temperature afforded cyclohexenone **28** in 91% yield.

Our studies established that the presence of a siloxy alkyne moiety in the enyne cycloisomerization precursor was responsible for the novel skeletal reorganization to furnish 1,4- or 1,3-cyclohexadienes. In the absence of the siloxy alkyne, the cyclization afforded exclusively the [3.1.0] bicyclohexene. The two alternative mechanistic pathways are depicted in Scheme 7. The initial step is the formation of a cyclopropyl metal carbene **L**, which can undergo two alternative transformations depending on the substitution at the C(1) and the C(3) position of enyne. Indeed, the presence of a siloxy group at the alkyne terminus (R^4 = OTIPS) strongly favors mechanistic path B due to efficient stabilization of cationic intermediate **O**. In the absence of such stabilization and the presence of a β-hydrogen (R^3 = H) the reaction follows path A leading to formation of [3.1.0] bicyclohexene **N** via an alternative 1,2-shift, followed by demetalation. This mechanistic analysis suggested to us that removal of the labile hydrogen at the C(3) of the enyne by incorporation of the quaternary center (R^2, R^3 = Alkyl) may favor the formation of cyclohexene **S** even in the absence of the siloxy group at the alkyne terminus. This intriguing possibility would result in significant expansion of the alkyne

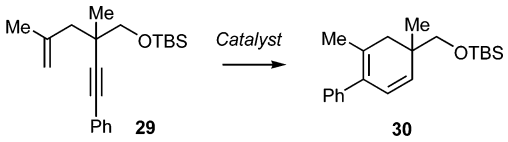
Scheme 7



scope of the cycloisomerization process. It was our expectation that the presence of the quaternary center at the C(3) should disfavor path A due to the lower migratory aptitude of the C(3) alkyl substituents. The reaction would then proceed via path B leading to [2.1.1] bicyclic intermediate **O**, followed by another 1,2-alkyl shift, fragmentation, and elimination to give cyclohexadiene **S**.

To test this mechanism-based hypothesis, we examined cycloisomerization of enyne **29** containing a phenyl-substituted alkyne (Table 3). Subjection of enyne **29** to AuCl indeed

Table 3. Optimization of Pt-Catalyzed 1,5-Enyne Cycloisomerization

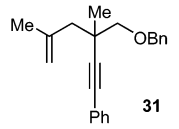
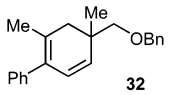
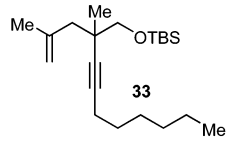
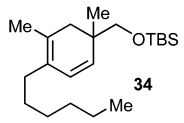
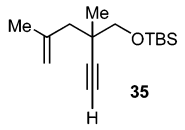
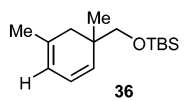
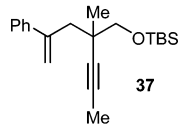
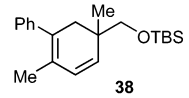
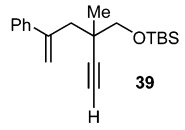
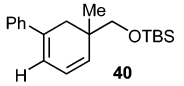
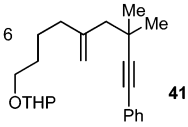
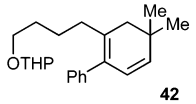
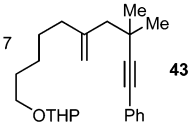
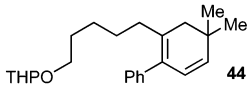
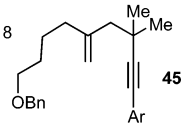
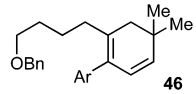
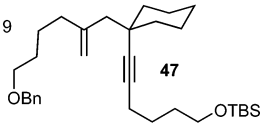
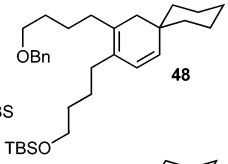
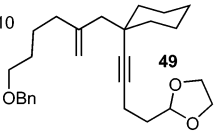
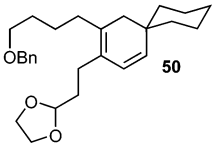
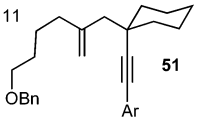
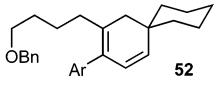


entry	catalyst	solvent	temp, °C	yield,[a] %
1	AuCl (5 mol %)	CH_2Cl_2	20	16
2	$AuCl_3$ (5 mol %)	CH_2Cl_2	20	22
3	PPh_3AuCl (5 mol %)	CH_2Cl_2	20	<5
4	PPh_3AuSBF_4 5(mol %)	CH_2Cl_2	20	<5
5	$AgNTf_2$ (5 mol %)	toluene	80	<5
6	$PtCl_2$ (15 mol %)	toluene	20	<5
7	$PtCl_2$ (15 mol %)	toluene	80	62
8	$PtCl_2$ (5 mol %)	toluene/MeCN	80	66

[a] Refers to isolated yields of spectroscopically pure products that were full characterized by NMR, IR, and MS.

produced the desired cyclohexadiene **30** albeit in a disappoint-

Table 4. Pt-Catalyzed Cycloisomerization of 1,5-Enynes

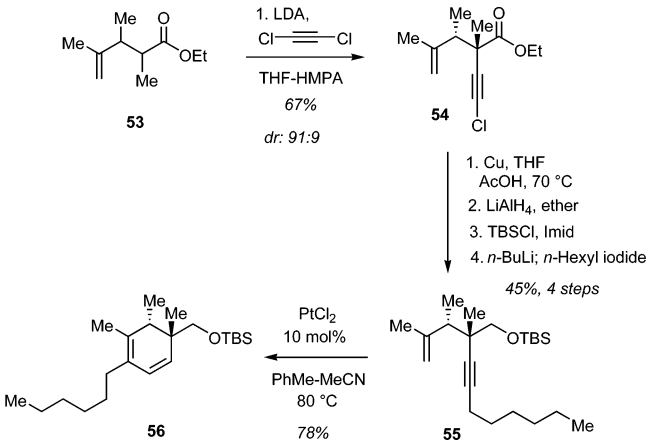
Entry	*Enyne*	*Product*	*Yield, %*[a]
1	 **31**	 **32**	63
2	 **33**	 **34**	81
3	 **35**	 **36**	73
4	 **37**	 **38**	70
5	 **39**	 **40**	77
6	 **41**	 **42**	72
7	 **43**	 **44**	69
8	 **45**	 **46** Ar = p-MeOC$_6$H$_4$	82
9	 **47**	 **48**	77
10	 **49**	 **50**	78
11	 **51**	 **52** Ar = p-MeOC$_6$H$_4$	78

[a] Refers to isolated yields of spectroscopically pure products that were full characterized by NMR, IR, and MS.

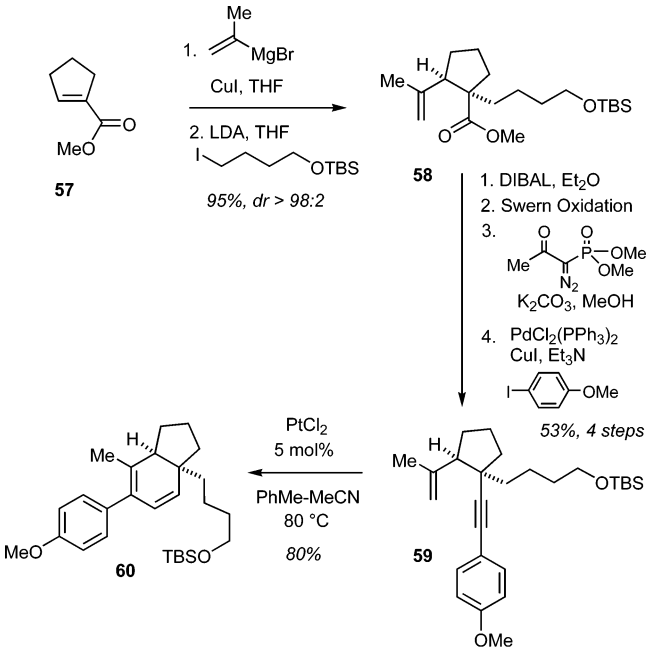
ingly low yield accompanied by several other products (entry 1). The use of $AuCl_3$, as well as a range of other gold-based and silver-based compounds, proved inefficient at catalyzing the reaction (entries 2−5). These results could be explained by a highly reactive nature of electrophilic gold carbene **L** (M = Au, Scheme 7) leading to a competition between the two possible reaction pathways A and B. Indeed, Toste reported the Au(I)-catalyzed formation of [3.1.0] bicyclohexene-type products as a result of the C(3)-alkyl group migration,[2c] corresponding to reaction pathway A in Scheme 7. We decided to examine the use of Pt(II)-based catalysts to promote the desired transformation, since platinum carbene **L** (M = Pt, Scheme 7) would be expected to exhibit lower reactivity and could potentially lead to a higher selectivity for the desired path B. While $PtCl_2$ (15 mol %) proved to be unreactive at ambient temperature (entry 6), the reaction proceeded at 80 °C in toluene to give cyclohexadiene **30** in 62% yield, a much higher efficiency compared to that when using gold complexes. Aiming at further reduction in the catalyst loading and improvement of the reaction efficiency, we examined a range of additives and found that the use of toluene containing a stoichiometric amount of MeCN gave the best results. Cyclohexadiene **30** was produced in 66% isolated yield using 5 mol % of $PtCl_2$. Overall, these studies revealed that Pt-based catalysis proved to be more effective than Au-based systems for cycloisomerization of 1-phenyl-substituted enyne **29**.

Investigation of the scope of Pt-catalyzed 1,5-enyne cycloisomerization revealed that a range of substituted and terminal alkynes can efficiently participate in this process (Table 4), significantly expanding a range of cyclohexadienes that can be assembled by the cycloisomerization process. Subjection of the benzyl ether containing 1-phenyl enyne **31** to the cycloisomerization protocol afforded the expected diene **32** in 63% yield (entry 1). Furthermore, the use of either 1-alkyl-substituted or terminal alkynes **33** and **35** resulted in efficient skeletal reorganizations into the reaction products **34** and **36**, obtained in 81% and 73% yield, respectively (entries 2 and 3). The results presented in entries 4 and 5 indicated that aryl substitution at the C(5) position of the enyne was well tolerated. Removal of the siloxy group at the C(3) position did not have any effect on the efficiency of the cycloisomerization. Indeed, subjection of alkynes **41**, **43**, and **45** to standard catalytic protocol afforded the corresponding cyclohexadienes **42**, **44**, and **46** in 72−82% yield (entries 6, 7, and 8). Furthermore, the process enabled rapid construction of spirocyclic dienes **48**, **50**, and **52** (entries 9, 10, and 11) from the corresponding cyclohexane-containing enynes. While cycloisomerizations were successful using a range of enynes containing disubstituted alkenes, at present, trisubstituted and terminal olefins did not afford the cycloisomerization products with high efficiency.

Scheme 8



Scheme 9



To probe the effect of increased steric congestion in the tether between the alkene and alkyne units of the cyclization substrate, we assembled enyne **55** (Scheme 8) by treatment of lithium enolate of ester **53** with dichloroacetylene in THF−HMPA using the protocol developed by Kende.[11] To our delight, this transformation afforded ester **54** with good diastereoselectivity. Reduction of chloroalkyne **54** with Cu powder and AcOH, conversion of the resulting ester to the corresponding alcohol with $LiAlH_4$, installation of the TBS group, and alkylation of the terminal alkyne with hexyl iodide afforded enyne **55**. Subjection of **55** to the general cyclization protocol afforded the expected cyclohexadiene **56** in 78% yield as a single diastereomer. The structure of **56** was unambiguously established by a combination of the COSY and NOESY experiments, validating the initial diastereochemical prediction of the outcome of the alkylation of ester **53**. This example provides another demonstration of the synthetic potential of the enyne cycloisomerization process to enable effective control of the final substitution of a complex cyclohexadiene product by the construction of the corresponding acyclic 1,5-enyne precursor.

To probe the utility of the cycloisomerization process for the assembly of fused bicyclic systems incorporating multiple stereogenic centers, enoate **57** was subjected to conjugate addition and alkylation, which delivered ester **58** as a single detectable diastereomer (Scheme 9). Conversion of ester **58** to enyne **59** was based on a four-step sequence entailing a DIBAL reduction, Swern oxidation, alkyne formation, and Sonogashira cross-coupling. Subjection of 1,5-enyne **59** to the standard cyclosiomerization conditions (5 mol % of $PtCl_2$, toluene−acetonitrile, 80 °C) afforded [4.3.0] bicyclononadiene **60** in 80% yield. It is noteworthy that the compatibility of a range of hydroxyl and carbonyl protecting groups with the $PtCl_2$-based cycloisomerization protocol, as well as the ability to readily assemble spirocyclic and fused bicyclic dienes, indicates a significant potential of this reaction for subsequent applications in the area of complex molecule synthesis.

Conclusion

In closing, we have described how the initial discovery and elucidation of the reaction mechanism of the Au-catalyzed cycloisomerization of 1-siloxy-5-en-1-ynes had resulted in the development of the corresponding Pt-catalyzed process that enabled significant expansion of the substrate scope. Indeed, a wide range of 1,5-enynes containing terminal, internal, arene-conjugated, and electron-rich alkynes participate in the cycloisomerization under mild conditions and with high efficiency. These unique catalytic transformations proceed via an unusual mechanism involving a series of 1,2-alkyl shifts resulting in a rapid assembly of a variety of densely functionalized cyclohexadienes as well as the corresponding cyclohexenones.

Acknowledgment. This work was supported by the NSF CAREER (CHE-0447751). S.A.K. thanks the Dreyfus Foundation, the Alfred P. Sloan Foundation, Amgen, and GlaxoSmithKline for additional financial support.

Supporting Information Available: Full characterization of new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

JA063384N

(11) Kende, A. S.; Fludzinski, P.; Hill, J. H. *J. Am. Chem. Soc.* **1984**, *106*, 3551.