Organic LETTERS

Letter

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Ruthenium Catalyzed Cycloisomerization of Silicon-Tethered 1,7-Enynes To Give Exocyclic 1,3-Dienes

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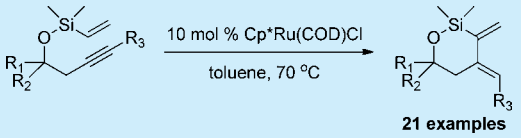
Supporting Information

ABSTRACT: The cycloisomerization of vinyl silicon-tethered 1,7-enynes has been accomplished using catalytic Cp*Ru(COD)Cl. The products possess a new silane moiety and trisubstituted alkenes as part of the diene system. The reaction scope includes aryl, alkyl, vinyl, and cyclopropyl alkyne functionalities. Silicon was found not to be a mandatory component of the tether. The utility of the products was demonstrated through manipulation of the vinyl silane and Diels−Alder chemistry.



Transition-metal-catalyzed C−C bond forming reactions offer a convenient synthetic protocol for the formation of conjugated dienes.[1] Conjugated dienes are of great importance due to their prominence in a variety of natural products that possess a wide array of biological activity.[2] These functionalities are also found in myriad synthetic intermediates in route to the aforementioned naturally occurring medicinally relevant compounds. One of the most common synthetic methods for acquiring dienes is the cycloisomerization of enynes. Cycloisomerization protocols are beneficial because these reactions generate minimal byproducts and require few reagents.[3] Another advantage is the relative ease of synthesizing the enyne starting materials.[3a] Furthermore, cycloisomerization reactions are facile and allow for the rapid generation of molecular complexity; this is particularly true when the process is facilitated by a metal catalyst.[4] The use of transition metals to catalyze the cycloisomerizations of enynes is an atom-economical process to form diene scaffolds.[1b] The use of ruthenium and other transition metals to catalyze the cycloisomerization of 1,5- and 1,6-enynes has previously been explored.[5]

While the above systems have been thoroughly investigated, similar systems of 1,7-enynes have received only cursory attention. The cycloisomerization of 1,7-enynes can proceed to give products which contain diene functionality[4,6] and products which do not contain diene functionality.[7] Typically, the ruthenium-catalyzed cycloisomerization of 1,7-enynes afford 1,4-dienes. Trost and coworkers have extensively explored ruthenium catalyzed methods for the synthesis of 1,4-dienes (Figure 1, eq 1).[3a,d,8] We believe a complementary transformation that proceeds through a ruthenacyclopentene[9] could undergo endocyclic β-H elimination followed by reductive elimination to give the desired 1,3-diene product (Figure 1, eq 2).

We recently reported the silylvinylation of alkynes to give **2a** as the major product. We observed diene **3a** as the minor byproduct of this process (Scheme 1, eq 1).[10]

Interestingly, when alkyl-substituted alkynes were employed, the cycloisomerization adducts were the only product observed (Scheme 1, eq 2). We sought to design a route to selectively obtain **3a** by moving away from ruthenium hydride complexes,

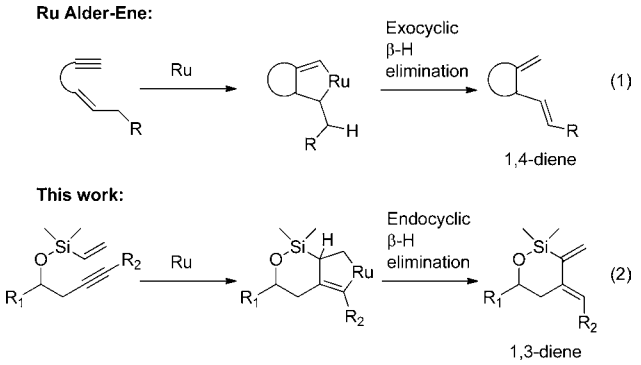
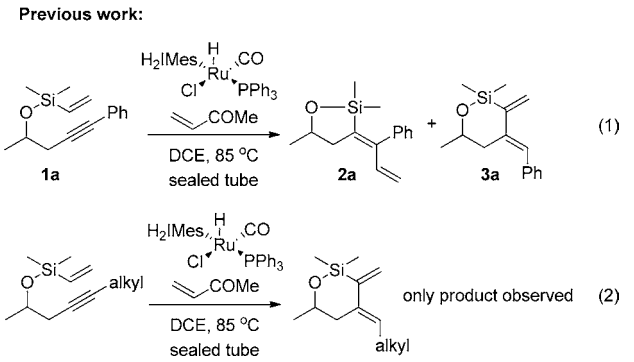


Figure 1. Ruthenium-catalyzed cycloisomerization.

Scheme 1. Trans-silylvinylation of Alkynes



which are known to form dienes from enynes through hydrometalation reactions.[11] Thus, we began by exploring Ru complexes that have previously displayed a propensity for ruthenacycle formation, thereby suppressing formation of **2a**.

Initially, alkyne **1a** was reacted with 10 mol % of the ruthenium *p*-cymene dimer **4** (Table 1, entry 1) in toluene at 70 °C.

Received: September 11, 2014
Published: October 9, 2014

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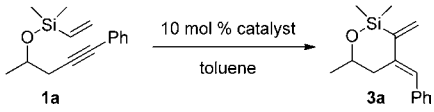
dx.doi.org/10.1021/ol5026926 | Org. Lett. 2014, 16, 5450−5453

Table 1. Catalyst Screen



1a 3a

entry	catalyst	temp (°C)	time (h)	yield[a]
1	(**4**) $[RuCl_2(p\text{-cymene})]_2$	70	8	NR
2	(**5**) RuCl(Ind)(dppm)	70	18	NR
3	(**6**) CpRuCl(dppm)	70	17	NR
4	(**7**) $[CpRu(MeCN)_3]PF_6$	70	6	NR
5	(**8**) $RuCl(Ind)(PPh_3)_2$	70	17	13
6	(**9**) $CpRuCl(PPh_3)_2$	70	18	86
7	(**10**) $Cp^*RuCl(PPh_3)_2$	70	2	>98
8	(**11**) Cp*RuCl(COD)	70	1	>98
9[b]	(**11**) Cp*RuCl(COD)	70	20	90
10	(**11**) Cp*RuCl(COD)	50	16	>98
11	(**11**) Cp*RuCl(COD)	23	16	11

[a]Crude using ^{1}H NMR vs mesitylene internal standard. NR = no reaction. [b]Reaction run with 5 mol % of **11**

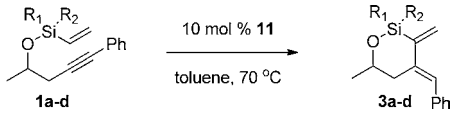
However, no reaction was observed after 8 h. Complexes **5** and **6**, bearing the chelating dppm ligand, also proved ineffective for the cyclization (entries 2 and 3). Switching to a cationic ruthenium source **7** gave no success (entry 4). When the indenyl triphenylphosphine complex **8** was examined we were delighted to observe the desired product **3a** as the sole product by ^{1}H NMR, albeit in 13% yield (entry 5). Due to the poor conversion with complex **8** after 17 h, analogous ruthenium complexes were examined. The cyclopentadienyl (Cp) complex **9** in entry 6 gave full conversion of the starting alkyne after 18 h and 86% yield of **3a** (entry 6). Switching to the pentamethylcyclopentadienyl (Cp*) ligand (complex **10**) proved more effective giving a quantitative crude yield of **3a** in only 2 h (entry 7). Our current hypothesis is that the bulky Cp* moiety increases the rate of product dissociation from the metal.[12] We were pleased to discover that exchanging the triphenylphosphine ligand for the cyclooctadiene (COD) ligand (complex **11**) reduced the reaction time to 1 h without adversely affecting the yield of **3a** (entry 8). Complex **11** has previously been reported to facilitate inter- and intramolecular cycloisomerization reactions with ethylene gas.[9,13] The reaction of **1a** with 5 mol % of **11** proved capricious and resulted in a 90−95% conversion after 17−20 h (entry 9). More consistent results were obtained utilizing 10 mol % of **11**.

Having established Cp*RuCl(COD) (**11**) as the most suitable catalyst for this reaction, additional temperatures were examined. Decreasing the temperature to 50 °C (entry 10) resulted in a significantly longer reaction time, and reactivity at rt (entry 11) was poor. Therefore, entry 8, 10 mol % of **11** at 70 °C, proved to be superior for the transformation. A solvent screen was conducted; toluene proved superior for this reaction.[14] Consequently, *10 mol % ruthenium complex **11** in toluene at 70* °C was implemented as the standard conditions for this reaction.

Utilizing the optimized conditions, variations to the substituents on silicon were explored (Table 2). Both methyl and phenyl moieties were very well tolerated in the reaction (entries 1−3). The methyl-phenyl (entry 2) and diphenyl (entry 3) substituted silanes gave shorter reaction times than entry 1, presumably due to the increased Thorpe−Ingold effect.[15]

Having isopropyl groups on the silicon hindered the reaction and resulted in only a 26% crude yield of **3d** after 2 days (entry 4). We attributed this to the increased steric bulk on the silicon,

Table 2. Variation of Silicon Tether



1a-d 3a-d

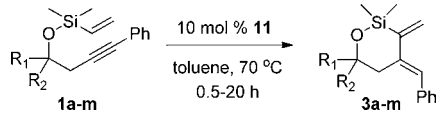
entry	R_1	R_2	time (h)	conv	yield[a,b]
1 (**1a**)	Me	Me	1	100	>98 (82)
2 (**1b**)	Me	Ph	0.5	100	>98 (83)
3 (**1c**)	Ph	Ph	0.5	100	>98 (85)
4 (**1d**)	*i*Pr	*i*Pr	45	26	26

[a]Crude using ^{1}H NMR vs mesitylene internal standard. [b]Isolated yield reported in parentheses.

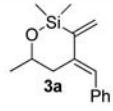
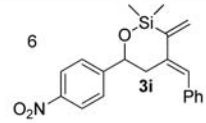
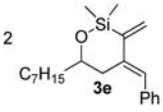
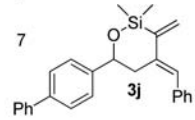
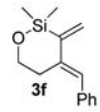
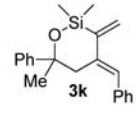
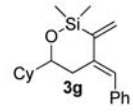
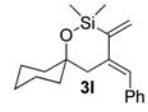
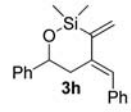
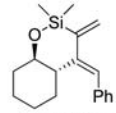
which impeded formation of the ruthenacyclopentene. Replacement of the dimethylvinyl silicon with dimethylallyl silicon resulted in no conversion after 7 h. The dimethyl vinyl silicon tether was chosen due to the availability and affordability of the starting chlorodimethylvinylsilane.[16]

Utilizing the dimethylvinyl silicon tethers, examination of the scope of this reaction was undertaken (Table 3). Exploration

Table 3. Phenyl Substituted Alkyne Substrate Scope[a]



1a-m 3a-m

entry	product	yield	entry	product	yield
1	 **3a**	82	6	 **3i**	71
2	 **3e**	80	7	 **3j**	93
3	 **3f**	77	8	 **3k**	94
4	 **3g**	88	9	 **3l**	94
5	 **3h**	75	10	 **3m** (racemic)	73

[a]Reaction times for each substrate can be found in the Supporting Information.

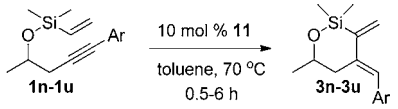
began with substrates that bear a phenyl moiety on the alkyne terminus. We elected to employ these substrates, as the cycloisomerization products were only observed as a minor component in our previous work. Having a phenyl group at the alkyne terminus, alkyl functionality (methyl and *n*-heptyl) at R_1 and R_2 was well tolerated giving **3a** and **3e** in 82% and 80% isolated yields, respectively (entries 1−2). In addition, hydrogen at the R_1 and R_2 positions (entry 3) was acceptable and a 77% isolated yield of **3f** was obtained. Cyclohexyl and phenyl

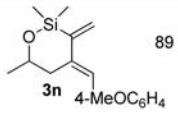
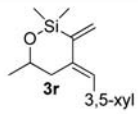
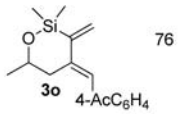
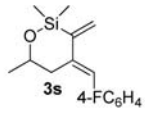
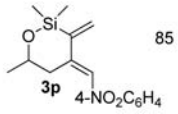
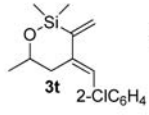
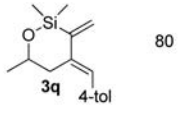
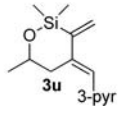
dx.doi.org/10.1021/ol5026926 | *Org. Lett.* 2014, 16, 5450−5453

containing moieties performed well (entries 4−5), affording the desired products **3g** and **3h** in 88% and 75% yields, respectively. The transformation was tolerable to a nitro substituent on the aryl ring, giving **3i** in 71% yield (entry 6). The *para*-biphenyl moiety performed exceptionally well, yielding **3j** in 93% yield (entry 7). Increasing the Thorpe−Ingold effect[15a] (entries 8 and 9) gave excellent yields of **3k** and **3l** in 94% and 94%, respectively. In addition, the formation of a *trans*-6,6-fused bicyclic system **3m** was accomplished in 73% yield (entry 10).

Variations of the aryl functionality at the alkyne terminus were also well tolerated. As depicted in Table 4, electron-donating

Table 4. Substituted Aryl Alkyne Substrate Scope[a]



entry	product	yield	entry	product	yield
1	 **3n** 4-$MeOC_6H_4$	89	5	 **3r** 3,5-xyl	80
2	 **3o** 4-AcC_6H_4	76	6	 **3s** 4-FC_6H_4	81
3	 **3p** 4-$NO_2C_6H_4$	85	7	 **3t** 2-ClC_6H_4	95
4	 **3q** 4-tol	80	8[b]	 **3u** 3-pyr	52

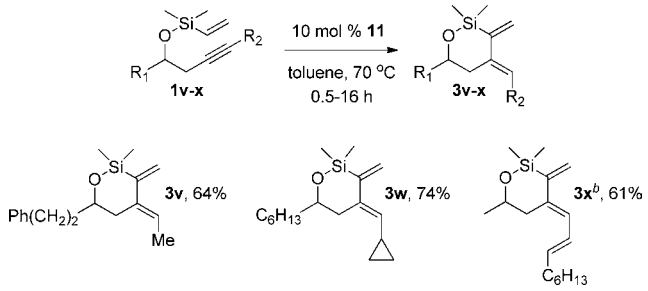
[a]Reaction times for each substrate can be found in the Supporting Information. [b]Reaction run with 12 mol % of **11**

methoxy performed well with an 89% yield of **3n** (entry 1). The electron-withdrawing acetyl and nitro groups gave 76% and 85% isolated yields of **3o** and **3p**, respectively (entries 2 and 3). Alkynes bearing tolyl and 3,5-xylyl groups produced the desired dienes **3q** and **3r**, each in 80% yield (entries 4 and 5). *para*-Fluoro and *ortho*-chloro substituents gave 81% and 95% yields of **3s** and **3t**, respectively (entries 6 and 7). Of note, the potentially chelating and basic pyridine moiety was tolerated in the reaction, giving 52% of diene **3u** (entry 8).

In addition to aryl functionality on the alkyne terminus, the substrate scope can be extended to alkyl functionality (Scheme 2). Methyl substituted alkyne **1v**, a substrate prone to β-hydride elimination, proceeded to give the desired diene **3v** as the sole product in 64% yield. Utilizing the current methodology, an increased yield of **3v** was accomplished compared to our previous methodology utilizing ruthenium hydrides.[10]

It is important to note the reaction and isolation of **3v** is more facile utilizing the current methodology in comparison to the ruthenium hydride methodology. We were pleased to find that the cyclopropane substituted alkyne **1w** gave **3w** in 74% yield with no observable ring opening events. Typically, vinylcyclopropanes react under such conditions to give seven-membered rings via a [5 + 2] cycloaddition pathway. Wender *et al.* have studied the reactivity of Rh-mediated cyclizations of

Scheme 2. Alkyl Substrate Scope[a]

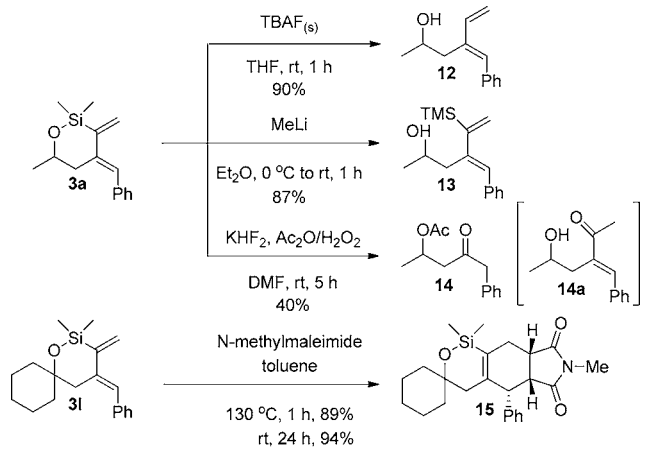


[a]Reaction times for each substrate can be found in the Supporting Information. [b]Reaction run with 15 mol % of **11**.

vinylcyclopropanes with alkynes to give seven-membered carbocyclic ring systems and applied the methodology toward the synthesis of natural products.[17] Additionally, Trost demonstrated a related [5 + 2] cycloaddition using a cationic Ru complex **7**.[18] The substrate scope was expanded to include olefinic substitution on the alkyne (**1x**). The cycloisomerization proceeded to give triene **3x** in 61% yield. The modest yield in this case can be partially attributed to the unexpected volatility of **3x**. The crude yield of triene **3x** versus the mesitylene internal standard indicated the quantitative formation of **3x**.

The synthetic utility of the cycloisomerization adducts was demonstrated using further synthetic transformations (Scheme 3). Protiodesilylation of **3a** using TBAF gave known alcohol **12**

Scheme 3. Derivatization of Dienes 3a and 3l



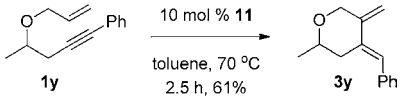
in 90% yield.[19] Addition of methyllithium gave hydroxyl silane **13** in 87% yield and required no purification of the diene product.[20] The transformation of **3a** to dienes **12** and **13** affords regioselective delivery of vinyl and vinyl-TMS moieties, respectively. Regio- and stereoselective hydrovinylation of internal alkynes are not generally selective.[21] After numerous attempts, conditions to facilitate a Fleming−Tamao oxidation[22] were discovered; however, the expected product from this transformation (**14a**) was not obtained. Instead, keto-ester **14** was isolated in 40% yield.[23] The Diels−Alder reaction[24] with substrate **3l** gave the highly substituted tetracyclic system **15** in good yield (Scheme 3) as the endo isomer as determined by NOESY correlations.[25]

Finally, we questioned whether silicon was needed in the tether for the cycloisomerization to proceed. An answer to this intriguing question was accomplished by synthesizing allyl-

dx.doi.org/10.1021/ol5026926 | Org. Lett. 2014, 16, 5450−5453

tethered alkyne **1y** and subjecting it to our standard reaction conditions (Scheme 4). The transformation proceeded smoothly

Scheme 4. Non-Silicon Tether Variation



to give the expected diene **3y** in 61% yield. This indicated that silicon is not a necessity in the tether and further extended the diversity of the substrate scope.

In conclusion, we have demonstrated the novel formation of exocyclic 1,3-dienes by a Ru-catalyzed cycloisomerization of 1,7-enynes. The transformation is believed to proceed through a ruthenacyclopentene, followed by a rare endocyclic β-H elimination. This methodology tolerates a wide variety of substitution on the starting enynes both with and without the use of silicon in the tether. The dienes are obtained rapidly and in excellent yield. The dienes produced by this method were further derivatized by Diels–Alder cycloaddition and Fleming–Tamao oxidation to give highly functionalized cyclic and acyclic substrates primed for further elaboration.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the donors of the ACS PRF (DNI 50787), the NSF (CAREER CHE-1352432), the GAANN Fellowship (P200A090277), and Syracuse University for generous financial support. We thank Dr. Chisholm for critically reading this manuscipt and Dr. Hahn for copious sharing of chemicals.

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