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Highly Selective Ring Expansion of Bicyclo[3.1.0]hexenes

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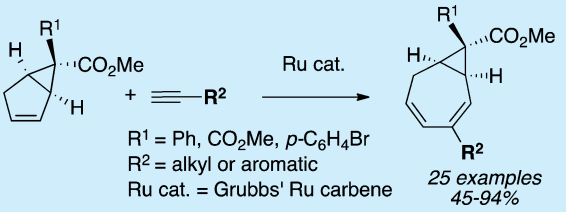
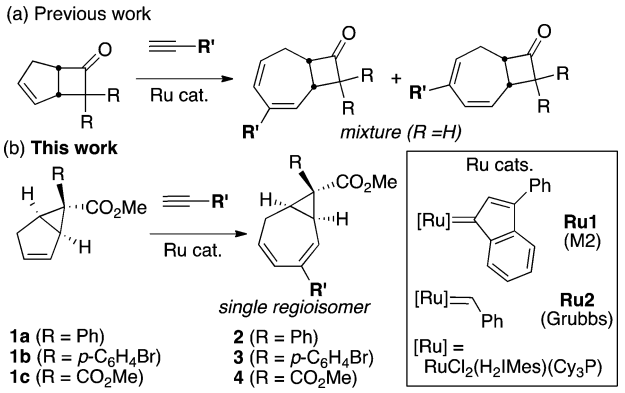
Supporting Information

ABSTRACT: A Ru-carbene-promoted ring expansion of bicyclo-[3.1.0]hexenes with terminal alkynes is reported. The reaction delivers seven-membered carbocycles starting from readily available starting materials and was found to be highly regioselective. The resulting seven-membered ring products contain both conjugated diene and cyclopropane substructures that could be selectively reacted in subsequent transformations.



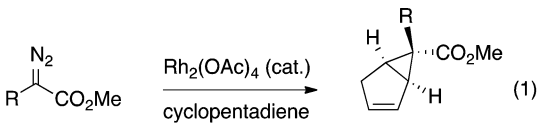
Seven-membered rings appear in a diverse array of natural products and bioactive molecules, and their synthesis remains a challenge.[1] A conventional approach is predicated on transition-metal-mediated cycloaddition reactions.[1b] Less often, ring expansion of cyclopentenes has been used to access the seven-membered ring structure.[2] Though rare, catalytic methods for ring expansion are potentially powerful due to their atom economy, efficiency, and the accessibility of the substrates. Several years ago, our laboratory developed a Ru-carbene-catalyzed ring expansion of cyclopentene.[2a] A similar fused ring system gave a mixture of regioisomers depending on the degree of alkyl substitution (Scheme 1a).[2b] In this report, we show that a cyclopentene fused with a cyclopropane (hereafter bicyclo-[3.1.0]hexene) underwent regiocontrolled ring expansion with terminal alkynes (Scheme 1b). Products **2**–**4** are uniquely substituted bicyclic dienes which have additional value due to their potential for chemoselective functionalization.

Scheme 1. Ring-Expanding Ene-Yne Metathesis



Ring expansion of bicyclo[3.1.0]hexenes gives dienyl cyclopropanes, a unique cyclic structure amenable to chemoselective modification. Their reactivity should be similar to that of vinyl cyclopropanes. Vinyl cyclopropanes provide an excellent platform for the synthesis of heterocycles and natural products.[3] For example, vinyl cyclopropanes bearing electron-withdrawing groups undergo addition reactions with amines,[4] aldehydes,[5] nitrones,[6] and imines[7] to provide diverse chemical structures. Cyclic dienes also undergo chemoselective reactions, such as Diels–Alder cycloaddition. The products of Scheme 1b contain both 1,3-diene and cyclopropane moieties, providing two sites for functionalization. We were interested to see if complementary functionalization of these groups would be possible in this compact, conjugated system.

Bicyclic substrates were prepared using a simple and scalable cyclopropanation procedure. The cyclopropanation was based on the asymmetric cyclopropanation of cyclopentadiene using the chiral catalyst $Rh_2(DOSP)_4$, as developed by Davies and coworkers.[8] In our case, we did not require enantiomerically enriched material, so $Rh_2(OAc)_4$ was substituted as the catalyst, providing racemic products. Employing the requisite diazocarbonyl compound, excess 1,3-cyclopentadiene and catalytic $Rh_2(OAc)_4$, three bicyclo[3.1.0]hexenes were prepared in moderate isolated yields (eq 1). The bicyclic substrates containing aromatic rings were conveniently purified by recrystallization from ethanol. Diester **1c** was obtained as a solid after chromatography.



1a (R = Ph), 50%
1b (R = *p*-C_6H_4Br), 75%
1c (R = CO_2Me), 68%

The ring expansion was optimized for a branched terminal alkyne (Table 1). Alkyne addition over a 2 h period gave a 45% isolated yield, but extending the addition time to 4 h resulted in an improved 68% yield (Table 1, entries 1 and 2). Using fewer equiv of **1a** was detrimental to the product yield (entry 3). Next, aromatic solvents were examined. Toluene gave results comparable to those of benzene, but the yield was found to be

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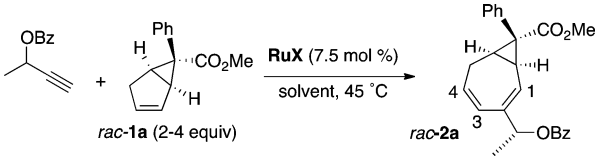
Table 1. Optimization Studies for the Ring Expansion of Bicyclo[3.1.0]hexene



entry[a]	Ru cat	equiv of **1a**	solvent	addition (h)	yield (%)[b]
1	**Ru1**	4	C_6H_6	2	45
2	**Ru1**	4	C_6H_6	4	68
3	**Ru1**	2	C_6H_6	4	28
4	**Ru1**	4	$PhCH_3$	4	60
5	**Ru1**	4	$PhCF_3$ (TFT)	4	81
6	**Ru1**	4	CH_2Cl_2	4	38
7	**Ru1**	4	THF	4	49
8	**Ru2**	4	$PhCF_3$	4	67
9	**Ru2**	4	CH_2Cl_2	4	77
10	**Ru3**[c]	4	$PhCF_3$	4	12

[a]Conditions: 2−4 equiv of **1a**, **RuX** (7.5 mol %), solvent at 45 °C. The alkyne was added as a solution over 2 or 4 h. [b]Isolated yield. [c]**Ru3** is the Hoveyda−Grubbs precatalyst, $(H_2IMes)Cl_2Ru$ = CH(2-*i*-$PrOC_6H_4$).

slightly lower (cf. entry 2 vs 4). Suspecting that benzylic CH insertion might explain the difference between benzene and toluene, we investigated trifluorotoluene (TFT), a lightly fluorous solvent that lacks benzylic CH bonds.[9] With precatalyst **Ru1**, the highest yield (81%) was obtained in this solvent (entry 5). Other nonaromatic solvents such as THF and CH_2Cl_2 proved inferior for this catalyst, giving lower isolated yields of the diene product (entries 6 and 7). The second-generation Grubbs precatalyst **Ru2** was found to perform well in TFT at 45 °C and even better in CH_2Cl_2 (entries 8 and 9). Last, the Hoveyda−Grubbs precatalyst **Ru3** gave low yields in TFT solvent (entry 10), whereas the other precatalysts worked well under these conditions. From the optimization experiments, two different solvents emerged as optimal using either the Umicore M2 catalyst (**Ru1**) or the Grubbs catalyst (**Ru2**) (entries 5 and 9, respectively). The slow addition rate of the alkyne proved to be essential to obtain the highest product yields. In each run, a ∼10:1 mixture of diastereomers of **2a** was obtained. The major diastereomer of **2a** is shown in Table 1.

The excess cyclopentene reactant **1a** could be recovered and reused. In Table 1, isolated yields of **1a** ranged from 70 to 85% yield. This material was recrystallized from EtOH and reused in subsequent ring expansions without any effect on yield. Recovery of unchanged starting material indicates that little bicycloalkene polymerization (ROMP), if any, occurred under the reaction conditions.

The product in Table 1 was produced as a single regioisomer. Proton NMR spectroscopy allowed a structure assignment that was most consistent with the regioisomer shown. The C1−H appeared at 6.34 ppm as a doublet, coupled to a single cyclopropane methine proton. The C3−H appeared as a doublet at 5.86 ppm with a 10.8 Hz coupling constant, shared with the adjacent C4−H located at 6.17 ppm, as a ddd. The coupling pattern of these three protons would not be consistent with the alternative regioisomer.

Additional structural data came from a single-crystal X-ray structure determination (Figure 1). Diene **2a** was recrystallized from IPA/hexanes, giving cubes: mp 119−121 °C. The structure corroborates the structure assignment and regiochemistry

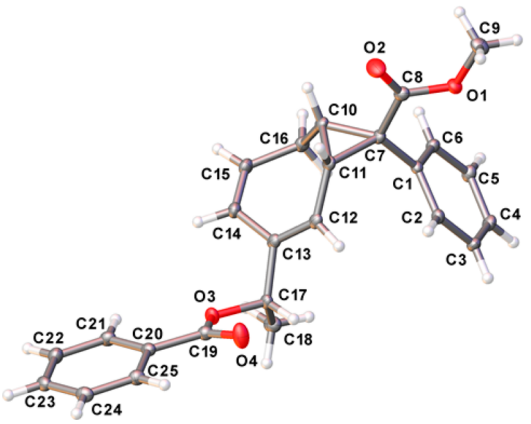


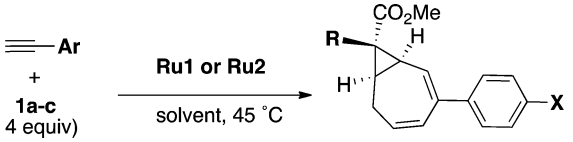
Figure 1. Crystal structure of product **2a**.

assigned on the basis of proton NMR spectroscopy. Interestingly, the structure shows that the 1,3-diene is distorted from planarity: the dihedral angle (C12−C13−C14−C15) was found to be 36.8°. Last, the structure proof also revealed the relative stereochemistry of the major diastereomer. The high diastereoselectivity observed in this reaction (10:1 for **2a**) was unexpected.[10]

With the optimization studies complete, we investigated the scope of the ring expansion. Two conditions were used with equal success: (1) precatalyst **Ru1** in benzene or TFT or (2) **Ru2** in CH_2Cl_2 or benzene. The standard reaction temperature was 45 °C. The data are presented for two classes of terminal alkyne, that of aromatic and aliphatic alkynes. In all ring expansions, no side products were identified. It is assumed that the major competing reaction is polymerization of the terminal alkyne. Excess cycloalkene is thought to limit the competing diester polymerization pathway. Excess cycloalkene was recovered in all cases.

Table 2 summarizes the ring expansion of aromatic alkynes for a variety of bicyclo[3.1.0]hexenes. Phenylacetylene gave a single product in good yield (NMR), but separation from the excess cycloalkene proved difficult. In this case, 4-phenyl-1,2,4-triazole-

Table 2. Terminal Aromatic Alkyne Bicyclo[3.1.0]hexene Ring Expansion[a]



R	entry	X	yield, %[b]
Ph (alkene **1a**)	1	H	**2b**, 61[c]
	2	OMe	**2c**, 68
	3	CO_2Me	**2d**, 77
	4	Br	**2e**, 51[c]
	5	Me	**2f**, 57[c]
	6	NO_2	**2g**, 67
p-BrC_6H_4 (alkene **1b**)	7	H	**3a**, 94
	8	OMe	**3b**, 72
CO_2Me (alkene **1c**)	9	H	**4a**, 82[c]
	10	OMe	**4b**, 80
	11	CO_2Me	**4c**, 74

[a]Conditions: 0.25 mmol alkyne added to 1.0 mmol **1a−c** and **Ru1** and **Ru2** (7.5 mol %) in solvent at 45 °C, over a 4 h period. [b]Isolated yields. [c]Trapped as PTAD cycloadduct; yield over two steps.

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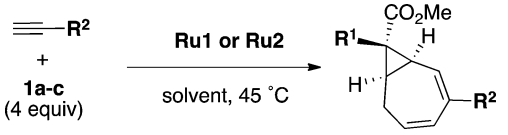
3,5-dione (PTAD) was added directly to the crude reaction, and the cycloadduct was isolated in 61% yield. Para-substituted phenyl acetylenes all gave ring expansion with similar yields, but no electronic trend emerged from these data (entries 2−6). Another aromatic substituted bicyclo[3.1.0]hexene **1b** gave excellent results (entries 7 and 8). The diester-substituted cyclopropane derivative **1c** gave similar yields, suggesting that there was not a significant electronic effect exerted by the additional electron-withdrawing ester group (entries 9−11).

Table 3 summarizes the ring expansion of aliphatic alkynes for a variety of bicyclo[3.1.0]hexenes. In general, oxygen sub-

Table 3. Terminal Aliphatic Alkyne Bicyclo[3.1.0]hexene Ring Expansion[a]



R^1	entry	R^2	yield, %[b]
Ph (alkene **1a**)	1	$-CH_2OBz$	**2h**, 65[c]
	2	$-(CH_2)_4CH_3$	**2i**, 65[d]
	3	$-(CH_2)_4OBz$	**2j**, 45
	4	$-CH(OBn)CH_3$	**2k**, 83
	5	$-CH(OAc)CH_2CH_2Ph$	**2l**, 79
	6	$-CH_2N(Ts)$ (Boc)	**2m**, 55
p-BrC_6H_4 (alkene **1b**)	7	$-CH_2OBz$	**3c**, 73
	8	$-CH(OBz)CH_3$	**3d**, 48
	9	$-CH(OBn)CH_3$	**3e**, 71
	10	$-CH(OAc)CH_2CH_2Ph$	**3f**, 77
CO_2Me (alkene **1c**)	11	$-CH_2OBz$	**4d**, 54
	12	$-CH(OBz)CH_3$	**4e**, 49
	13	$-CH(OAc)CH_2CH_2Ph$	**4f**, 74

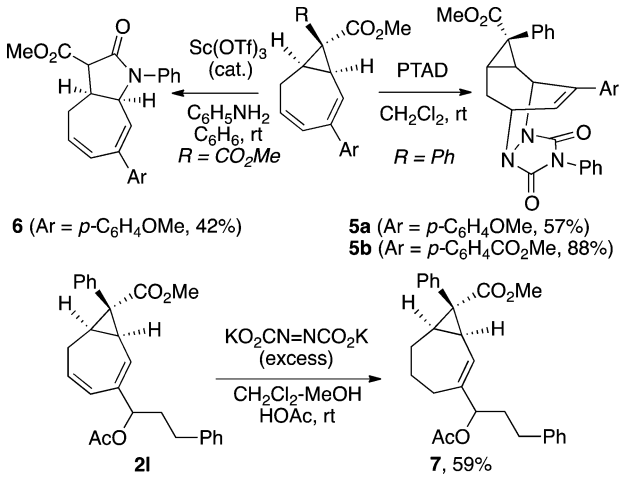
[a]Conditions: 0.25 mmol alkyne added to 1.0 mmol **1a−c** and **Ru1** and **Ru2** (7.5 mol %) in solvent at 45 °C, over a 4 h period. [b]Isolated yields. [c]Average of three runs. [d]Trapped as PTAD cycloadduct; yield over two steps.

stituents were well-tolerated and gave the resulting bicyclo-[5.1.0]octadienes in good yields (entries 1−5). In all cases, a single regioisomer was obtained. The product from the hydrocarbon 1-octyne was difficult to separate from unreacted alkene **1a**, so the 1,3-diene was trapped as the PTAD cycloadduct (entry 2). Additional substitution in the R^2 group was well-tolerated (entries 4 and 5). With a benzyloxy group, potential chelation did not affect the success of the ring expansion (entry 4). A protected nitrogen-based functional group was also acceptable (entry 6). Similar results were seen with the *p*-bromophenyl-substituted cyclopropanes derived from alkene **1b** (entries 7−10). With bicycloalkenes **1b** and **1c**, lower yields were found with a branched alkyne, which was opposite to that observed with bicycloalkene **1a** (entries 8 and 12 vs Table 1).

The case in Table 3, entry 1, deserves further comment. The alkyne $BzOCH_2CCH$ gave variable yields due to alkyne-promoted catalyst decomposition. The 65% yield in entry 1 is an average of three yields. Three separate trials gave 74, 56, and 69% isolated yields (Grubbs **Ru2**, CH_2Cl_2, 45 °C). Unbranched alkynes can undergo polymerization, and this process can lead to catalyst decomposition.[11] This variability can be overcome by use of higher catalyst loadings.

The diene products were further transformed by three different chemoselective reactions (Scheme 2). First, rapid

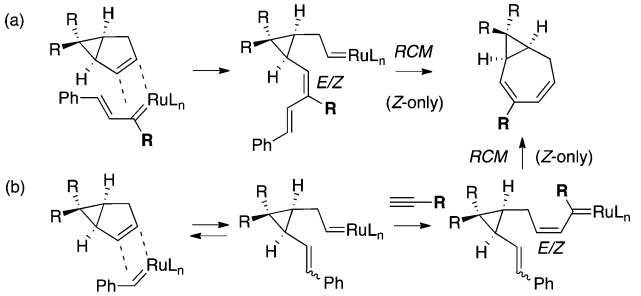
Scheme 2. Additional Transformations



cycloaddition with PTAD was observed, affording **5a** and **5b** in good to excellent yields. Next, a reaction of the cyclopropane was desired. Vinyl cyclopropane diesters are known to react with nucleophiles in Michael-like fashion,[6a,4a] thereby opening the cyclopropane ring. 1,3-Diene stabilization was expected to enhance this reactivity profile. Accordingly, aniline addition occurred at room temperature (vs elevated temperature for vinyl cyclopropanes), giving primarily the lactam **6**. After nucleophilic addition, lactamization results due to the proximity of the secondary amine with the malonyl appendage and is Lewis acid promoted. To our knowledge, lactamization has not been observed previously. Though further studies are warranted, it is likely that dienyl stabilization results in a carbocation that can be attacked *syn* or *anti* to the alkyl substituent.[12] Last, treatment of diene **2l** with diimide gave position-selective reduction of the 1,3-diene, yielding **7** in good yield.[13]

Two plausible mechanistic scenarios can explain these data. First, the initiator **RuX** may insert the alkyne, giving a vinyl carbene intermediate which can ring open the cycloalkene (Scheme 3, path a). Regiochemistry is controlled in the ring-

Scheme 3. Plausible Mechanisms To Explain Regioselectivity



opening step, where the bulky ligands on the metal are furthest from the substituted allylic carbon. Only the major pathway is shown. Second, the initiator (e.g., **Ru2**) may open the cycloalkene with the bulky ligands averting the allylic cyclopropane ring (path b). The resulting Ru-carbene can either revert to the reactants by RCM or give alkyne insertion. Subsequent RCM of the *Z*-vinyl carbene could form the seven-membered ring product. Each mechanism requires a ring-opening step of the bicyclo[3.1.0]hexene, which rationalizes why excess cycloalkene is needed for a successful ring expansion. For path a, the fleeting

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intermediate must engage the cycloalkene over alkyne to avoid alkyne polymerization. In path b, the first ring-opening step is reversible and unfavorable; mass action would help form the reactive intermediate. At present, there is not enough supporting mechanistic work that favors one pathway over the other; additional mechanistic studies are ongoing.

In conclusion, a Ru-carbene-promoted ring expansion of bicyclo[3.1.0]hexenes with terminal alkynes has been developed. Distinct optimized conditions were identified using two different precatalysts. The starting materials are easy to prepare, and excess bicyclo[3.1.0]hexene can be recovered in good yield and reused. The reaction can give two different regioisomers, but only a single regioisomeric product is formed. Two plausible mechanisms were proposed based on either an alkyne-first or a bicycloalkene-first pathway involving different Ru-carbene intermediates. The products contain 1,3-diene and cyclopropane moieties: each of these can be selectively reacted in subsequent transformations, illustrating the reactivity and versatility of these products. Further efforts to expand the scope of this reaction and mechanistic studies are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02641.

Experimental procedures and characterization data for new compounds (PDF)

X-ray data for JMC_031601 (CIF)

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Notes

The authors declare no competing financial interest.

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