Syntheses of Seven-Membered Rings: Ruthenium-Catalyzed Intramolecular [5+2] Cycloadditions

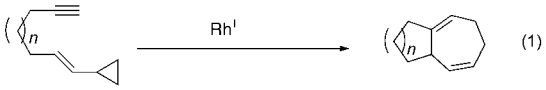
Barry M. Trost,* Hong C. Shen, Daniel B. Horne, F. Dean Toste, Bernhard G. Steinmetz, and Christopher Koradin[a]

Abstract: The Ru-catalyzed intramolecular [5+2] cycloaddition of cyclopropylenynes is investigated with respect to the regio- and diastereoselectivity as well as the functional group compatibility of the reaction. Evidence for the mechanism as occurring through a ruthenacyclopentene intermediate is elucidated from 1) the study of the diastereoselectivity of the cycloaddition; 2) the effect of variation of substituents on the regioselectivity of cyclopropyl bond cleavage in 1,2-*trans*- and 1,2-*cis*-disubstituted cyclopropanes and 3) examples that clearly do not involve ruthenacyclohexene as intermediates as products still incorporate the cyclopropyl moiety. The scope and limitations of the Ru-catalyzed cycloaddition are discussed and compared with the Rh-catalyzed reaction. The potential power of this methodology towards natural product total synthesis is demonstrated by the formation of several polycyclic systems with the chosen reaction conditions and readily available cyclopropylenyne substrates.

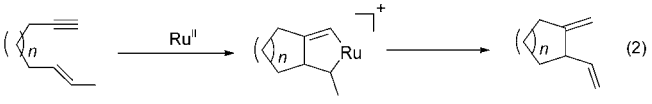
Keywords: cycloaddition · diastereoselectivity · enynes · homogeneous catalysis · ruthenium

Introduction

The development of new chemical reactions involving the serial formation and cleavage of multiple C–C bonds leads to powerful synthetic tools in organic synthesis. As such, cycloaddition reactions catalyzed by transition metals[1] have been of continuing interest to us due to their efficiency in constructing complicated structures from much simpler starting materials in an atom-economical fashion.[2] Wender's group pioneered the development of both inter- and intramolecular Rh-catalyzed [5+2] cycloadditions of cyclopropyl enynes [Eq. (1)].[3] This reaction involves the formal cleavage of two bonds and the formation of three new bonds. Exceptional control over the direction of cyclopropane bond cleavage was exercised through the selection of substituents and/or catalyst. Inspired by the mechanistic pathways of the ruthenium catalyzed Alder–ene reaction [Eq. (2)][4] and the Rh-catalyzed [5+2] cycloaddition, we envisioned that the Ru-catalyzed [5+2] cycloaddition reaction [Eq. (3)] may proceed and thereby generate various mechanistic questions and synthetic opportunities.[5]



(1)



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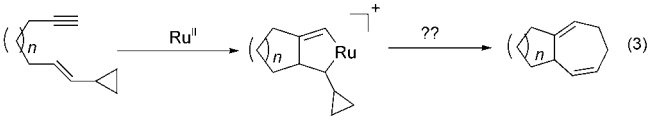

(3)

In this article we report the scope of Ru-catalyzed intramolecular [5+2] cycloadditions regarding the functional group tolerance of the reaction, and the length and atom type of the tether between alkyne and vinylcyclopropane. To probe the reaction mechanism, we systematically studied the effects of substituents on the regio- and diastereoselectivity of the Ru-catalyzed reaction. The utility of this meth-

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odology is reflected by the synthesis of the core structures of several biologically important natural products (Figure 1) that contain a polyhydroazulene moiety, such as rameswaralide **1**,[6] dilatriol **2**,[7] and grayanotoxin **3**,[8] which represent

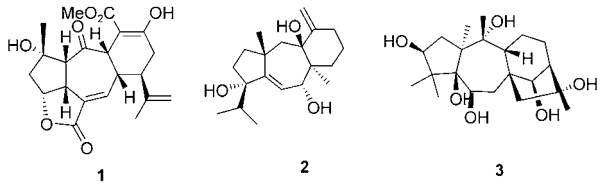
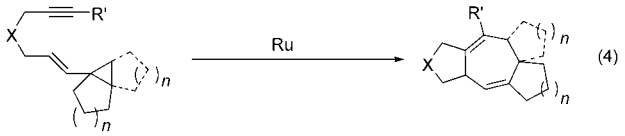


Figure 1. Polycyclic natural products containing seven-membered rings.

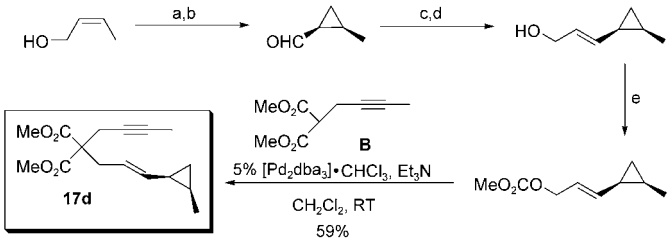
demanding synthetic challenges. The opportunity to apply the Ru-catalyzed [5+2] cycloaddition should offer short, atom-economical routes to such targets. The model systems as shown in Equation (4) raise a number of reactivity and selectivity issues that are addressed herein.[5]



Results and Discussion

Substrate synthesis: We initiated our investigation of the Ru-catalyzed [5+2] cycloaddition by preparation of the vinylcyclopropyl alkyne substrates. Various methods were utilized to access the range of substrates described herein and are illustrated in detail in the Supporting Information. A recurring theme in many of the synthetic sequences was the utilization of palladium catalyzed allylic alkylation as a key step for substrate formation. The synthesis of substrate **17d** is illustrated by this technique (Scheme 1).

Scope and limitations: Cyclopentadienyltris(acetonitrile) ruthenium(II) hexafluorophosphate **4**,[9] readily available on a multigram scale following a procedure recently developed by our group,[9c] was found to catalyze the intramolecular Alder–ene reaction of enynes.[4d] Based on this observation,



Scheme 1. Preparation of vinylcyclopropyl alkyne **17d**: a) CH_2I_2, Et_2Zn, CH_2Cl_2, 70%. b) PCC, CH_2Cl_2, 44%. c) $(EtO)_2P(O)CH_2CO_2Et$, *n*BuLi, THF, 88%. d) DIBAL-H, CH_2Cl_2, 94%. e) *n*BuLi, THF; $ClCO_2Me$, 76%. PCC = pyridinium chlorochromate, DIBAL-H = diisobutylaluminium hydride.

we envisioned that it may also catalyze the [5+2] cycloaddition of vinylcyclopropyl alkynes, primarily due to the possibility of generating an intermediate ruthenacyclopentene which may then undergo ring expansion to form the seven-membered ring [Eq. (3)].

We were pleased to observe that this Ru catalyst can indeed catalyze the desired intramolecular [5+2] cycloaddition of a broad range of vinylcyclopropyl alkyne substrates under ambient conditions (room temperature in acetone or DMF) (Table 1). All reactions were run with 5–10% [CpRu-$(CH_3CN)_3PF_6$] (**4**), 0.1–0.2 M in acetone, at room temperature, unless otherwise noted. Other Ru complexes also ex-

Table 1. Scope of substrates in the Ru-catalyzed [5+2] cycloadditions.

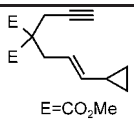
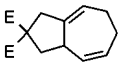
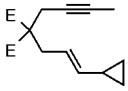
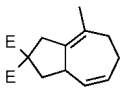
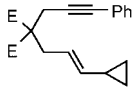
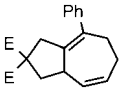
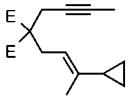
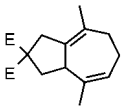
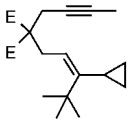
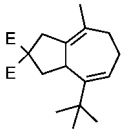
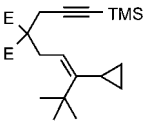
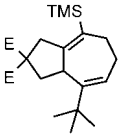
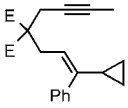
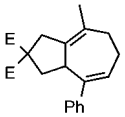
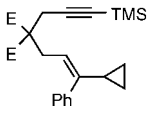
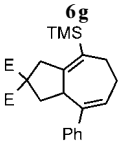
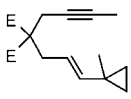
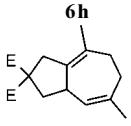
Entry	Substrate	Product	Yield [%]
1	 E=CO_2Me		83
2	**5a** 	**6a** 	82
3	**5b** 	**6b** 	82
4	**5c** 	**6c** 	87
5[a]	**5d** 	**6d** 	83
6[b]	**5e** 	**6e** 	95
7[c]	**5f** 	**6f** 	84
8[d]	**5g** 	**6g** 	75
9[e]	**5h**  **5i**	**6h**  **6i**	75

Table 1. (Continued)

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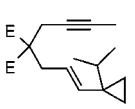
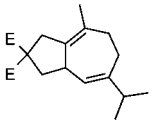
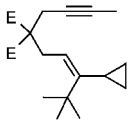
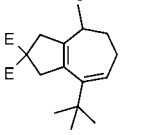
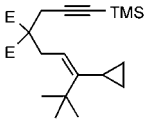
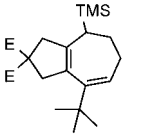
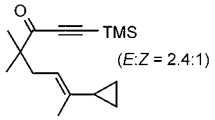
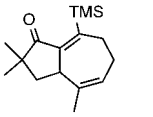
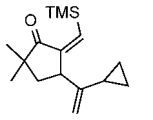
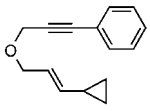
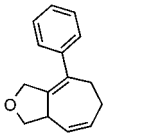
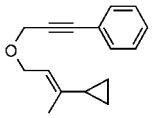
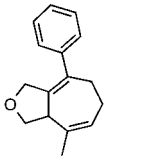
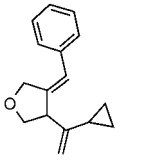
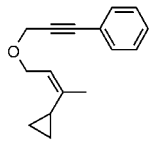
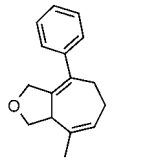
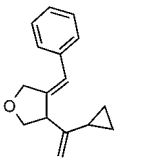
10	 **5j**	 **6j**	88
11[f]	 **5e**	 **6k**	75
12[g]	 **5f**	 **6l**	73
13	 **5m**	 **6m**	82 (3.7:1)
		 **6m′**	
14	 **5n**	 **6n**	77
15	 **5o**	 **6o**	82 (6.2:1)
		 **6o′**	
16	 **5o′**	 **6o**	78 (1:14)
		 **6o′**	

Table 1. (Continued)

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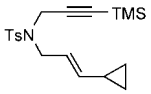
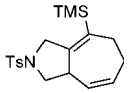
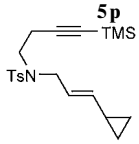
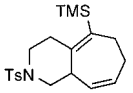
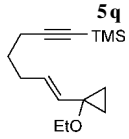
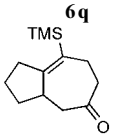
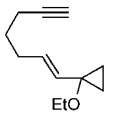
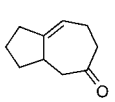
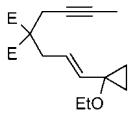
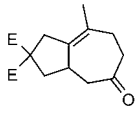
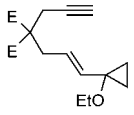
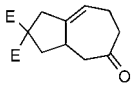
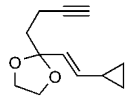
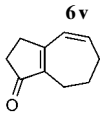
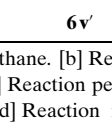
17	 **5p**	 **6p**	84
18[h]	 **5q**	 **6q**	67
19	 **5r**	 **6r**	73
20	 **5s**	 **6s**	72
21	 **5t**	 **6t**	71
22	 **5u**	 **6u**	74
23	 **5v**	 **6v**	68 (5:1)
		 **6v′**	

[a] Reaction performed in 1,2-dichloroethane. [b] Reaction performed in 1,2-dichloroethane and 25% catalyst. [c] Reaction performed in the presence of water in 1,2-dichloroethane. [d] Reaction run in 1,2-dichloroethane with 30% catalyst. [e] Reaction performed at 50°C. [f] Reaction run in dichloromethane with 10% [Ru(cod)(cot)] and HPF_6 (aq.) at RT. [g] Reaction run in dichloromethane with 10% $[Ru(ind)_2]$ and HPF_6 (aq.) at RT. [h] Reaction run with 20% catalyst at 50°C. See Experimental Section for General Procedure for Ruthenium Catalyzed [5+2] Cycloadditions.

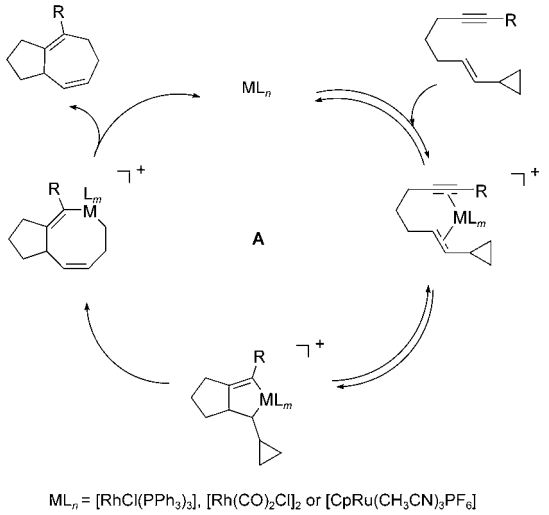
amined for catalytic activity are [Ru(cod)(cot)], $[Ru(\eta^5\text{-}C_8H_{11})_2H]BF_4$, $[Ru(\eta^5\text{-}C_8H_{11})(CH_3CN)_3]BF_4$, and [(bis-indenyl)Ru]. In an attempt to "activate" (bis-indenyl)Ru, it was treated with fluoroboronic acid in acetonitrile to generate in situ $[(indenyl)Ru(CH_3CN)_3]BF_4$. The intermolecular reaction between 1-alkoxyvinylcyclopropanes and alkynes was also examined and found to proceed, albeit only in moderate (50–70%) yields.[10]

Table 1 shows that the catalyst is compatible with a variety of functional groups and substitution patterns on the alkyne, alkene and cyclopropane. Importantly, a number of

trisubstituted alkenes react cleanly at room temperature to afford cycloadducts without any observable trace of olefin isomerization (entries 4–8). Bicyclic carbocycles, and O- and N-containing heterocycles can be obtained in good to excellent yields.

For a few sterically encumbered substrates, the reaction gave better yields when conducted in dichloroethane (entries 5–8), but required increased catalyst loading (entries 6 and 8). If other highly coordinatively unsaturated ruthenium complexes were used, such as 10% [Ru(cod)(cot)] or [Ru(ind)$_2$] in the presence of aqueous HPF_6 (entries 11 and 12), the reaction cleanly afforded the seven-membered 1,3-dienes, which were presumably derived by isomerization of the initially formed 1,4-dienes. As shown in entries 19–22, the cycloaddition of alkoxy group substituted cyclopropanes form useful cycloheptenone derivatives in good yields. Entry 23 shows a ketal converted in situ to a ketone followed by isomerization of the olefin to form a more stabilized conjugated diene **6v′**.

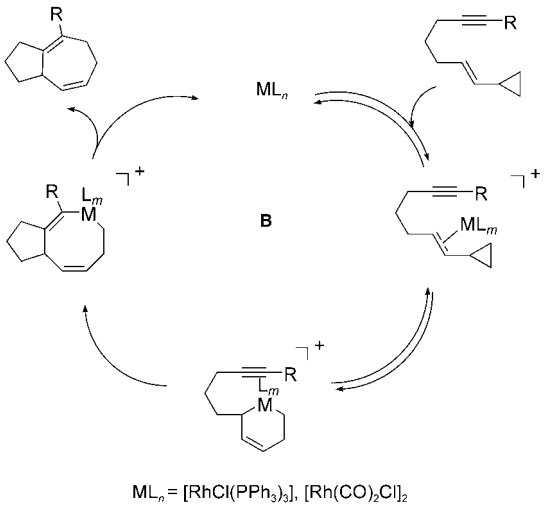
There are two plausible mechanisms for the transition metal catalyzed [5+2] cycloaddition.[3] Mechanism A involves metallacyclopentene formation followed by ring expansion to a metallacyclooctadiene (Scheme 2). Subsequent



Scheme 2. Mechanism A for transition metal-catalyzed [5+2] cycloadditions.

reductive elimination affords the seven-membered ring product. In contrast, in mechanism B cleavage of the cyclopropane occurs first to form a metallacyclohexene, which undergoes addition to the alkyne to form a metallacyclooctadiene (Scheme 3). So far mechanism B has been suggested for the Rh-catalyzed [5+2] cycloaddition in a computational study by Wender and Houk,[3n] whereas the Ru-catalyzed reaction most likely proceeds according to mechanism A depicted in Scheme 2 according to our study.

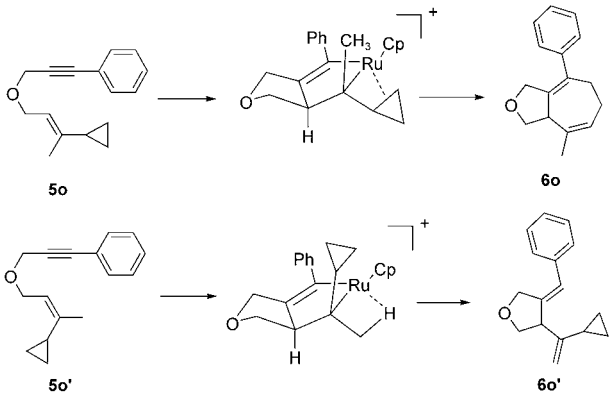
The evidence to support mechanism A is first drawn by comparison with the Ru-catalyzed Alder–ene reaction, in which a ruthenacyclopentene nicely accommodates all ob-



Scheme 3. Mechanism B for transition metal-catalyzed [5+2] cycloadditions.

servations. Clearly, a simple enyne system with an appropriate linker could form a ruthenacyclopentene.

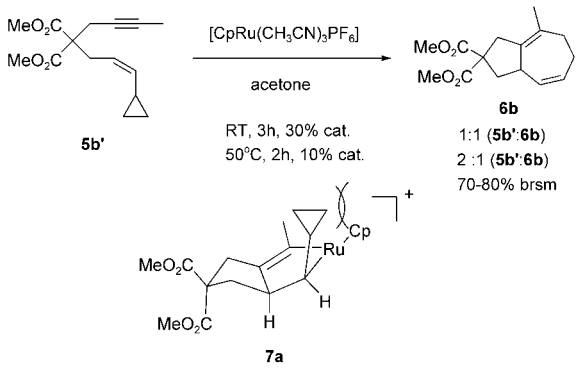
In addition, the contrasting results obtained in entries 15 and 16 can be explained by an intermediate ruthenacyclopentene as follows (Scheme 4). The reaction of *E*-olefin **5o**



Scheme 4. Proposed ruthenacyclopentenes derived from *trans*- and *cis*-olefins **5o** and **5o′**.

afforded a 6.2:1 mixture of products favoring cycloaddition product **6o**. Conversely, the reaction of the *Z*-olefin **5o′** afforded a 78% yield of products as a 14:1 mixture in favor of the 1,4-diene **6o′** which arises from β-hydride elimination. Examining the ruthenacyclopentene intermediates derived from *E*- and *Z*-olefins, it is apparent that the group that is *trans* in the starting olefin is placed in a pseudoequatorial position on the convex face of the metallacycle intermediate. The pseudoequatorial group is geometrically better suited for interaction with the ruthenium center, a situation similar to what was recently observed in β-hydride elimination in titanacyclopentenes.[11]

By invoking the same ruthenacycle intermediate, it is also understandable why substrate **5b′** bearing a *cis*-alkene was far less reactive (Scheme 5) than its *trans*-counterpart **5b**



Scheme 5. Cycloaddition of *cis*-olefin **5b′**.

(entry 2, Table 1). The steric interaction between the Cp ligand and the cyclopropyl group in intermediate **7a** likely disfavors the formation of the intermediate that leads to cycloadduct **6b**.

Substrates **5w**–**5z** (Figure 2) are not reactive even at 50 °C for extended periods (such as 14 h), a feature that appears to be related to the linker length between the alkyne and the vinyl group. Furthermore, no reaction was observed with compounds **5w** and **5x** at elevated temperature even in the presence of a stoichoimetric amount of ruthenium complex **4**, ruling out the possibility of forming ruthenenacyclohexene, an irreversible process in mechanism B. Three examples (entries 13, 15 and 16 in Table 1) led to products containing

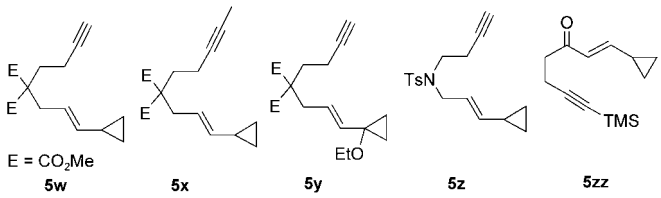


Figure 2. Failed substrates for Ru-catalyzed [5+2] cycloaddition.

the vinylcyclopropyl moiety. These observations suggest that mechanism B is not likely to be operational in these cases.

Presumably, the 6,5-bicyclic system of the ruthenacyclopentene intermediate is considerably more difficult to form than the 5,5-bicyclic system. However, a substrate (entry 18, Table 1) bearing a trimethylsilyl alkyne as well as a nitrogen atom in the linker was successfully converted to the desired 6,7-fused bicyclic compound in good yield. Substrate **5zz** is also unreactive under the standard reaction conditions. The ketone carbonyl group may interact with Ru and inhibit its catalytic ability in the [5+2] cycloaddition reaction. A more detailed explanation of the poor reactivity seen with some substrates bearing proximal carbonyl groups is given later in the manuscript (see Figure 4, and the corresponding text).

Diastereoselectivity of Ru-catalyzed [5+2] intramolecular cycloadditions: One major concern in the endeavors to synthesize 5,7-fused bicyclic structures is the diastereoselectivity of the [5+2] cycloaddition. In particular, we are interested in how the relative stereochemistry of substituents in the tether affects the relative stereochemistry of the newly created stereogenic center at the bridgehead carbon atom. To shed light on this issue, we prepared a range of cycloaddition precursors with one or more substituents in the carbon tether and subjected them to the Ru-catalyzed [5+2] cycloaddition conditions. The results are shown in Table 2. All reactions were run with 5–10 % $[CpRu(CH_3CN)_3]PF_6$ (4), 0.1–0.2 M in acetone, at room temperature, unless otherwise noted.

Table 2. Diastereoselectivity of the Ru-catalyzed [5+2] cycloadditions.[a]

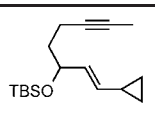
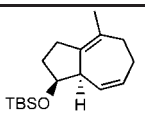
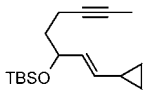
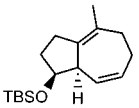
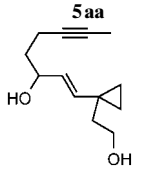
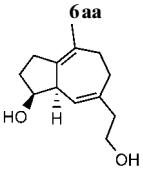
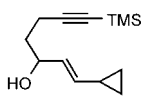
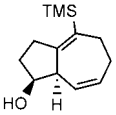
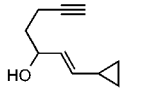
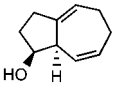
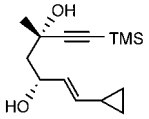
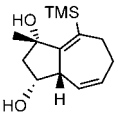
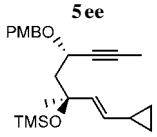
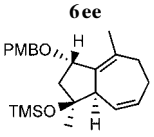
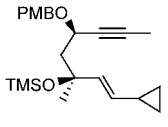
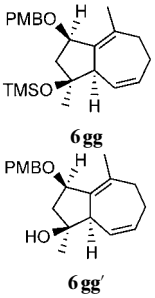
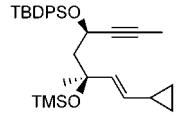
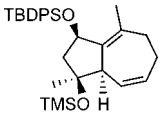
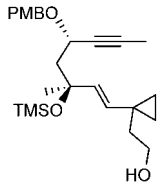
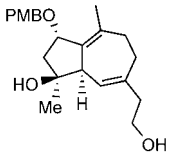
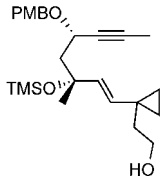
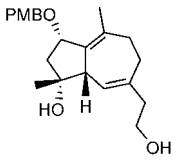
Entry	Substrate	Product	Yield [%][b]
1	 **5aa**	 **6aa**	92 (*dr* 3.1:1)
2[c]	 **5aa**	 **6aa**	73 (*dr* 5.1:1)
3	 **5bb**	 **6bb**	75 (*dr* >20:1)
4	 **5cc**	 **6cc**	86 (*dr* >10:1)
5	 **5dd**	 **6dd**	86 (*dr* >20:1)
6[d]	 **5ee**	 **6ee**	81 (*dr* >20:1)
7[e]	 **5ff**	 **6ff**	70 (*dr* >20:1)[e]
8	 **5gg**	 **6gg** **6gg′**	72 (*dr* >20:1)

Table 2. (Continued)

Entry	Substrate	Product	Yield [%][b]
9	 **5hh**	 **6hh**	65 (dr >20:1)
10	 **5ii**	 **6ii**	90 (dr >20:1)
11	 **5jj**	 **6jj**	70 (dr >20:1)

[a] Reaction was run with 0.1–0.2 M substrate in acetone at RT from 0.5–6 h unless otherwise noted. [b] Isolated yield and diastereomeric ratio were determined by ^{1}H NMR. [c] Reaction was run with 0.1 M substrate in DMF at RT for 6 h. [d] Reaction was run in dichloromethane at −80 to 15 °C over 2.5 h. [e] 65 % product shown +5 % desilylated product.

In all cases, good to excellent yields of the desired hydroazulene products were obtained despite the presence, in all the substrates, of an ionizable functional group at the allylic position. Modest to excellent diastereoselectivities were observed. In all cases investigated so far, the bridgehead hydrogen atom and the hydroxyl group show a *trans* relationship, which was revealed by NOE experiments and in one case, by X-ray crystallography (Figure 3).

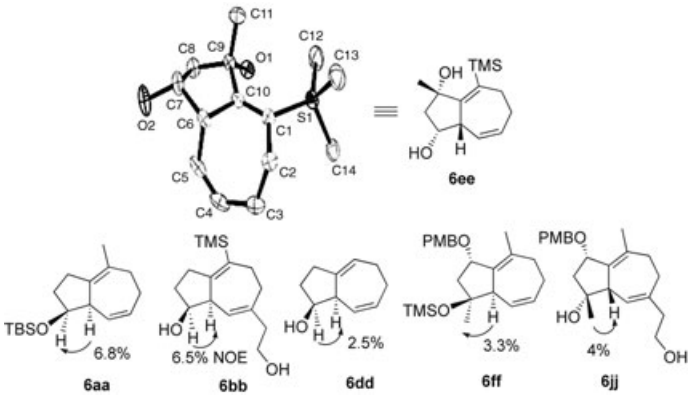
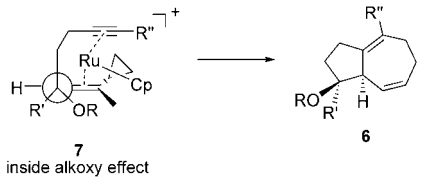


Figure 3. X-ray and NOE data of representative compounds.

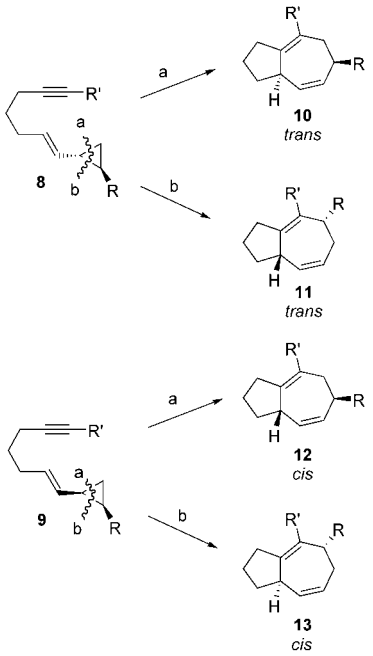
The proposed mechanism (Scheme 2) of the cycloaddition involves the coordination of Ru^{II} to both alkene and alkyne followed by the ruthenacyclopentene formation in which the Ru^{II} is oxidized to Ru^{IV}. Presumably, the σ-donating ability of the alkene π bond to cationic Ru species plays a more important role for the coordination of the alkene to Ru than the back bonding of the d orbital of the metal to the alkene. The observation that the angular hydrogen is *anti* to the homoallylic OR substituent in the major diasteromeric cycloadduct is in agreement with the Stork/Houk–Jäger "inside alkoxy" model (Scheme 6).[12] In the electrophilic coordination of the alkene with the cationic Ru catalyst to form ruthenacyclopentene, the allylic electron-donor substituent should stabilize the transition state whereas the electron-withdrawing substituent such as OR should destabilize the transition state. If the σ^*_{CO} orbital overlaps with the alkene π orbital, the alkene becomes less prone to donate electrons to cationic Ru and slows down the reaction. Conversely, if the σ^*_{CO} orbital is orthogonal to the alkene π orbital (alkoxy group is "inside"), the overlap of σ^*_{CO} orbital with the π orbital of the alkene is minimized. Meanwhile, the electron-donating $\sigma_{C-R'}$ or σ_{C-C} will stabilize the transition state. Therefore, the most reactive conformation should place the allylic alkoxy group inside (Scheme 6) so that the σ-donating effect of the alkene π bond to the Ru species is maximized. This reactive conformation will then lead to the formation of the diastereomer with the angular hydrogen and alkoxy group in a *trans* relationship.



Scheme 6. Mechanistic rationale for diastereoselectivity.

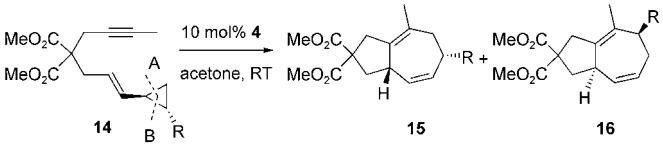
Regioselectivity of Ru-catalyzed [5+2] intramolecular cycloadditions: To further explore the scope and mechanistic details of Ru-catalyzed intramolecular [5+2] cycloadditions, we have extensively studied the influence of a substituent R on the cleavage of disubstituted cyclopropanes (Scheme 7). For *trans* disubstituted cyclopropane **8** or *cis*-disubstituted cyclopropane **9**, either the more- or the less-substituted C–C bond of the cyclopropane can be cleaved to form two possible regioisomeric products. We chose the same substrate system already explored by the Wender group as a probe to compare the Rh- and Ru-catalyzed [5+2] cycloadditions. The Wender group found that regioselective cleavage of either the more-substituted or the less-substituted σ bond of the cyclopropane could be achieved depending on the choice of catalyst.[3k] However, no rationale is provided to explain this interesting observation. Our results reveal several divergent mechanistic aspects for the [5+2] cycloadditions catalyzed by Ru versus Rh.

The regioselectivity of this cycloaddition reaction was explored with a variety of *trans*- and *cis*-1,2-disubstituted cyclopropanes, summarized in Tables 3 and 4, respectively. In these reactions, Ru-catalyst **4** displays excellent compatibili-



Scheme 7. Regioselectivity of the Ru-catalyzed intramolecular [5+2] cycloaddition.

Table 3. Regioselectivity of the cycloaddition of *trans* substrates.

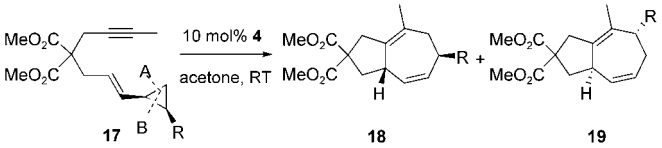


Entry[a]	R	15:16[b]	Yield [%]
1	CO_2CH_3 (**14a**)	**15a**:**16a** 1:2	90
2[c]	CO_2CH_3 (**14a**)	**15a**:**16a** 1:2.5	88
3[d]	CO_2CH_3 (**14a**)	**15a**:**16a** 1:2.3	80
4[e]	CO_2CH_3 (**14a**)	**15a**:**16a** 1:2	78
5	$COCH_3$ (**14b**)	**15b**:**16b** 2:1	83
6[d]	$COCH_3$ (**14b**)	**15b**:**16b** 1:1.2	88
7	COOH (**14c**)	**15c**:**16c** 1:3	78
8[f]	COOH (**14c**)	NA	0
9	(*E*)-CH=CH-CHO (**14d**)	**15d**:**16d** 1:1.6	82
10	(*E*)-CH=CH-CO_2Et (**14e**)	**15e**:**16e** 1:2.5	87
11	C≡CH (**14f**)	**15f**:**16f** 1:2.5	85
12	CH_2OTBS (**14g**)	**15g**:**16g** 1.5:1	90
13	CH_2OTIPS (**14h**)	**15h**:**16h** 3:1	81
14[c]	CH_2OTIPS (**14h**)	**15h**:**16h** 2:1	88
15	CH_2O-4-Br-Bz (**14i**)	**15i**:**16i** 1.6:1	71
16	CN (**14j**)	**15j**:**16j** 1:1.9	87
17	SO_2Ph (**14k**)	**15k**:**16k** 1:1	80
18	CHO (**14l**)	**15l**:**16l** 1:15	78

[a] All reactions performed with 10% catalyst by using 0.1–0.2 M substrate in acetone unless otherwise noted. [b] Ratio determined by proton NMR. [c] Reaction performed in DMF. [d] Reaction performed in the presence of 10–15% $In(OTf)_3$. [e] Reaction performed in the presence of 10% HMPA. [f] Reaction performed in the presence of 10% Bu_4NOH.

ty with substrates containing various functional groups such as esters, carboxylic acids, aldehydes, ketones, amides, enals, sulfonamides, sulfones. The Ru catalyst is able to catalyze the [5+2] cycloaddition of many substrates at room temperature in a short period of time (30 min to 2 h).

Table 4. Regioselectivity of cycloaddition of *cis* substrates.



Entry[a]	R	18:19[b]	Yield [%]
1	CO_2CH_3 (**17a**)	**18a**:**19a** > 20:1	87
2	CN (**17b**)	**18b**:**19b** >20:1	81
3	CH_2OTIPS (**17c**)	**18c**:**19c** >20:1	85
4	CH_3 (**17d**)	**18d**:**19d** >20:1	87
5	$COCH_3$ (**17e**)	**18e**:**19e** 2:1	93
6	C≡CH (**17f**)	NA	NR
7	CHO (**17g**)	**15l**:**16l**[c] 1:12	82

[a] All reactions were performed with 10% catalyst using 0.1–0.2 M substrate in acetone. [b] Ratio determined by proton NMR. [c] See Scheme 9.

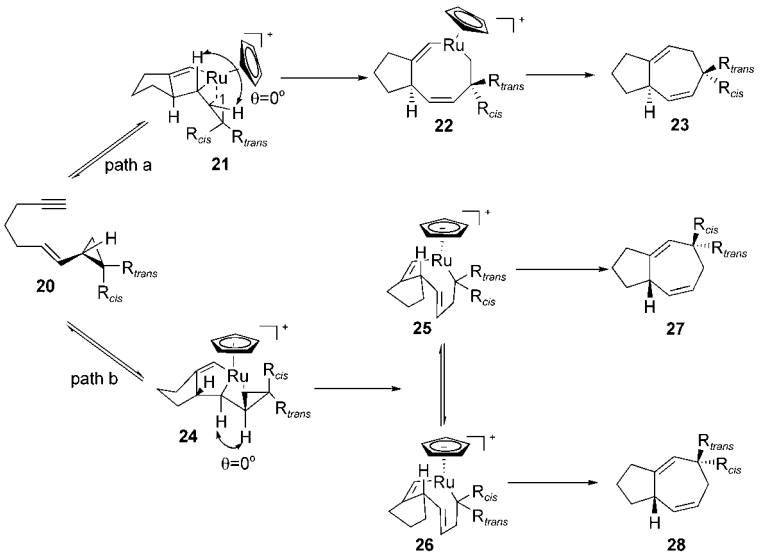
In order to test the possibility of constructing nine-membered rings by an analogous [7+2] approach, vinylogous aldehyde **14d** and vinylogous ester **14e** were examined (entries 9 and 10, Table 3). However, only seven-membered ring compounds were obtained with moderate regioselectivity. Vinylogous aldehyde **14d** exhibits a dramatically diminished bias for migration of the more substituted cyclopropyl carbon compared to the aldehyde and shows the same preference as for the vinylogous ester **14e**.

The [5+2] cycloaddition of *trans*-cyclopropyl alkyne **14f** proceeds under mild conditions with a regioselectivity of 2.5 to 1 (entry 11, Table 3). Presumably the [5+2] cycloaddition is so facile that the formation of a ruthenium vinylidene[13] structure is negligible. However, *cis*-cyclopropyl alkyne **17f** failed to react even at elevated temperature (entry 6, Table 4).

The use of $[In(OTf)_3]$ as an additive had an intriguing impact on the regioselectivity of the reaction of substrate **14b**. This substrate gave a mixture of two regioisomers favoring the formation of **15b** in the absence of any additive (entry 5, Table 3), but favored the other regioisomer **16b** in the presence of 10 mol% $[In(OTf)_3]$ (entry 6, Table 3). Presumably, the coordination of $[In(OTf)_3]$ to the ketone carbonyl in **14b** facilitated the cleavage of the more substituted C–C bond of the cyclopropane due to the electronic activation of the C–C bond proximal to the ketone.

Regarding diastereoselectivity, *trans* cyclopropanes give *trans* products, and *cis*-cyclopropanes, except aldehyde **17g** (Table 4, entry 7), give *cis* products (the *cis* or *trans* geometry of the products refers to the relationship of the angular hydrogen and the R group, see Scheme 7).

To rationalize the regioselectivity of the cycloaddition of disubstituted cyclopropanes, both electronic and steric factors have to be considered (Scheme 8). If R is an electron-withdrawing group, electronically, path b should be favored resulting from the σ-bond activation by the electron-withdrawing group. Sterically, path a is favored particularly for *cis*-cyclopropanes, since R_{cis} is distal to the Cp ligand in intermediate **21** but proximal to Cp in intermediate **24**. For *trans*-cyclopropanes, path a should still be favored but only

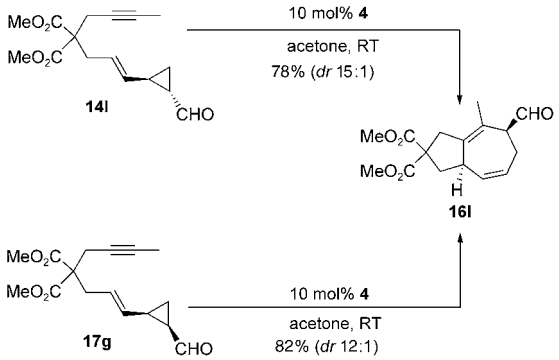


Scheme 8. Proposed mechanistic rationale for the regio- and diastereoselectivity of cyclopropane ring opening for disubstituted cyclopropanes.

slightly over path b, because the steric interaction between R_{trans} and Cp in intermediate **21** is slightly more severe than that in intermediate **24**. Therefore, *trans* cyclopropanes bearing an electron-withdrawing R group, such as an ester, ketone, carboxylic acid, enal, α,β-unsaturated ester, cyanide or sulfone (entries 1–10, 16–17 in Table 3) give a mixture of two diastereomers. This result indicates a small to almost negligible bias in cleavage of the more substituted cyclopropyl carbon bond despite the large differences of the steric size of the substituents. In contrast, *cis*-cyclopropanes bearing an electron-withdrawing R group such as ester or cyano (entries 1 and 2, Table 4) give one diastereomer almost exclusively.

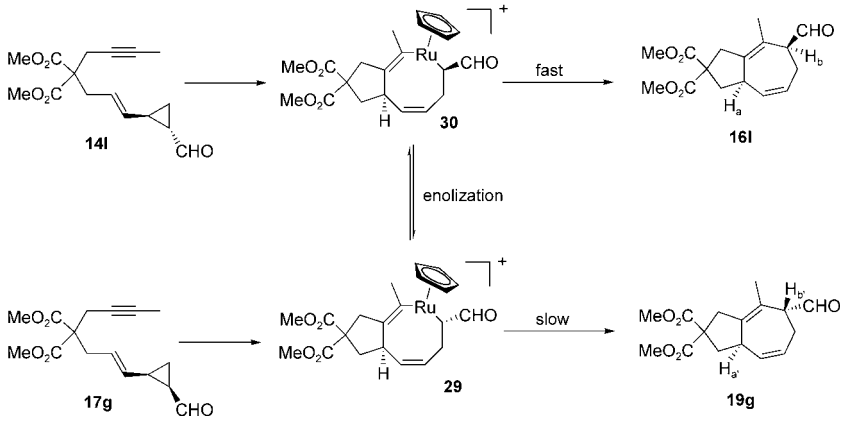
If R is not an electron-withdrawing group, path a appears to be favored for both *cis*- and *trans*-cyclopropanes. For *cis*-cyclopropane substrate **17c** (entry 3, Table 4), the steric repulsion between Cp and R_{cis} is much more severe in intermediate **24** than that in **21**, so path a is preferred and proceeds to give product **18c**. In comparison, for *trans*-cyclopropane substrate **14g** and **14h** (entries 12 and 13 in Table 3), the steric repulsion between Cp and R_{trans} is only moderately more severe in intermediate **24** than that in **21** so both cycloheptadiene regioisomers were obtained. Furthermore, the migration of the less substituted cyclopropyl carbon is favored, in contrast to the case of the *trans*-cyclopropylester **14a**, where the migration of the more substituted cyclopropyl carbon is preferred. Therefore, in cases where R is not an electron-withdrawing group, steric effects appear to dominate. This conclusion is further supported by the comparison of entries 12 and 13 in Table 3. As the steric size of R group increases from *tert*-butyldimethylsilyloxy methylene to triisopropylsilyloxy methylene, the product derived from the less substituted C–C bond cleavage of the cyclopropane is increased from 1.5:1 to 3:1.

If R is a formyl group, polyhydroazulene **16l** is formed independent of the relative stereochemistry of the starting vinylcyclopropane (Scheme 9). The regiochemical preference of this reaction can be explained by the presence of an electron withdrawing group which should stabilize the intermediate cyclooctene **25**:**26**, as well as weaken the carbon–carbon bond bearing the aldehyde. To the extent that the regiochemistry is determined by the relative rate of cyclopropane ring opening, this explains the regiochemical preference for cleavage of the cyclopropane carbon–carbon bond substituted with the aldehyde. Once again, metallacyclopentene formation is reversible and the product ratios are determined by the relative rate of C–C bond breaking to from the metallacyclooctenes.



Scheme 9. Ru^{II}-catalyzed regioselective [5+2] cycloadditions of **14l** and **17g**.

The diastereoselectivity of the reaction can be explained by considering the structure of proposed intermediate ruthenacycles **29** and **30** (Scheme 10). These ruthenacycles can readily equilibrate via an O-bound ruthenium(+4) enolate.[13] To the extent that this equilibrium is rapid relative to the rate of reductive elimination, the diastereoselectivity of the reaction will depend on the relative rates of reductive elimination. The remarkable preference to form the *trans*-product **16l** (>10:1 *dr*) regardless of the geometry of the starting cyclopropane suggests that the rate of reductive elimination of **30** is greater than that of **29**. This behavior is unique to aldehyde-substituted cyclopropanes. For example, replacing the aldehyde with an acetyl group has a dramatic effect on the course of the reaction. Although, the possibility of equilibration of the intermediate ruthenacycloctadienes via an *O*-bound ruthenium enolate remains, the acetyl substituted-cyclopropanes behave like the siloxymethyl-substituted cyclopropanes (Scheme 8) rather than the formyl-substituted cyclopropanes (Scheme 9). This suggests that, in



Scheme 10. Proposed mechanism to account for selective formation of **16l**.

order for the equilibration of **29** and **30** to occur, the relatively small steric size of the aldehyde is also necessary. Calculation (MM2) of the relative energies of the product aldehydes (**16l** and **19g**) shows that **16l** is 1.8 kcal mol^{-1} (95:5 ratio) more stable than diastereomer (**19g**). The difference may primarily be due to placement of the aldehyde into a pseudoaxial position in **19g** compared to the pseudoequatorial position in **16l**. This energy difference is presumably reflected in the transition state for reductive elimination and therefore in the difference in the relative rates of reductive elimination.

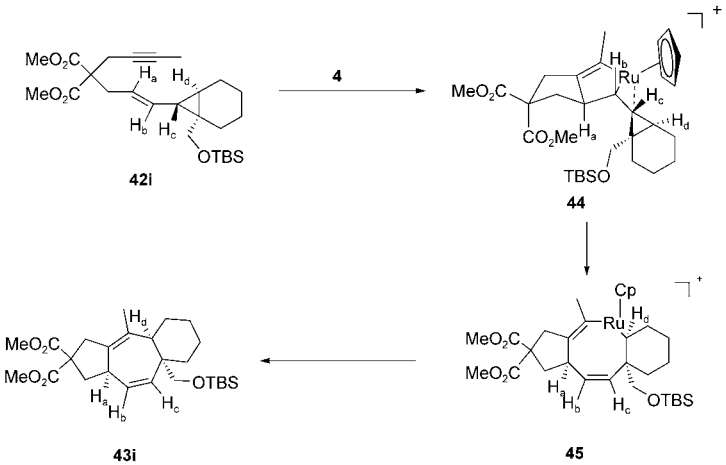
Three aspects of our observations should be noted. First, the aldehyde substrate gave different results compared to other substrates (Scheme 9), perhaps deriving from the combination of both electronic and steric effects. Second, the C–C bond energy of cyclopropyl appears to be important in the *trans* series. All substituents, in particular the electron-withdrawing substituents, show significant migration of the more substituted cyclopropyl carbon. The steric effects appear to be quite variable for these cases. They seem to play a more significant role in entries 12 and 13 compared with entries 1 and 15 in Table 3. Third, the steric effects seem to dominate for the *cis* substrates. Excellent regioselectivity for migration of the less substituted carbon was observed in this series apart from the examples with formyl or acetyl substituents.

There are several significant differences between the Rh and the Ru systems. First, aldehyde substrates **14l** and **17g** do not lead to the same cycloaddition product with Rh catalysis. With $[Rh(CO)_2Cl]_2$, the cycloaddition of **14l** gave **16l** with the angular hydrogen *trans* to the aldehyde group. Conversely, **17g** afforded a diastereomer of **16l** with the angular hydrogen *cis* to the aldehyde group. Second, the siloxy substrate **14g** shows the contrasting regioselectivity with the two different catalytic systems, leading with Wilkinson's catalyst to exclusive formation of **15g**, whereas the Ru complex **4** leads to an equimolar mixture of **15g** and **16g**. Third, the ester substituent influences the regioselectivity of the Rh-catalyzed reaction by favoring the cleavage of the more substituted C–C bond of cyclopropane, but does not effect regioselectivity in the *cis* series with the Ru catalyst (entry 1, Table 4).

Construction of tricyclic compounds containing a seven-membered ring: In order to showcase the above described methodology, we also utilized Ru-catalyzed [5+2] cycloaddition to construct the core skeleton of the natural products depicted in Figure 1. In all cases good to excellent yields and diastereoselectivities were observed in the key reaction despite the steric encumbrance of the cycloaddition substrates increasing from 1,1,2-trisubstituted, to 1,2,3-trisubstituted, to tetrasubstituted cyclopropanes (entries 2–10 in Table 5). The relative stereochemistry of the angular substituents was assigned by NOE studies.

The mechanism involving a ruthenacyclopentene again accounts for the observed stereochemistry (Scheme 11). Coordination of the double bond results in a dihedral angle of 0° between H_b and H_c, since the double bond is formed between the corresponding carbon atoms. This leads to the propagation of the stereochemistry in a 1,4-manner. It is particular striking that tetrasubstituted substrates such as **42i** or trisubstituted substrates such as **42g**, **h**, and **j** can be employed, invoking a secondary carbon–ruthenium bond.

An interesting regioselectivity question arises with ketone **42h**. Previous work in entries 5 and 6 of Table 3 showed that an acetyl substituent in a 1,2-disubstituted cyclopropane produced nearly equal amounts of the two regioisomers. On the other hand, in the case of **42h** in which both cyclopropyl bonds are substituted, a selectivity in favor of **43h** was observed, accompanied by a small amount of **43h′** (84% yield, **43**/**43h′** 6:1). This observation suggests that electronic factors can dominate when steric effects are equivalent, but the



Scheme 11. Rationale for diastereoselectivity of cycloaddition of **42i**.

Table 5. Ru-catalyzed intramolecular [5+2] cycloadditions of vinylcyclopropyl alkynes.[a]

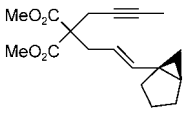
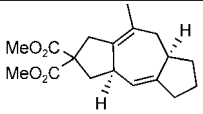
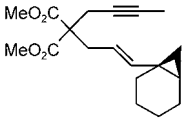
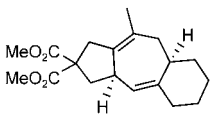
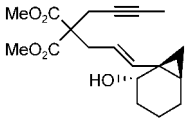
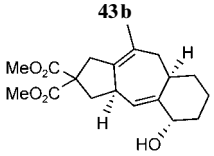
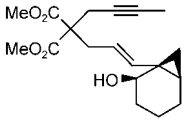
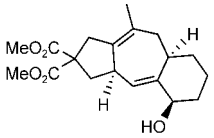
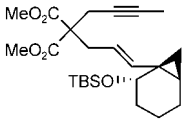
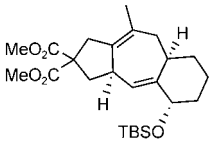
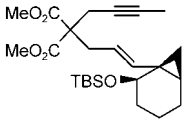
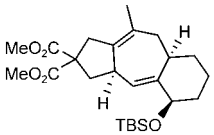
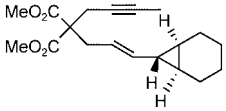
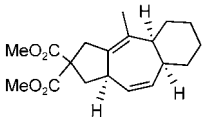
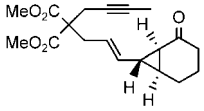
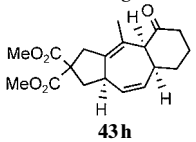
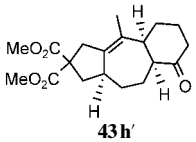
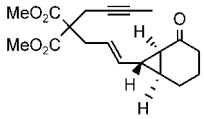
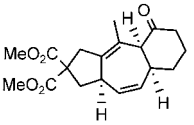
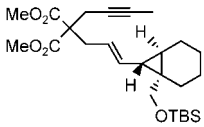
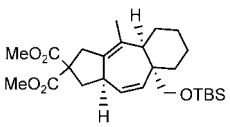
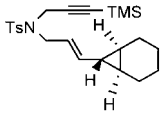
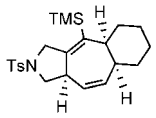
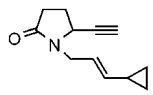
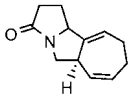
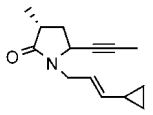
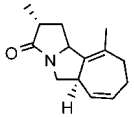
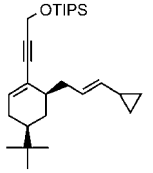
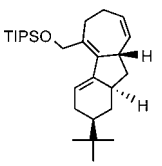
Entry	Substrate	Product	Yield [%]
1	 **42a**	 **43a**	85 (dr >20:1)
2	 **42b**	 **43b**	81 (dr >20:1)
3	 **42c**	 **43c**	80 (dr >20:1)
4	 **42d**	 **43d**	81 (dr >20:1)
5	 **42e**	 **43e**	69 (dr >10:1)
6	 **42f**	 **43f**	81 (dr >20:1)
7	 **42g**	 **43g**	93 (dr >20:1)
8	 **42h**	 **43h**  **43h′**	84 (**43h**:**43h′** 6:1)
9[b]	 **42h**	 **43h**	78 (dr >20:1)
10	 **42i**	 **43i**	85 (dr >20:1)

Table 5. (Continued)

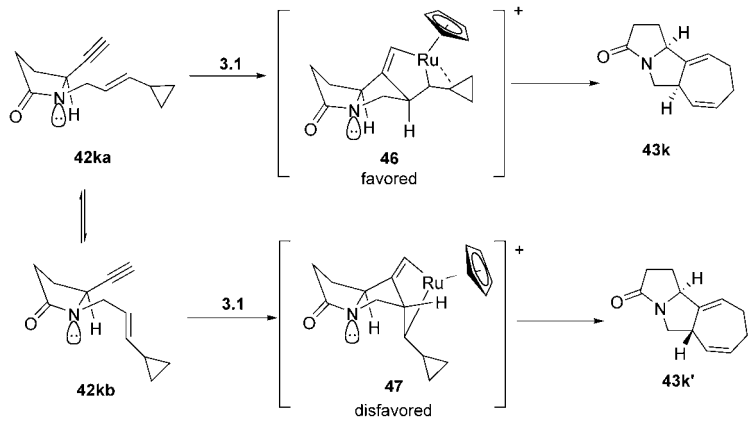
Entry	Substrate	Product	Yield [%]
11	 **42j**	 **43j**	72 (dr >15:1)
12	 **42k**	 **43k**	72 (dr >20:1)
13	 **42l**	 **43l**	84 (dr 10:1)
14	 **42m**	 **43m**	91 (dr 10:1)

electronic effects are not overwhelming. Interestingly, the addition of indium triflate as a cocatalyst further increased the selectivity to favor **43h** (83% yield) such that none of isomer **43h′** was detected. Apparently, Lewis acid complexation of the carbonyl group activates the adjacent cyclopropyl bond towards cleavage.

Substrate **42k**, derived from ketoglutamic acid (entry 12 in Table 5), does not react at room temperature but cycloaddition occurs once heated to 50°C. The terminal alkyne of **42k** was methylated accompanied with simultaneous diastereoselective methylation of the α carbon of the lactam[14] to form **42l**. In contrast to substrate **42k**, this substrate smoothly afforded tricyclic product **43l** in 84% yield and 10:1 diastereoselectivity at room temperature (entry 13, Table 4). This observation suggests that reversible formation of a vinylidene–ruthenium complex by the reaction of the terminal alkyne with the Ru catalyst slows down but does not inhibit the cycloaddition pathway when terminal alkynes are used as substrates.[17]

The diastereoselectivity of the cycloaddition presumably results from the stability and reactivity of ruthenacyclopentane intermediates **46** and **47** (Scheme 12). Apparently, intermediate **47** is disfavored relative to intermediate **46**, an explanation similar to the rationale provided in Scheme 6 can be given. The considerably higher activation energy for the transformation of **42kb** to **47**, compared with that of **42ka** to **46**, dictates the stereochemical outcome of the reaction.

Varying the placement of the cyclohexyl ring provides an entry to alternative tricycles. For example, dienyne **42m** was exposed to Ru catalyst **4** at room temperature in acetone to



Scheme 12. Rationale for the diastereoselectivity of the cycloaddition of **42k**.

In contrast to substrates **42k** and **l**, substrates **42p–s** bearing a basic nitrogen atom failed to react even at elevated temperature or in the presence of a Lewis acid such as $MeAlCl_2$ (Figure 5). This lack of reactivity most likely results from the basicity of the tertiary amine which leads to a Lewis acid–base interaction with the Ru catalyst, a rationale already discussed to account for the lack of reactivity of a suitably juxtaposed carbonyl group.

give a 91% yield of the triene **43m** (*dr* 10:1) within 4 h (entry 14, Table 5). The use of a conjugated enyne for the acetylene segment provides an entry to 1,3-dienes and thus sets the stage for further elaboration by means of Diels–Alder reactions.

In sharp contrast to the facile cycloaddition of **42h**, which was complete within 4 h, aldehyde **42n** and ketone **42o** failed to react even at elevated temperature (50 °C), longer reaction time (24 h), and increased catalyst loading (25 mol%). Previous work clearly established that the functionality present in this substrate is compatible with the cycloaddition reaction, hence we examined the reduced forms of ketone **42o** (entries 3–6 in Table 5). Gratifyingly, alcohols **42c** and **42d**, and also the more sterically demanding silyl ethers **42e** and **42f** reacted normally to give tricyclic compounds with excellent diastereoselectivity. One explanation for these differences in reactivity can be explained by bidendate coordination of the carbonyl group and the alkene with ruthenium; a coordination possible in **42n** and **42o**, but not in **42c–f**, thus resulting in decreased propensity to form the ruthenacycle intermediate. An alternative explanation (Figure 4), is that the carbonyl group in ruthenacyclopentene intermediates **46** and **47** may occupy one coordination site of the Ru catalyst, thus the free coordination site required for the ring expansion to occur is blocked.

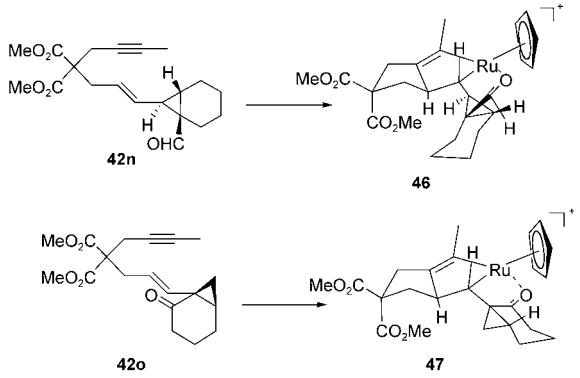


Figure 4. Ruthenacyclopentene intermediates that failed to undergo cyclopropyl ring opening.

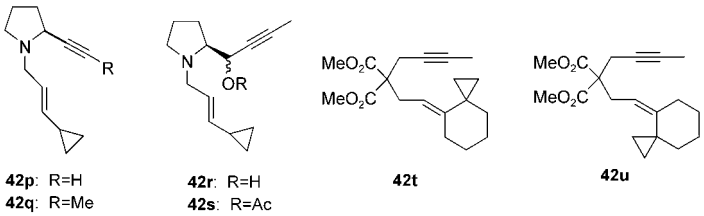


Figure 5. Unreactive substrates for the Ru-catalyzed [5+2] cycloaddition.

Substrates **42t** and **42u** were unreactive towards cycloaddition. This presumably is due to the steric demand of the substrates which precludes formation of the ruthenacyclopentene intermediate. The sensitivity of this family of Ru catalysts to steric hindrance has been noted in other reactions, notably enyne additions.[17]

Conclusion

Ru-catalyzed intramolecular [5+2] cycloadditions proceed under very mild conditions and usually the reactions are complete at room temperature within a few hours. The reactions generally show excellent chemoselectivity. High diastereoselectivities can be achieved in the intramolecular Ru-catalyzed [5+2] cycloaddition of cyclopropylenynes. A systematic study of 1,2-*trans*- and -*cis*-disubstituted cyclopropylenynes provides tremendous insight towards the understanding of the reaction mechanism. Based on our observations, a mechanism involving a ruthenacyclopentene intermediate is proposed. A ruthenacyclopentene intermediate nicely explains all the results, particularly regarding the reactivity of substrates and the stereochemistry of the cycloadducts.

A further extrapolation of this methodology led to the synthesis of 5,7,6-fused, 5,5,7-fused, and 6,5,7-fused ring systems with high yields and diastereoselectivities. The synthesis of 5,7,6-fused ring systems also serves as a model study to some biologically important natural products. The high diastereoselectivity of the reaction is remarkable, likely re-

sulting from the additional ring on the tether between the alkene and alkyne, which serves to rigidify the substrate to favor one particular reactive conformation. Given the reactivity of this catalytic system and the breath of its scope, this atom economical process holds much promise to enhance the efficiency of the total synthesis of polycyclic natural products containing seven-membered rings.

Experimental Section

Selected experimental procedures for preparation of **6h**, **6l**, **6q**, **6r**, **6ee**, **6gg**, **6ii**, **16j**, **16l**, **18b**, **18c**, **43d**, and **43i** appear below. Full experimental details for all substrates and cycloaddition products reported herein are given in the Supporting Information.

General procedure: **Ruthenium catalyzed [5+2] cycloadditions**: 10% $[CpRu(CH_3CN)_3]PF_6$ was added to a oven-dried test tube and the flask purged with Ar three times. A solution of eneyne-cyclopropane in freshly distilled acetone was added via cannula and the solution stirred under Ar at RT until TLC showed the reaction was complete. The solvent was removed in vacuo, and the residue purified by flash chromatography on silica gel.

4-Phenyl-8-trimethylsilyl-3,3α,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic dimethyl ester (6h) (Table 1, entry 8): Malonate **5h** (10.1 mg, 0.025 mmol) and $[CpRu(CH_3CN)_3]PF_6$ (3.1 mg, 0.0076 mmol) were dissolved in dichloroethane (0.25 mL) and stirred under argon at room temperature for 24 h. The solvent was removed in vacuo and the residue purified by flash chromatography (silica gel, petroleum ether/diethyl ether 3:1) to afford cycloadduct **6h** (7.6 mg, 0.019 mmol, 75%) as a pale yellow oil. R_f=0.43 (petroleum ether/diethyl ether 3:1); IR (film): $\tilde{\nu}$ = 2953, 2180, 1738, 1629, 1435, 1251, 1198, 1163, 1077, 838, 734, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (m, 5H), 5.61 (m, 1H), 4.34 (m, 1H), 3.72 (s, 3H), 3.62 (s, 3H), 3.01 (d, J=15.9 Hz, 2H), 2.59 (m, 2H), 2.32 (m, 2H), 2.18 (m, 2H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 171.8, 171.7, 152.3, 145.3, 140.2, 135.6, 131.1, 127.8, 127.4, 125.9, 58.2, 52.7, 52.6, 43.1, 41.7, 40.7, 28.8, 28.5, −0.3; elemental analysis calcd (%) for $C_{23}H_{30}O_4Si$: C 69.31, H 7.59; found: C 69.17, H 7.50.

8-*tert*-Butyl-4-trimethylsilyl-3,4,5,6-tetrahydro-1*H*-azulene-2,2-dicarboxylic dimethyl ester (6l) (Table 1, entry 12): A solution of $[Ru(ind)_2]$ (0.8 mg, 2.4×10^{-3} mmol) in CH_2Cl_2 (0.2 mL) under argon was treated with 0.5 μL of a 5.5 M solution of HPF_6 in water (3×10^{-3} mmol). The yellow solution immediately turned orange-brown. This solution was stirred 10 min, before malonate **5f** (9.1 mg, 0.024 mmol) was added and the solution stirred at room temperature for 12 h. The solvent was removed in vacuo and the residue purified by flash chromatography (silica gel, petroleum ether/diethyl ether 3:1) to afford cycloadduct **6l** (6.6 mg, 0.017 mmol, 73%) as a colorless oil. R_f=0.55 (petroleum ether/diethyl ether 3:1); IR (film): $\tilde{\nu}$= 2956, 2871, 2180, 1738, 1436, 1363, 1251, 1200, 1029, 845, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.25 (m, 1H), 3.73 (s, 6H), 3.39 (t, J=7.2 Hz, 2H), 2.87 (s, 2H), 2.40 (m, 1H), 2.08 (m, 2H), 1.91 (m, 2H), 1.01 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 170.5, 149.7, 149.1, 147.2, 119.4, 57.3, 57.2, 52.7, 52.6, 36.8, 36.7, 31.8, 30.2, 29.4, 22.4, 1.0, −0.1; elemental analysis calcd (%) for $C_{21}H_{34}O_4Si$: C 66.62, H 9.05; found: C 66.40, H 8.99.

***N*-(4-Methylbenzenesulfonyl)-5-(trimethyl-silyl)-2,3,4,6,7,9α-hexahydro-1*H*-cyclohepta[c]pyridine (6q)** (Table 1, entry 18): A solution of vinylcyclopropane **5q** (18 mg, 0.048 mmol) in acetone (0.4 mL) was added to a test tube containing $[CpRu(CH_3CN)_3]PF_6$ (4 mg, 0.009 mmol) and the resulting orange solution stirred at 50°C for 2 h. The reaction mixture was concentrated in vacuo and purified by chromatography eluting with petroleum ether/diethyl ether 6:1 to afford **6q** (12 mg, 67%) as a clear film. IR (film): $\tilde{\nu}$ = 2955, 2923, 2852, 1599, 1346, 1248, 1161, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, J=8.0 Hz, 2H), 7.27 (d, J= 8.0 Hz, 2H), 5.33 (m, 1H), 5.18 (m, 1H), 4.82 (m, 1H), 3.89 (m, 1H), 3.09 (m, 3H), 2.43 (s, 3H), 2.16 (m, 1H), 2.05 (m, 2H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.9, 139.3, 136.5, 135.2, 129.6, 128.5, 127.4, 127.2, 52.4, 46.4, 31.1, 30.7, 30.3, 25.3, 21.5, −1.7; HRMS (EI+): m/z: calcd for $C_{20}H_{29}NO_2SSi$: 375.1688; found: 375.1689 $[M]^+$.

8-Trimethylsilyl-2,3,3α,4,6,7-hexahydro-1*H*-azulen-5-one (6r) (Table 1, entry 19): A solution of **5r** (74.2 mg, 0.296 mmol) in acetone (2.2 mL) was added under argon to a test-tube with $[CpRu(CH_3CN)_3]PF_6$ (9.6 mg, 0.022 mmol). The reaction was stirred at room temperature for 10 h. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (silica gel, petroleum ether/diethyl ether 10:1) to yield **6r** (48.4 mg, 0.217 mmol, 73%) as a clear light yellow oil. R_f=0.68 (petroleum ether/diethyl ether 1:1); IR (film): $\tilde{\nu}$ = 2955, 2851, 1707, 1430, 1319, 1284, 1260, 1204, 1138, 1073, 804 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.52–2.28 (m, 6H), 1.99 (m, 2H), 1.90 (dd, J=13.1, 10.3 Hz, 1H), 1.36–1.25 (m, 4H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.1, 145.2, 132.4, 41.9, 40.2, 39.8, 36.5, 36.4, 31.1, 21.2, 0.1; elemental analysis calcd (%) for $C_{13}H_{22}OSi$: C 70.21, H 9.97; found: C 70.45, H 10.05.

1-Methyl-8-(trimethylsilyl)-1,2,3,3α,6,7-hexahydroazulene-1,3-diol (6ee) (Table 1, entry 19): $[CpRu(CH_3CN)_3]PF_6$ (5 mol%, 52 mg, 0.118 mmol) at −78°C was added to a solution of **5ee** (600 mg, 2.38 mmol) in dichloromethane (12 mL). The solution was warmed to 15°C over 2.5 h. Without workup, the reaction mixture was purified by chromatography (silica gel, petroleum ether/diethyl ether 1:1) to give **6ee** (485 mg, 1.92 mmol, 81%) as a white solid. M.p. 137°C; IR (film): $\tilde{\nu}$= 3277brm, 2919w, 1390w, 1246w, 1072w, 920w, 838w cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.72–5.60 (m, 1H), 5.55–5.50 (m, 1H), 4.11 (brs, 1H), 3.77 (brs, 1H), 2.60–2.30 (m, 3H), 2.30–2.10 (m, 2H), 2.06–1.88 (m, 1H), 1.97 (dd, J=13.6, 2.8 Hz, 1H), 1.72 (dd, J=13.6, 4.0 Hz, 1H), 1.39 (s, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7, 138.4, 132.2, 125.8, 79.6, 74.1, 51.0, 49.5, 31.8, 28.5, 27.6, 1.3; elemental analysis calcd (%) for $C_{14}H_{24}O_2Si$: C 66.61, H 9.58; found: C 66.70, H 9.44. See Supporting Information for X-ray data.

(1*R,3*R**,10*R**)-[3-(4-Methoxy-benzyloxy)-1,4-dimethyl-1,2,3,5,6,8α-hexahydro-azulen-1-yloxy]-trimethylsilyl ether (6gg) and (1*R**,3*R**,10*R**)-3-(4-methoxy-benzyloxy)-1,4-dimethyl-1,2,3,5,6,8α-hexahydroazulen-1-ol (6gg′)** (Table 2, entry 8): $[CpRu(CH_3CN)_3]PF_6$ (25 mg, 0.057 mmol) at RT was added to cyclopropane **5gg** (0.44 g, 1.14 mmol) in distilled acetone (2 mL). The solution was stirred for 1.5 h. After removal of the solvent, the residue was separated by flash chromatography eluting with 5 → 20% diethyl ether in petroleum ether to afford **6gg** (140 mg, 0.45 mmol, 39%) and **6gg′** (144 mg, 0.37 mmol, 33%) both as a colorless oil. For **6gg**: IR (film): $\tilde{\nu}$=2960m, 2930m, 1613m, 1514s, 1442m, 1375m, 1302m, 1249s, 1173s, 1150m, 1108s, 1074m, 1036s, 889, 840s, 764m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, J=8.5 Hz, 2H), 6.90 (d, J= 8.5 Hz, 2H), 5.89 (m, 1H), 5.63 (m, 1H), 4.53 (d, J=11.5 Hz, 1H), 4.41 (m, 1H), 4.35 (d, J=11.5 Hz, 1H), 3.82 (s, 3H), 3.55 (m, 1H), 3.31 (s, 1H), 2.58 (m, 1H), 2.40–2.15 (m, 4H), 1.98 (m, 1H), 1.84 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 139.4, 135.3, 131.0, 129.0, 128.7, 128.6, 122.3, 78.0, 69.9, 55.2, 54.3, 52.1, 44.5, 32.9, 28.9, 25.9, 20.7; HRMS: m/z: calcd for $C_{22}H_{31}O_3Si$: 371.2042; found: 371.2041 $[M-CH_3]^+$.

For **6gg′**: IR (film): $\tilde{\nu}$ = 3496b, 2959m, 2929m, 1613m, 1586w, 1514s, 1438w, 1303w, 1249s, 1174m, 1116m, 1089m, 1034s, 923w, 825m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, J=8.5 Hz, 2H), 6.88 (d, J= 8.5 Hz, 2H), 5.86 (dd, J=1.5, 11.0 Hz, 1H), 5.82 (m, 1H), 4.53 (d, J= 11.0 Hz, 1H), 4.46 (d, J=4.5 Hz, 1H), 4.40 (d, J=11.0 Hz, 1H), 3.82 (d, J=0.5 Hz, 3H), 3.55 (s, 1H), 3.34 (d, J=2.0 Hz, 1H), 2.52 (m, 1H), 2.32 (m, 1H), 2.20 (m, 2H), 2.00 (dd, J=6.0, 13.0 Hz, 1H), 1.75 (d, J=2.0 Hz, 3H), 1.59 (dd,=4.5, 14.5 Hz, 1H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 138.4, 138.1, 129.9, 129.8, 128.1, 113.7, 94.1, 79.2, 78.6, 69.8, 55.2, 51.5, 43.0, 32.8, 25.9, 24.7, 21.4; HRMS: m/z: calcd for $C_{20}H_{26}O_3$: 314.1882; found: 314.1880.

(1*S,3*S**,9*R**)-7-(2-Hydroxyethyl)-3-(4-methoxybenzyloxy)-1,4-dimethyl-1,2,3,5,6,8α-hexahydro-azul-en-1-ol (6ii)** (Table 2, entry 10): $[CpRu(CH_3CN)_3]PF_6$ (22 mg, 0.051 mmol) was added under argon at RT to enyne **5ii** (220 mg, 0.512 mmol) in distilled acetone (3 mL). The reaction was stirred for 2 h and directly purified by flash chromatography (silica gel, petroleum ether/diethyl ether 20:1→10:1) to yield **6ii** (183 mg, 0.461 mmol, 90%) as a single diastereomer as a pale yellow oil. IR (film): $\tilde{\nu}$ = 3407b, 2958s, 2926s, 2856m, 1728s, 1613w, 1514m, 1464m,

1378w, 1282m, 1249s, 1121m, 1073m, 1037m, 861w, 821w, 773w, 741w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, J=9.0 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 5.52 (s, 1H), 4.46 (t, J=7.0 Hz, 1H), 4.46 (d, J=11.0 Hz, 1H), 4.39 (d, J=11.0 Hz, 1H), 3.82 (s, 3H), 3.86 (m, 2H), 3.50 (m, 1H), 2.47 (t, J=11.5 Hz, 1H), 2.35 (m, 4H), 2.08 (m, 2H), 1.78 (d, J=2.0 Hz, 3H), 1.72 (dd, J=8.0, 13.0 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 141.1, 136.9, 130.4, 129.8, 125.5, 124.3, 113.7, 78.5, 70.4, 60.1, 55.3, 51.1, 45.8, 42.6, 33.1, 30.3, 29.5, 25.7, 22.0; HRMS: m/z: calcd for $C_{22}H_{30}O_4$: 358.2144; found: 358.2143 $[M]^+$.

***trans*-6-Cyano-8-methyl-3,3α,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic dimethyl ester (15j) and *trans*-6-cyano-8-methyl-3,3α,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic dimethyl ester (16j)** (Table 3, entry 16): Malonate ester **14j** (15 mg, 0.052 mmol) in distilled acetone (0.3 mL) was degassed by argon before the addition of $[CpRu(CH_3CN)_3]PF_6$ (2 mg, 0.005 mmol). The resulting brown solution was stirred at RT for 3 h and directly purified by flash chromatography (silica gel, petroleum ether/diethyl ether 20:1→10:1) to afford **15j** and **16j** as an inseparable mixture of regioisomers (13 mg, 0.045 mmol, 87%, *dr* 1:1.9) as a pale yellow oil. IR (film): $\tilde{\nu}$ = 2921s, 2851s, 2234w, 1733s, 1456m, 1435m, 1270m, 1201m, 1165m, 1072w, 949w, 844w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) for major isomer **16j**: δ = 5.68 (m, 1H), 5.60 (d, J=10.5 Hz, 1H), 3.772 (s, 3H), 3.766 (s, 3H), 3.62 (m, 1H), 3.05 (d, J=17.0 Hz, 1H), 2.95 (d, J=17.0 Hz, 1H), 2.74 (m, 1H), 2.61 (m, 1H), 2.48 (m, 1H), 2.30 (m, 1H), 2.04 (t, J=13.0 Hz, 1H), 1.88 (s, 3H); ^1H NMR (500 MHz, $CDCl_3$) for minor isomer **15j**: δ = 5.72 (dd, J=11.0 Hz, 1H), 5.60 (d, J=10.5 Hz, 1H), 3.768 (s, 3H), 3.766 (s, 3H), 3.56 (m, 1H), 3.05 (d, J=17.0 Hz, 1H), 2.95 (d, J=17.0 Hz, 1H), 2.74 (m, 2H), 2.64 (m, 1H), 2.20 (m, 1H), 2.05 (t, J=11.0 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) for major isomer **16j**: δ = 171.7, 171.4, 137.3, 133.4, 126.4, 123.2, 120.4, 58.1, 52.9, 41.3, 39.6, 39.2, 33.8, 32.0, 29.7, 22.7; ^{13}C NMR (75 MHz, $CDCl_3$) for minor isomer **15j**: δ = 171.8, 171.5, 139.4, 135.6, 127.5, 125.5, 122.7, 58.1, 53.0, 41.2, 39.6, 39.7, 34.9, 30.0, 29.4, 22.0; HRMS: m/z: calcd for $C_{16}H_{19}O_4N$: 289.1314; found: 289.1313.

***cis*-6-Cyano-8-methyl-3,3α,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic dimethyl ester (18b)** (Table 4, entry 2): Ester **17b** (21 mg, 0.073 mmol) in distilled acetone (0.8 mL) was degassed by argon before the addition of $[CpRu(CH_3CN)_3]PF_6$ (3.2 mg, 0.007 mmol). The resulting red solution was stirred at RT for 4 h. Flash chromatography eluting with 5→25% diethyl ether in petroleum ether afforded **18b** (17 mg, 0.059 mmol, 81%) as a single diastereomer as a pale yellow oil. IR (film): $\tilde{\nu}$= 2954w, 2855w, 2238w, 1783s, 1435m, 1258s, 1204s, 1165s, 1062m, 756w, 668w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.61 (dt, J=2.5, 11.5 Hz, 1H), 5.50 (dq, J=4.0, 11.5 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.66 (bm, 1H), 3.33 (m, 1H), 2.98 (d, J=16.5 Hz, 1H), 2.93 (d, J=13.0 Hz, 1H), 2.85 (m, J=17.0 Hz, 1H), 2.73 (ddd, J=2.0, 8.5, 13.0 Hz, 1H), 2.24 (dt, J=1.5, 11.5 Hz, 1H), 1.96 (dd, J=11.0, 13.0 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.61, 171.55, 138.9, 134.4, 126.4, 122.9, 120.8, 58.1, 52.9, 52.8, 41.5, 39.9, 38.9, 36.0, 29.7, 20.8; HRMS: m/z: calcd for $C_{16}H_{19}O_4N$: 289.1314; found: 289.1320.

2,2-Bis(methoxycarbonyl)-8-methyl-6-(triisopropylsilyloxymethyl)-1,2,3,3α,6,7-hexahydroazulene (18c) (Table 4, entry 3): A solution of vinylcyclopropane **17c** (33 mg, 0.073 mmol) in acetone (0.7 mL) was added to a test tube containing $[CpRu(CH_3CN)_3]PF_6$ (3 mg, 0.007 mmol) and the resulting orange solution stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo and purified by chromatography eluting with 5% diethyl ether/petroleum ether to afford **18c** (28 mg, 85%) as a colorless liquid. IR (film): $\tilde{\nu}$ = 2944, 2865, 1738, 1434, 1256, 1202, 1164, 1111, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.47 (m, 1H), 5.43 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.57 (dd, J=9.3, 6.0 Hz, 1H), 3.55 (m, 1H), 3.47 (dd, J=9.3, 7.5 Hz, 1H), 3.02 (d, J=16.3 Hz, 1H), 2.89 (dd, J=16.3, 2.1 Hz, 1H), 2.68 (ddd, J=12.4, 8.5, 1.8 Hz, 1H), 2.44 (t, J=12.4 Hz, 1H), 2.30 (m, 1H), 1.99 (ddd, J=13.0, 2.0, 1.7 Hz, 1H), 1.95 (dd, J=13.0, 11.0 Hz, 1H), 1.75 (s, 3H), 1.08 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0, 136.6, 131.1, 130.6, 129.0, 68.1, 58.5, 52.7, 52.6, 42.0, 40.2, 39.5, 38.8, 37.6, 20.9, 18.0, 12.0; HRMS: m/z: calcd for $C_{25}H_{42}O_5Si$: 450.2802; found: 450.2837.

***trans*-2,2-Bis(methoxycarbonyl)-7-formyl-8-methyl-1,2,3,3α,6,7-hexahydroazulene (16l)** (Scheme 9): Compound **14l** (72 mg, 0.25 mmol) in distilled acetone (0.6 mL) was degassed with argon for 5 min before $[CpRu(CH_3CN)_3]PF_6$ (**4**; 11 mg, 0.025 mmol) was added. The resultant yellow solution was stirred at RT. for 1 h. Flash chromatography afforded **16l** (56 mg, 0.19 mmol, 78%) as colorless oil. It was a mixture of two isomers with the ratio of 15:1. The relative stereochemistry was determined by NOE between the angular proton and α-proton of aldehyde. COSY spectra also confirmed the structure of this compound. IR (film): $\tilde{\nu}$= 2955m, 2850w, 2723w, 1734s, 1437m, 1274s, 1202m, 1163m, 1078m, 953w, 885w, 822w, 804w, 749w cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.67 (d, J=1.8 Hz, 1H), 5.70 (dtd, J=2.7, 6.0, 10.2 Hz, 1H), 5.61 (dt, J=2.2, 10.5 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.60 (m, 1H), 3.17 (m, 1H), 3.06 (d, J=17.2 Hz, 1H), 2.91 (d, J=1.8, 17.2 Hz, 1H), 2.66 (m, 2H), 2.32 (dt, J=5.7, 15.3 Hz, 1H), 2.04 (t, J=12.4 Hz, 1H), 1.66 (s, 3H), 1.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.8, 172.0, 171.8, 138.4, 134.5, 127.7, 124.3, 58.0, 55.0, 52.9, 52.8, 41.2, 41.0, 39.7, 26.0, 19.9; HRMS: m/z: calcd for $C_{16}H_{20}O_5$: 292.1311; found: 292.1106.

***trans*-2,2-Bis(methoxycarbonyl)-7-formyl-8-methyl-1,2,3,3α,6,7-hexahydroazulene (16l)**: A solution of *cis*-vinylcyclopropane **17g** (20 mg, 0.068 mmol) in acetone (0.7 mL) was added to a test tube containing $[CpRu(CH_3CN)_3]PF_6$ (3 mg, 0.007 mmol) and the resulting orange solution stirred at room temperature for 30 min. The reaction mixture was concentrated in vacuo and purified by chromatography eluting with diethyl ether/petroleum ether 1:1 to afford aldehyde **16l** (16 mg, 82%) as a 12:1 mixture of diastereomers. The ratio of diastereomers was determined by ^1H NMR integration of the aldehydic proton: for the major diastereomer a doublet at 9.67 ppm (1H) and for the minor diastereomer a doublet at 9.62 ppm (1H). IR (film): $\tilde{\nu}$ = 2954, 2851, 1732, 1434, 1273, 1200, 1163, 1078, 952, 886 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.67 (d, J=1.8 Hz, 1H), 5.70 (dtd, J=10.2, 6.0, 2.7 Hz, 1H), 5.61 (dt, J=10.2, 2.2 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.60 (m, 1H), 3.17 (m, 1H), 3.06 (d, J=17.2 Hz, 1H), 2.91 (dd, J=17.2, 1.8 Hz, 1H), 2.66 (m, 2H), 2.32 (m, 1H), 2.04 (t, J=12.4, Hz, 1H), 1.66 (s, 3H), 1.08 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.8, 172.0, 171.8, 138.4, 134.5, 127.7, 124.3, 58.0, 55.0, 52.9, 52.8, 41.2, 41.0, 39.7, 26.0, 19.9; HRMS: m/z: calcd for $C_{16}H_{19}O_5$: 291.1232; found: 291.1258 $[M-H]^+$. Additional signals for minor diastereomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 9.62 (d, J=1.1 Hz, 1H), 5.75 (m, 2H), 3.71 (s, 3H), 3.32 (m, 1H), 2.99 (d, J=16.3 Hz, 1H), 2.83 (br d, J=16.3 Hz, 1H), 2.16 (m, 1H), 1.40 (s, 3H).

5-Hydroxy-10-methyl-3,3α,5,6,7,8,8α,9-octahydro-1*H*-benzo[*f*]azulene-2,2-dicarboxylic dimethyl ester (43d) (Table 5, entry 4): $[CpRu(CH_3CN)_3]PF_6$ (1.0 mg, 0.0024 mmol) at RT was added to **42d** (8.0 mg, 0.024 mmol) in distilled acetone (0.2 mL). The solution was stirred for 4 h. Without further work-up, flash chromatography eluting with 20→50% diethyl ether in petroleum ether to afford **43d** (5.6 mg, 0.017 mmol, 81%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3408b, 2926s, 2855m, 1736s, 1434m, 1268s, 1203s, 1162m, 1121m, 1169m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.34 (br s, 1H), 4.10 (dd, J=2.5, 3.0 Hz, 1H), 3.75 (s, 6H), 3.56 (m, 1H), 2.93 (d, J=1.0 Hz, 2H), 2.84 (d, J=14.5 Hz, 1H), 2.73 (ddd, J=1.0, 9.0, 13.0 Hz, 1H), 2.65 (m, 1H), 1.97 (dd, J=9.0, 13.0 Hz, 1H), 1.87 (m, 1H), 1.80 (dd, J=4.0, 14.0 Hz, 1H), 1.73 (d, J=1.5 Hz, 3H), 1.58 (m, 1H), 1.53 (m, 2H), 1.44 (m, 1H), 1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0, 143.9, 137.4, 128.0, 126.0, 76.1, 58.9, 52.74, 52.66, 42.3, 38.6, 38.5, 37.8, 34.7, 34.6, 33.3, 30.3, 29.7; HRMS: m/z: calcd for $C_{19}H_{26}O_5$: 334.1780; found: 334.1778.

4-Methyl-5-oxo-3,4α,5,6,7,8,8α,10α-octahydro-1*H*-benz[*f*]azulene-2,2-dicarboxylic acid dimethyl ester (43h) (Table 5, entry 9): $[CpRu(CH_3CN)_3]PF_6$ (1.5 mg, 0.0036 mmol) and $In(OTf)_3$ (9 mg, 0.018 mmol) was added under argon at RT to a solution of **42h** (12 mg, 0.036 mmol) in acetone (0.5 mL). The mixture was stirred for 4 h and purified by flash chromatography eluting with 5→20% diethyl ether in petroleum ether without workup, to afford **43h** (9.3 mg, 0.028 mmol, 78%) as a pale yellow oil. IR (film): $\tilde{\nu}$ = 3008w, 2953m, 2923m, 2852w, 1736s, 1689s, 1437m, 1329w, 1287m, 1246m, 1210s, 1123w, 1066m, 1031w, 967w, 899w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.76 (dt, J=10.0, 2.5 Hz, 1H), 5.52 (ddd, J=2.5, 6.5, 9.5 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.55 (br s, 1H), 3.50 (m, 1H), 3.24 (br s, 1H), 3.10 (d, J=17.5 Hz, 1H), 2.97 (dd, J=1.5, 17.5 Hz, 1H), 2.61 (ddd, J=2.0, 8.0, 12.5 Hz, 1H), 2.39 (m, 2H), 2.14 (t, J=12.5 Hz, 1H), 2.08 (m, 2H), 1.90 (m, 1H), 1.84 (m, 1H), 1.56 (s,

3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.5, 172.3, 171.8, 135.2, 134.9, 129.9, 124.6, 59.1, 57.8, 52.8, 52.7, 42.3, 40.7, 40.6, 39.71, 39.65, 30.0, 24.1, 22.3; HRMS: *m*/*z*: calcd for $C_{19}H_{24}O_5$: 332.1624; found: 332.1622.

8α-(*tert*-Butyldimethylsilyloxymethyl)-4-methyl-3,4α,5,6,7,8,8α,10α-octahydro-1*H*-benzo[*f*]azulene-2,2-dicarboxylic dimethyl ester (43i) (Table 5, entry 10): $[CpRu(CH_3CN)_3]PF_6$ (2 mg, 0.004 mmol) was added to malonate ester **42i** (19 mg, 0.047 mmol) in acetone (0.5 mL). The resulting red solution was stirred at RT for 3 h. Without workup, flash chromatography of the reaction mixture eluting with 5→10% diethyl ether in petroleum ether afforded a yellow oil isolated as a single diastereomer of the tricyclic compound **43i** (16 mg, 0.040 mmol, 85%). IR (film): $\tilde{\nu}$ = 2930s, 2857s, 1768s, 1462w, 1435w, 1258s, 1197m, 1162m, 1108m, 1076m, 1007w, 939w, 837m, 775m, 667w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.63 (d, *J* = 11.5 Hz, 1H), 5.36 (d, *J* = 11.0 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.35 (d, *J* = 9.5 Hz, 1H), 3.24 (m, *J* = 11.0 Hz, 1H), 2.99 (d, *J* = 17.5 Hz, 1H), 2.88 (d, *J* = 17.5 Hz, 1H), 2.53 (dd, *J* = 6.5, 14.0 Hz, 1H), 1.98 (m, 2H), 1.70 (m, *J* = 8.0 Hz, 2H), 1.64 (s, 3H), 1.60 (m, 1H), 1.51 (m, 2H), 1.22 (m, 4H), 0.89 (s, 9H), −0.004 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7, 172.5, 134.7, 130.1, 130.0, 128.3, 66.4, 56.8, 52.79, 52.75, 47.9, 45.3, 42.7, 41.6, 39.7, 36.4, 30.1, 27.3, 25.9, 22.5, 22.2, 18.3, −5.59, −5.72; HRMS: *m*/*z*: calcd for $C_{22}H_{33}O_5Si$: 405.2097; found: 405.2103; elemental analysis calcd (%) for $C_{26}H_{42}O_5Si$: C 67.49, H 9.16; found: C 67.35, H 9.33.

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