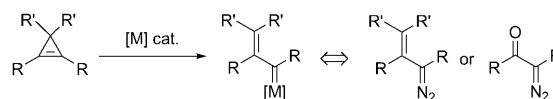


Rhodium-Catalyzed Cycloisomerization Involving Cyclopropenes: Efficient Stereoselective Synthesis of Medium-Sized Heterocyclic Scaffolds

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The intramolecular cyclopropanation of an olefin using a carbene that is generated by the decomposition of a diazo compound in the presence of a catalytic amount of a transition-metal complex, is a powerful strategy for the synthesis of $[n.1.0]$ bicyclic ring systems.^[1] In recent years, the transition-metal-catalyzed cycloisomerization of enynes has emerged as a useful complementary alternative method that avoids the use of the potentially hazardous diazo compounds.^[2,3] In particular, the platinum- and gold-catalyzed cycloisomerization of enynes has attracted considerable interest. The selective activation of the alkyne by these Lewis π acids triggers the nucleophilic attack of the alkene and generates a metal carbene intermediate, the $[n.1.0]$ bicyclic core of which can be retained in the final product depending on the substitution pattern.^[2,4]

In particular, enynes **A**, which contain a propargylic ester, constitute interesting synthetic equivalents of α -diazo ketones since the initially generated cyclopropyl carbenes **B** can evolve by a 1,2-acyl shift to give enol esters **C** that produce bicyclo $[n.1.0]$ alkanones **D**, which include those possessing medium-sized rings, after cleavage of the acyl group (Scheme 1, Eq. (1)).^[5] The alternative mechanism, in which the 1,2-acyl shift leading to a metal carbene intermediate precedes the cyclopropanation of the olefin,^[6,7] can also



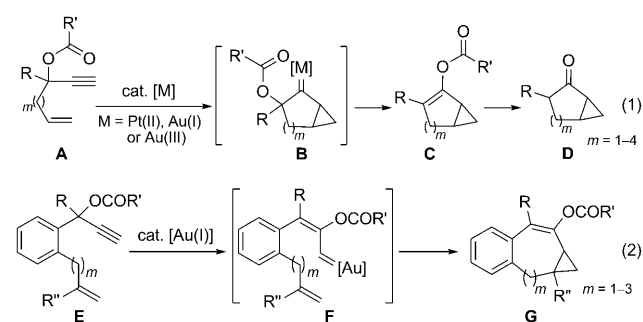
Scheme 2. Metal carbenes by ring opening of cyclopropenes.

operate for some substrates, such as the benzylic propargylic esters **E**. The cycloisomerization of **E** proceeds via the gold carbene intermediate **F** and leads to medium-sized rings **G**, which can be enantioenriched if chiral diphosphanes are used as ligands (Scheme 1, Eq. (2)).^[8]

The development of an efficient route toward bicyclo $[n.1.0]$ alkanes of various ring sizes and substitution patterns, which relies on a transition-metal-catalyzed intramolecular olefin cyclopropanation using carbenes that are not generated from diazo compounds, is an interesting challenge. Because of their ability to undergo ring opening in the presence of transition-metal complexes, cyclopropenes are interesting precursors of alkenyl carbenes,^[9] which can be viewed not only as synthetic equivalents of alkenyl diazoalkanes, but also of α -diazo ketones if the generated olefin is later subjected to an oxidative cleavage (Scheme 2).

The reactivity of alkenyl rhodium carbenoids, which are generated by the rhodium-catalyzed reaction of α -diazo ketones with alkynes, has been the subject of considerable investigation.^[10–12] Examples of intramolecular trapping with an alkene of such vinylogous acceptor-substituted carbenoids,^[13] which can in principle also be generated by the ring opening of cyclopropenyl ketones, have been reported.^[10–12] However, the synthetic potential of a transition-metal-catalyzed cycloisomerization of appropriately substituted cyclopropene-ynes that proceeds through the intramolecular cyclopropanation of the remote olefin, remains largely unexplored. The silver-catalyzed rearrangement of 3-allyl-1,2-diphenylcyclopropene into the corresponding substituted bicyclo $[3.1.0]$ hex-2-ene constitutes one of the first examples of such a process.^[14] Recently, we have reported the gold-catalyzed cycloisomerization of cyclopropene-ynes **H**, thus leading to the 3-oxa- or 3-azabicyclo $[4.1.0]$ heptanes **I** in high yields and excellent diastereoselectivities.^[15,16] Since the isopropylidene group can undergo subsequent ozonolysis to afford the corresponding $[4.1.0]$ bicycloheptan-2-ones **J**,^[15] this strategy favorably compares with the copper-catalyzed intramolecular cyclopropanation of the corresponding α -diazo δ -alkenyl ketones,^[17] in terms of efficiency and diastereoselectivity (Scheme 3).

Herein, we report a new highly efficient and diastereoselective rhodium-catalyzed cycloisomerization of cyclopro-

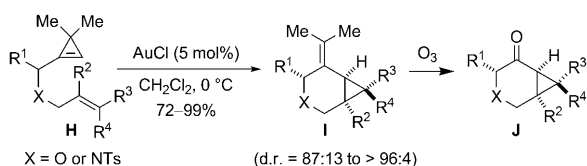


Scheme 1. Cycloisomerization of enynes bearing a propargyl ester.

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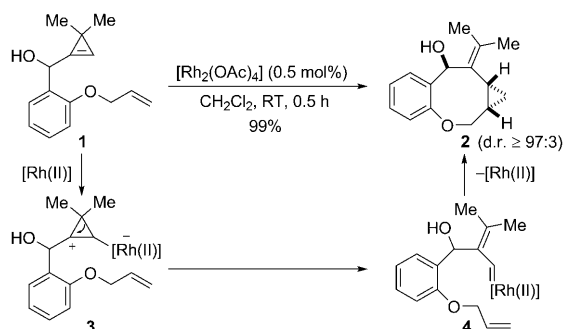


Scheme 3. Gold-catalyzed cycloisomerization of cyclopropene-ene compounds. Ts = *p*-toluenesulfonyl.

pene-enes that does not involve diazo compounds. This reaction proceeds by an intramolecular olefin cyclopropanation to afford functionalized unusual heterocyclic scaffolds, which possess a [6.1.0] bicyclic ring system fused to an aromatic ring.

To cycloisomerize cyclopropene-enes into medium-sized heterocycles, the reactivity of cyclopropenyl carbinol **1** (Scheme 4), which is readily available by condensation of 3,3-dimethylcyclopropenyl lithium to *O*-allyl salicylaldehyde,^[18] was investigated in the presence of gold catalysts. Whereas AuCl₃ (5 mol %) led to the complete conversion of **1** within 1 hour (CH₂Cl₂, RT), the reaction did not go to completion with AuCl (**2**/**1** = 60:40 after 12 h); in both cases, the expected cycloisomerized product **2** was accompanied by several unidentified by-products that could not be easily removed by flash chromatography on silica gel. The catalysts [(Ph₃P)AuSbF₆] and [(Ph₃P)AuNTf₂] (Tf = trifluoromethanesulfonyl)^[19] were even less satisfactory and led to complex mixtures that contained either none ([(Ph₃P)AuSbF₆]) or trace amounts of compound **2** ([(Ph₃P)AuNTf₂]). The use of rhodium catalysts was then considered, and [Rh₂(OAc)₄] (0.5 mol %) was found to smoothly catalyze the cycloisomerization of cyclopropenyl carbinol **1** into the desired eight-membered oxygen heterocycle **2**, which possesses a [6.1.0] bicyclic ring system, in almost quantitative yield (99 %) and with excellent diastereoselectivity (d.r. ≥ 97:3).^[20] The relative configuration of **2** was unambiguously determined by single-crystal X-ray diffraction of the corresponding *p*-nitrobenzoate derivative.^[21]

Other rhodium(I) and rhodium(II) catalysts were also screened but provided inferior results.^[22] Notably the cycloisomerization of the optically enriched (*S*)-**1** (94 % *ee*) led to **2** with the same optical purity, thereby indicating that the hydroxy-substituted stereocenter was not affected.^[23] As



Scheme 4. Rhodium-catalyzed cycloisomerization of cyclopropenyl carbinol **1**.

anticipated, the monosubstituted cyclopropene olefin in **1**, the stability of which is ensured by the vicinal *gem*-dimethyl group, underwent regioselective electrophilic activation by [Rh₂(OAc)₄] to generate the secondary cyclopropyl cation **3**, which has the rhodium atom at the less-hindered site. Ring opening of cation **3** would then generate the rhodium carbenoid **4** that promotes the intramolecular cyclopropanation of the alkene (Scheme 4). Rationalization of the observed high diastereoselectivity deserves further investigation but the *gem*-dimethyl substitution of the olefin in the rhodium carbenoid **4** is presumably a key control element, owing to minimization of the A^{1,3} strain in the cyclic transition state, as previously observed in the gold-catalyzed cycloisomerization of cyclopropenes **H**.^[15]

The conversion of cyclopropene **1** into benzoxocane **2** is clearly distinct from the previously reported rhodium-catalyzed cycloisomerizations that involve cyclopropenes and proceed by a ring-opening reaction.^[24] Notably the donor-substituted rhodium(II) carbenoid **4** displays an unprecedented high reactivity toward the olefin cyclopropanation, despite its lower electrophilicity compared with rhodium carbenoids that are generated from α -diazo carbonyl compounds that bear at least one electron-withdrawing group.^[1,13]

The scope of this new rhodium-catalyzed cycloisomerization involving cyclopropenes was first evaluated with (2-allyloxyphenyl)cyclopropenyl carbinols **5–11**, which bear a variety of substituents on the aromatic ring, and were synthesized in two steps from the corresponding substituted salicylaldehydes.^[25] Unsurprisingly, when a methyl or a methoxy group was present on the aromatic ring the corresponding cycloisomerization products **12** and **13** were isolated in 99 % and 97 % yield (Table 1, entries 1 and 2). The 5-fluoro-, 5-bromo-, or 3-bromo-substituted analogues **7–9**, also underwent a clean rhodium-catalyzed cycloisomerization to provide the corresponding eight-membered oxygen heterocycles **14–16**, in high yields (Table 1, entries 3–5). The presence of a bromide substituent, which could be potentially useful for further functionalization, was tolerated, and a nitro group was also compatible, as exemplified by the cycloisomerization of cyclopropenyl carbinol **10** leading to compound **17** (Table 1, entry 6). The alkynyl substituent in the cyclopropenyl carbinol **11** did not interfere with the reaction and the corresponding cycloisomerization product **18** was isolated in almost quantitative yield (Table 1, entry 7). In all cases, only a single diastereomer was detected by ¹H NMR spectroscopy (d.r. ≥ 96:4).

The scope of the cycloisomerization was then evaluated with (2-allyloxyphenyl)cyclopropenyl carbinols **19–23**, which bear substituted allylic ethers (Table 2).^[25] Methallyl ether **19** gave the eight-membered oxygen heterocycle **24** (95 %), which possesses a trisubstituted cyclopropane, as a single detectable diastereomer (Table 2, entry 1). An iodide substituent was tolerated, as shown for cyclopropene **20**, which led to the benzoxocane **25** in 96 % yield (Table 2, entry 2). The cinnamyl ether **21** was converted into the oxygen heterocycle **26** (99 %), which bears an additional stereocenter on the cyclopropane ring, as a single diastereomer (Table 2, entry 3). As anticipated, the cycloisomerization proceeds with the stereospecific cyclopropanation of the alkene; this stereo-

Table 1: Scope of the rhodium-catalyzed cycloisomerization of substituted (2-allyloxyphenyl)cyclopropenyl carbinols.

Entry	Substrate	Product ^[a]	Yield [%] ^[b]
1			99
2			97
3			91
4			95
5			99
6			99
7			99

[a] Reaction conditions: $[\text{Rh}_2(\text{OAc})_4]$ (0.5 mol %), CH_2Cl_2 (0.1 M), RT, 0.5 h. [b] Yield of isolated, analytically pure product (d.r. $\geq$ 96:4).

specificity is illustrated by the reaction of the geometric isomers **22** and **23**, which ultimately led to epimeric compounds **27** (95%) and **28** (98%), respectively (Table 2, entries 4 and 5).

Whether the 2-allyloxy ether linkage and the presence of the hydroxy group at the benzylic position were crucial for the success of the rhodium-catalyzed cycloisomerization was next investigated (Table 3). The allyloxy substituent could be replaced by a but-3-enyl group, as shown for compound **29**, which was efficiently converted into benzocyclooctane **34** in high yield (99%), albeit with slightly inferior diastereoselectivity (Table 3, entry 1). Removal of the benzylic hydroxy group also had no adverse effect on the reactivity since the (2-allyloxybenzyl)cyclopropene **30** was smoothly converted into

Table 2: Scope of the rhodium-catalyzed cycloisomerization.

Entry	Substrate	Product ^[a]	Yield [%] ^[b]
1			95
2			96
3			90
4			95
5			98

[a] Reaction conditions: $[\text{Rh}_2(\text{OAc})_4]$ (0.5 mol %), CH_2Cl_2 (0.1 M), RT, 0.5 h. [b] Yield of the isolated, analytically pure product (d.r. $\geq$ 96:4). PMB = *p*-methoxybenzyl.

the eight-membered oxygen heterocycle **35** (Table 3, entry 2). Interestingly, the hydroxy group could be replaced by an amino substituent, as illustrated with the *N*-(*tert*-butoxycarbonyl)cyclopropenylcarbinyl amines **31** and **32**, which were easily prepared by the addition of 3,3-dimethylcyclopropenyl lithium to the corresponding substituted *N*-Boc aldimines.^[26] The latter substrates underwent a slow cycloisomerization (20 h, RT), the diastereoselectivity of which was difficult to evaluate accurately by ^1H NMR spectroscopy because of the presence of rotamers. Thus, the crude cycloisomerization products were directly treated with TFA to afford the amino-substituted oxygen heterocycles **36** and **37** as single diastereomers (d.r. $\geq$ 96:4), isolated in 60% and 63% overall yield, respectively (Table 3, entries 3 and 4). Preliminary results also indicate that the rhodium-catalyzed cycloisomerization could be applied to the synthesis of eight-membered nitrogen heterocycles from *N*-allyl carbamates such as **33**. After palladium-catalyzed cleavage of the allyloxycarbamoyl protecting group, the desired benzazocane **38** was obtained as a single diastereomer and isolated in 50% yield (unoptimized; Table 3, entry 5).^[27]

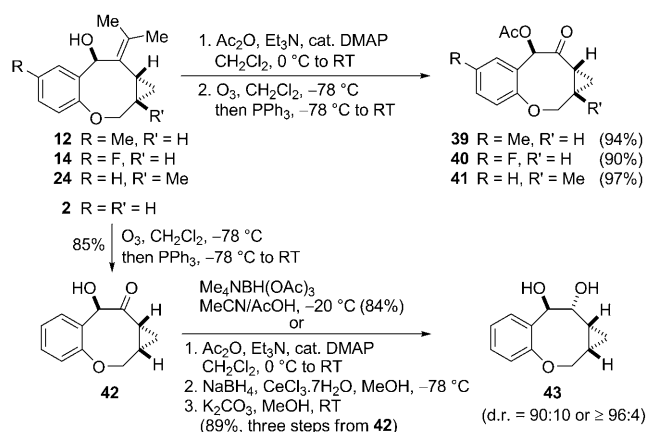
To illustrate that 3,3-dimethylcyclopropenes could be considered as α -diazo ketone surrogates, compounds **12**, **14**, and **24** were subjected to ozonolysis after protection of the alcohol as an acetate. The α -acetoxy cyclopropyl ketones **39** (94%), **40** (90%), and **41** (97%) were synthesized in excellent yields over the two-step sequence (Scheme 5). Ozonolysis could also be carried out without protection of the hydroxy

Table 3: Scope of the rhodium-catalyzed cycloisomerization.

Entry	Substrate	Product ^[a]	t [h]	Yield [%] ^[b]
1			0.5	99
2			0.75	93
3			20	60 ^[c]
4			20	63 ^[c]
5			1	50 ^[d]

[a] Reaction conditions: $[\text{Rh}_2(\text{OAc})_4]$ (0.5 mol%), CH_2Cl_2 (0.1 M), RT. [b] Yield of the isolated, analytically pure product (d.r. $\geq 96:4$, unless otherwise indicated). [c] After treatment with TFA (CH_2Cl_2 , RT). [d] After treatment with $[\text{Pd}(\text{PPh}_3)_4]$ (5 mol%), morpholine (THF, RT). Alloc = allyloxycarbonyl, Boc = *tert*-butoxycarbonyl, THF = tetrahydrofuran.

group as illustrated by the direct conversion of **2** into α -hydroxy ketone **42** (85%). Additionally, we showed that the diastereoselective reduction of ketone **42** could be achieved in comparable yields either directly with $\text{Me}_4\text{NBH}(\text{OAc})_3$ (d.r. = 90:10)^[28] or, after acetylation of the hydroxy group, with Luche's reagent^[29] to afford the same 1,2-diol **43** after methanolysis (d.r. $\geq 96:4$).^[30]


Scheme 5. Transformation of the cycloisomerization products into cyclopropyl ketones and cyclopropyl carbinols. DMAP = 4-dimethylaminopyridine.

In conclusion, we have reported a new rhodium(II)-catalyzed cycloisomerization of cyclopropenes that does not rely on diazo compounds as substrates or precursors, and in which the donor-substituted rhodium carbenoid generated by ring opening achieves the highly diastereoselective intramolecular cyclopropanation of an alkene. The starting cyclopropene-ene substrates are readily prepared from salicylaldehydes, and their rhodium-catalyzed cycloisomerization efficiently provides access to new functionalized carbocycles or heterocyclic scaffolds that contain a [6.1.0] bicyclic system fused to an aromatic ring.^[31] We are currently exploring the reactivity of these donor-substituted rhodium(II) carbenoids generated from cyclopropenes in other synthetically useful transformations.

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