Rhodium Catalysis

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

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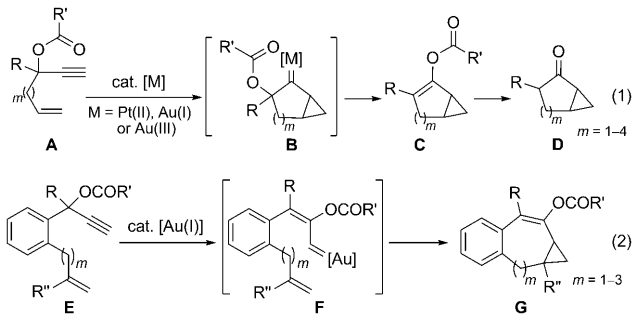
The intramolecular cyclopropanation of an olefin using a carbene that is generated by the decomposition of a diazo compound in the presence of a catalytic amount of a transition-metal complex, is a powerful strategy for the synthesis of [*n*.1.0] bicyclic ring systems.[1] In recent years, the transition-metal-catalyzed 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 1. Cycloisomerization of enynes bearing a propargyl ester.

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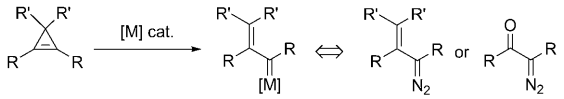


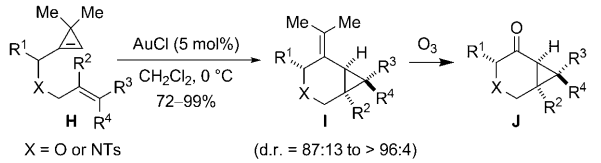
Scheme 2. Metal carbenes by ring opening of cyclopropenes.

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-enes 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-enes **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-

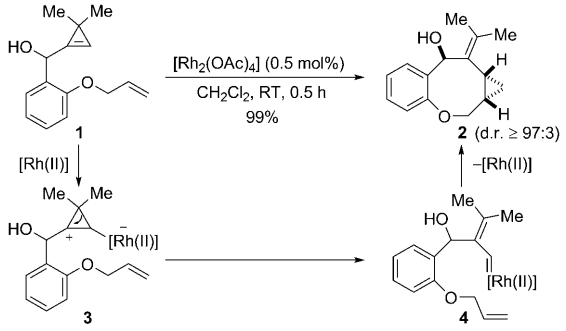


Scheme 3. Gold-catalyzed cycloisomerization of cyclopropene-ene compounds. Ts = *p*-toluenesulfonyl.

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 $AuCl_3$ (5 mol%) led to the complete conversion of **1** within 1 hour (CH_2Cl_2, 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 $[(Ph_3P)AuSbF_6]$ and $[(Ph_3P)AuNTf_2]$ (Tf = trifluoromethanesulfonyl)[19] were even less satisfactory and led to complex mixtures that contained either none ($[(Ph_3P)AuSbF_6]$) or trace amounts of compound **2** ($[(Ph_3P)AuNTf_2]$). The use of rhodium catalysts was then considered, and $[Rh_2(OAc)_4]$ (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 $[Rh_2(OAc)_4]$ 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 diasteromer (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	**5**	**12**	99
2	**6**	**13**	97
3	**7** X = F	**14** X = F	91
4	**8** X = Br	**15** X = Br	95
5	**9**	**16**	99
6	**10**	**17**	99
7	**11**	**18**	99

[a] Reaction conditions: $[Rh_2(OAc)_4]$ (0.5 mol%), CH_2Cl_2 (0.1 M), RT, 0.5 h. [b] Yield of isolated, analytically pure product (d.r. ≥ 96:4).

Table 2: Scope of the rhodium-catalyzed cycloisomerization.

Entry	Substrate	Product[a]	Yield [%][b]
1	**19** R = Me	**24** R = Me	95
2	**20** R = I	**25** R = I	96
3	**21**	**26**	90
4	**22**	**27**	95
5	**23**	**28**	98

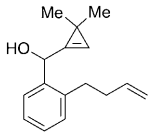
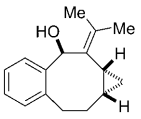
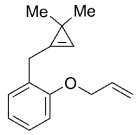
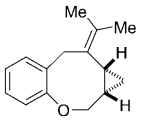
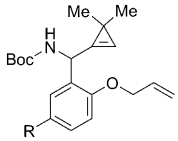
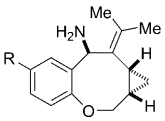
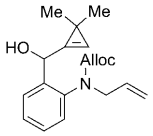
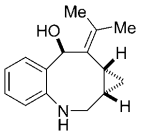
[a] Reaction conditions: $[Rh_2(OAc)_4]$ (0.5 mol%), CH_2Cl_2 (0.1 M), RT, 0.5 h. [b] Yield of the isolated, analytically pure product (d.r. ≥ 96:4). PMB = *p*-methoxybenzyl.

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 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 ^{1}H 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. ≥ 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]

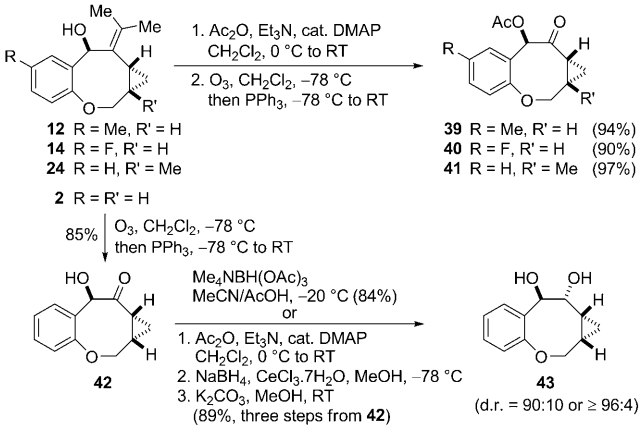
To illustrate that 3,3-dimethylcyclopropenes could be considered as α-diazo ketone surrogates, compounds **12**, **14**, and **24** were subjected to ozonolysis after protection of the alcohol as an acetate. The α-acetoxy cyclopropyl ketones **39** (94%), **40** (90%), and **41** (97%) were synthesized 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	 **29**	 **34** (d.r. = 93:7)	0.5	99
2	 **30**	 **35**	0.75	93
3	 **31** R = H	 **36** R = H	20	60[c]
4	**32** R = Br	**37** R = Br	20	63[c]
5	 **33**	 **38**	1	50[d]

[a] Reaction conditions: $[Rh_2(OAc)_4]$ (0.5 mol%), CH_2Cl_2 (0.1 M), RT. [b] Yield of the isolated, analytically pure product (d.r. ≥ 96:4, unless otherwise indicated). [c] After treatment with TFA (CH_2Cl_2, RT). [d] After treatment with $[Pd(PPh_3)_4]$ (5 mol%), morpholine (THF, RT). Alloc = allyloxycarbonyl, Boc = *tert*-butyloxycarbonyl, 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 $Me_4NBH(OAc)_3$ (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. ≥ 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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[21] CCDC 809808 (**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[22] The use of $[Rh_2(pfb)_4]$ (pfb = perfluorobutyrate) provided **2** in lower yield (71 %). None of the rhodium(I) catalysts screened appeared satisfactory, at least under the same mild reaction conditions. $[(Ph_3P)_3RhCl]$ showed no catalytic activity, in situ generated $[(Ph_3P)_3RhOTf]$ led to a complex mixture of products, and $[\{(cod)RhCl\}_2]$ (cod = 1,5-cyclooctadiene) provided only traces of **2** after 24 h at RT, along with unreacted **1** and other by-products.

[23] (*S*)-**1** was obtained by Sharpless kinetic resolution of (±)-**1** with (+)-diethyl tartrate, see: S. Simaan, A. Masarwa, P. Bertus, I. Marek, *Angew. Chem.* **2006**, *118*, 4067 – 4069; *Angew. Chem. Int. Ed.* **2006**, *45*, 3963 – 3965.

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