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Ruthenium-Catalyzed Highly Efficient Intramolecular Olefin Coupling of α,ω-Dienes. Facile and Regioselective Synthesis of *exo*-Methylenecyclopentanes

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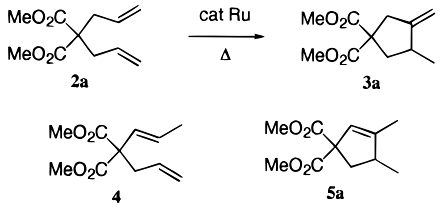
Intramolecular couplings of α,ω-diynes and enynes are useful tools in organic synthesis.[1] These cyclizations are efficiently mediated by stoichiometric amounts of zirconocene or titanocene derivatives with a variety of electrophiles trapping metallacyclic intermediates.[2] Catalytic methods using late transition metals such as Pd, Ni, and Rh widely expanded the scope of diyne and enyne cyclizations.[3] As for the corresponding coupling of α,ω-dienes, only a few successful examples have been reported, whereas α,ω-dienes with a wide variety of substitution patterns are readily accessible. This is mainly because their reactivity toward transition metal complexes is lower compared to the corresponding diynes or enynes. Recently, Molander's group[4] and Tanaka's group[5] developed organolanthanide-catalyzed sequential cyclization/silylation of 1,6- or 1,5-dienes, and a cationic palladium complex was also found to be effective to this type of cyclization by Widenhoefer et al.[6] Moreover, carbometalation of α,ω-dienes catalyzed by zirconium[7] or titanium[8] reagents also provided feasible routes to functionalized carbo- and heterocycles. In sharp contrast to the above examples, catalyzed cycloisomerization depicted in Scheme 1 requires no additional reagents except for an appropriate catalyst, and therefore, this process is the simplest but of considerable importance in terms of atom economy and environmental compatibility. Furthermore, the product *exo*-methylenecyclopentane is a valuable synthetic intermediate because its *exo*-methylene moiety can be easily converted into other functional groups such as ketone via ozonolysis, primary alcohol via hydroboration, etc. So far, few examples of this type of cyclization have been reported sporadically,[9−12] but further developments are expected. In this context, we independently found that some ruthenium(II) complexes efficiently catalyze cycloisomerization of α,ω-dienes in alcoholic solvents under air. Herein, we wish to report the first example of the highly selective formation of *exo*-methylenecyclopentanes from α,ω-dienes under the Ru catalysis.

Scheme 1



2a **3a** **4** **5a**

In the presence of 5 mol % of Cp*Ru(cod)Cl (**1a**: Cp* = pentamethylcyclopentadienyl), diene **2a** was heated at 80 °C in EtOH for 24 h under *air* to afford a *exo*-methylenecyclopentane **3a** in 82% yield as a sole product (Table 1, entry 1). The cycloisomerization was also catalyzed by simpler $RuCl_3{\cdot}3H_2O$ (entry 2) and $[Ru(cod)Cl_2]_n$ (**1b**: cod = cyclooctadiene) (entry 3), but other Ru(II) complexes, $[Ru(nbd)Cl_2]_n$ (nbd = norbornadiene), $[Ru(p\text{-cymene})Cl_2]_2$, $Ru(PPh_3)_3Cl_2$, and Ru(III) complexes, $[Cp^*Ru(cod)Cl_2]_2$ and $Ru(acac)_3$ were not effective at all under the same reaction conditions. The best result was realized by use of 5 mol % **1b**, and the desired **3a** was obtained in nearly quantitative yield (entry 3). It is noteworthy that the cyclization did not proceed in aprotic polar solvents such as 1,2-dichloroethane and acetonitrile, suggesting the importance of the alcohol solvent as a possible reductant (vide infra). In fact, 1 mol % of the catalyst was enough for the completion of the cyclization in *i*-PrOH at 90 °C (entry 4), although a 2.7:1:1.4 mixture of **3a**, a byproduct **4**, and the recovered diene **2a** was obtained in butanol at 100 °C (entry 5). In the absence of air, the highest TON of 39 h^{-1} was recorded (entry 6), although the present cyclization takes place under air to afford the cyclization product in high yield as shown above. Thus, 1 mol % **1a** gave **3a** in 87% yield (entry 7). It is surprising that *oligomeric, and almost insoluble*, **1b** exhibits the highest efficiency even under heterogeneous conditions, compared to monomeric, highly soluble **1a**, which is an effective catalyst for various C−C bond-forming reactions.[13] Related monomeric, soluble complexes $Ru(cod)(NCMe)_2Cl_2$ gave similar results, and oligomeric carbonyl complexes also catalyzed cycloisomerization (entry 9).

Under the optimized conditions, 1,6-heptadienes having various functional groups **2b−f** were isomerized to the

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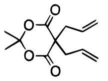
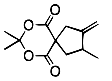
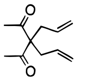
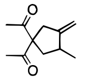
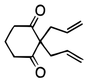
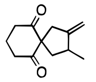
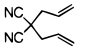
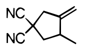
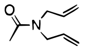
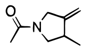
Table 1. Ru-Catalyzed Cycloisomerization of 1,6-Heptadiene 2a

entry	cat. (mol %)	solvent	T (°C)	products [yield (%)][b]
1	Cp*Ru(cod)Cl (5)	EtOH	80	**3a** [82]
2	$RuCl_3{\cdot}3H_2O$ (5)	EtOH	80	**3a** [54][c] + **4** [12][c]
3	$[Ru(cod)Cl_2]_n$ (5)	EtOH	80	**3a** [99]
4	$[Ru(cod)Cl_2]_n$ (1)	^{i}PrOH	90	**3a** [92]
5	$[Ru(cod)Cl_2]_n$ (1)	BuOH	100	**3a** [53][c] + **4** [20][c]
6	$[Ru(cod)Cl_2]_n$ (0.1)	^{i}PrOH[a]	90	**3a** [94]
7	Cp*Ru(cod)Cl (1)	^{i}PrOH[a]	90	**3a** [87]
8	$Ru(cod)(NCMe)_2Cl_2$ (1)	^{i}PrOH[a]	90	**3a** [78][c] + **5** [10][c]
9	$[Ru(CO)_2Cl_2]_n$ (5)	^{i}PrOH[a]	90	**2a** [87]
10	$(C_6Me_6)Ru(cod)$ (1)	$ClCH_2CH_2Cl$[a]	80	**3a** [87][c] + **5** [12][c]
11	Ru(cot)(cod) (1)	$ClCH_2CH_2Cl$[a]	80	**3a** [100]

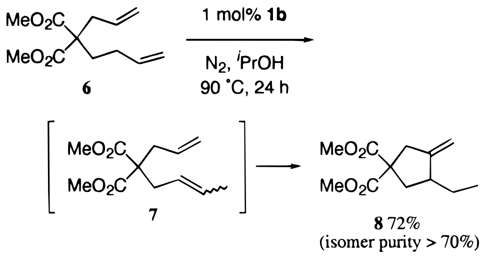
[a] Under N_2 atmosphere. [b] Isolated yields. [c] Product ratio was determined by ^1H NMR.

Table 2. Cycloisomerization of Dienes 2b−f[a]

diene (cat. amount)		product (yield)	
	**2b** (1 mol%)		**3b** (83%)
	**2c** (1 mol%)		**3c** (85%)
	**2d** (5 mol%)		**3d** (77%)
	**2e** (5 mol%)		**3e** (84%)
	**2f** (5 mol%)		**3f** (86%)

[a] The reaction was carried out by using $[Ru(cod)Cl_2]_2$ in i-PrOH at 90 °C for 24 h.

Scheme 2



corresponding methylenecyclopentanes **3b**−**f** by use of $[Ru(cod)Cl_2]_n$/i-PrOH combination catalyst as summarized in Table 2. In a similar manner with **2a**, a cyclic 1,3-diester **2b** gave **3b** in 83% yields. In addition to esters, ketones or nitriles are also compatible functional groups with our Ru catalysis. An acetylacetone derivative **2c**, cyclohexanone derivative **2d**, and malononitrile derivative **2e** were all converted into the corresponding products **3c**−**e** in high yields. N,N-Diallylacetoamide **2f** also gave a nitrogen heterocycle **3f** in 86% yield. Diallyl ether, however, gave no cyclization product.

Having elucidated the feasibility of 1,6-heptadiene cyclization, we then examined the cycloisomerization of a 1,7-octadiene **6** leading to six-membered ring products (Scheme 2). The reaction of **6** was carried out in the same manner; however, it gave the unexpected *exo*-methylenecyclopentane

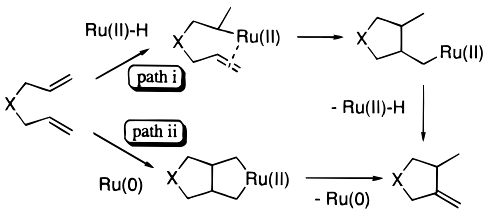
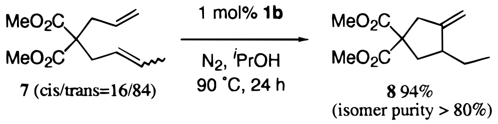


Figure 1.

Scheme 3



8 via fast isomerization of **6** to a 1,6-octadiene **7**. Similarly, a mixture of *cis*- and *trans*-**7** was converted into **8** in 94% isolated yield with over 80% isomer purity (Scheme 3). This result is in sharp contrast to the reported $RhCl(PPh_3)_3$-catalyzed system affording a mixture of five isomers with comparable ratio.[9g]

The mechanism of our isomerization is not clear at present, but two mechanistic possibilities can be envisaged: (i) in situ formation of ruthenium hydride species followed by hydroruthenation and subsequent carbaruthenation or (ii) initial reduction of Ru(II) to Ru(0) followed by ruthenacycle formation (Figure 1). Known ruthenium(II) hydrides $RuHCl(CO)(PPh_3)_3$, $CpRuH(PPh_3)_2$, and $Cp^*Ru(PPh_3)H_3$ all failed to effect cyclization of **2a** in refluxing 1,2-dichloroethane, indicative of the possibility of a nonhydride mechanism. On the other hand, ruthenium(0) complexes $(C_6Me_6)Ru(cod)$ and Ru(cot)(cod) exhibited excellent catalytic activities in refluxing 1,2-dichloroethane to give cyclized products quantitatively (Table 1, entries 10 and 11). Therefore, ruthenium(0) species generated by the reduction of Ru(II) complexes in alcohol might be involved in the catalytic cycle as path ii in Figure 1. In any event, the regiochemistry observed in the conversion of **7** into **8** cannot be explained in terms of the above two mechanisms.

In conclusion, we have provided a new and versatile protocol for the synthesis of functionalized cyclopentanes and a related nitrogen heterocycle via the first ruthenium-catalyzed regioselective cycloisomerization of 1,6-heptadienes and a 1,7-octadiene. The present method has considerable advantages compared to the known methods as follows: (1) The most effective catalyst $[Ru(cod)Cl_2]_n$ is readily available[14] and extremely stable for air and light so that it can be stored for a long period and handled without special precautions. (2) No additives such as acids, alkylating agents, oxidants, or other supporting ligands are required for the activation of the catalyst. (3) Environmentally less harmful alcohols can be used as solvent without purification. (4) Synthetically useful *exo*-methylene products are obtained selectively. (5) The catalyst system is tolerant of a wide variety of functional groups. Further extension and mechanism of our novel catalytic isomerization is now under investigation.

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Supporting Information Available: Experimental procedures and spectral data for selected compounds.

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