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Grubbs catalyst-mediated cycloisomerization of allenenes

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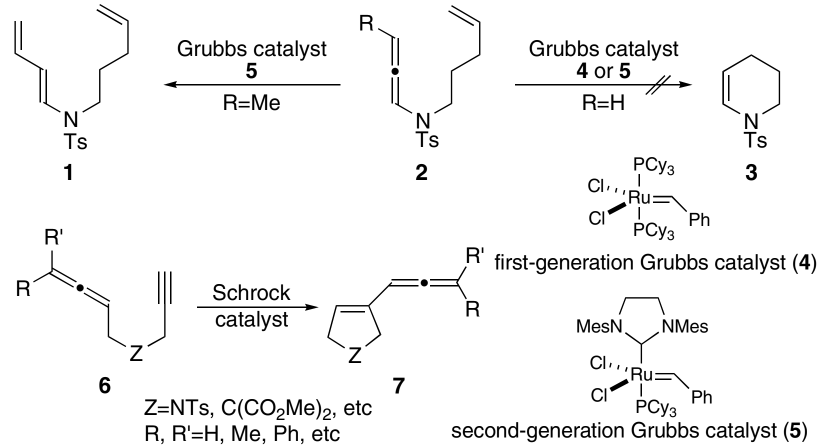
Abstract—The novel ruthenium benzylidene catalyst-mediated cycloisomerization of allenenes, having an alkyl appendage at the allenic terminus, resulting in the construction of cyclohexene, tetrahydropyran, and tetrahydropyridine skeletons was developed.

The ring-closing metathesis between two alkene π-bonds[1] is well recognized as one of the most powerful methodologies for the construction of a variety of cyclic compounds. This ring-closing reaction can be applicable to the enyne substrates (between the alkene π-bond and the alkyne π-bond),[2] leading to the formation of cyclic products having a 1,3-diene moiety. In contrast to these extensive studies, there are only two available examples[3,4] that investigated the ring-closing metathesis of allenene or allenyne derivatives.[5] In 2001, Rutjes and co-workers[3] examined the ring-closing metathesis of allenene **2** (R = H) in the presence of the ruthenium benzylidene complex **4** or **5** hoping for the construction of the tetrahydropyridine **3**, but no reaction took place and **2** was recovered intact. When allenene **2** (R = Me) was exposed to similar conditions [second-generation Grubbs catalyst (**5**)], the exclusive isomerization of the allenyl moiety to the (*E*)-1,3-diene functionality occurred to afford **1** in quantitative yield. On the other hand, Murakami et al.[4] reported the efficient ring-closing metathesis of the allenynes **6** in the presence of the Schrock catalyst resulting in the formation of the 1,2,4-triene compounds **7** (Scheme 1).

In line with our recent interest[6] in the metal-catalyzed cycloisomerization reactions of allenynes and allenenes,[7]



Scheme 1.

Keywords: Grubbs catalyst; Cycloisomerization; Allenene; Ring-closing reaction.

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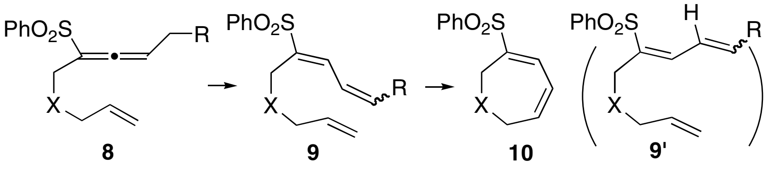
we became interested in the cycloisomerization of allenes in the presence of the ruthenium benzylidene complex. We envisaged that allene **8**, having a terminal alkyl appendage, would be susceptible to the ruthenium benzylidene complex-mediated isomerization to the (*Z*)-1,3-diene derivative **9** based on Rutjies' results.[3] The thus formed **9** would then undergo the ring-closing metathesis to produce the seven-membered 1,3-diene compound **10**. The selective formation of the (*Z*)-1,3-diene derivative **9** might be expected because the (*E*)-congener **9′** must be significantly destabilized due to the nonbonding interaction between a phenylsulfonyl group and a vinyl group. In addition, we anticipated that a phenylsulfonyl functionality (electron-withdrawing group) would possibly reduce the participation of the proximal double bond of the allenyl moiety in the metal-catalyzed reaction (Scheme 2). On the basis of these predictions, we investigated the ruthenium benzylidene complex-mediated reaction of allenenes.

The required allenenes **14** were prepared by the conventional procedures shown in Scheme 3. The acetylide, derived from the known malonate **11**,[8] was quenched by the carbonyl compounds **12** to afford adducts **13**, which were then converted into allenenes **14** by successive exposure to PhSCl and *m*CPBA.

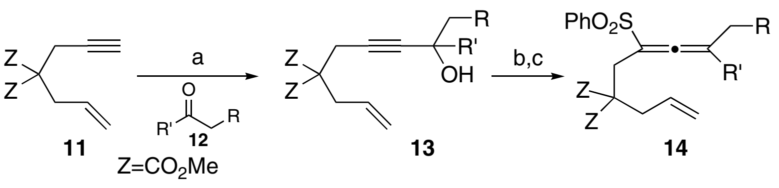
Our initial evaluation for the cycloisomerization of phenylsulfonylallenenes was carried out using compound **14a** (Table 1). A solution of **14a** in CH_2Cl_2 was refluxed for 10 h in the presence of 5 mol % of the ruthenium benzylidene complex **5**, but no cyclized product could be detected and the starting material was completely recovered (entry 1). Increasing the loading amounts of **5** from 5 to 20 mol % provided the cyclohexene derivative **15a** in 41% yield along with **14a** (54%) (entry 2). Contrary to our prediction described in Scheme 2, neither the seven-membered compound **10** $[X = C(CO_2Me)_2]$, or the acyclic 1,3-diene derivative [e.g., **9**, $X = C(CO_2Me)_2$, $R = H$] could be obtained. The benzyl and ethyl congeners **14b** and **14c** furnished the corresponding cyclohexene derivatives **15b** and **15c**[9] in higher yields (92% and 98%, respectively) (entries 3 and 4). The tetra-substituted allenes **14d** and **14e** were found to be inactive toward the ring-closing reaction resulting in the complete recovery of the starting materials (entries 5 and 6). No reaction occurred when **14c** was exposed to the first-generation Grubbs catalyst (**4**) (entry 7). The Hoveyda catalyst (**16**) was more ineffective than the second-generation Grubbs catalyst (**5**) during the conversion of **14c** into **15c** to provide the latter in 21% yield along with the starting material (59%) (entry 8).

The unexpected formation of the cyclohexene derivative **15** might be tentatively rationalized in terms of the intermediacy of the ruthenacyclopentene intermediate **A**.[10] The methyl (or methylene) hydrogen of the thus formed metallacycle **A** would be abstracted via β-hydride elimination[11] collapsing into the 1,3-diene derivative **15**. Alternatively, the formation of **15** might be interpreted as a result of the direct thermal ene-type reaction of **14**. To understand the latter process, compound **14b** was refluxed in CH_2Cl_2 without the ruthenium benzylidene catalyst for a prolonged time, but no reaction took place. In addition, when heated at a higher temperature (refluxing in toluene or in xylene), the thermal [2+2]cycloaddition between the terminal olefin and the distal double bond of the allenyl moiety[12] furnished the cyclobutane derivative **17**. On the basis of these experiments, the possibility of the ene-type reaction for the conversion of **14** into **15** could be ruled out.[13]

We next investigated the scope of the ruthenium benzylidene catalyst **5**-mediated cycloisomerization using several substrates **18**.[14] These results are summarized in Table 2. The 3,4,9-decatriene derivative **18a**, which does not provide the Thorpe–Ingold type effects[15] due to loss of a bis(methoxycarbonyl) group, also produced the cyclohexene derivative **19a**[9] in a good yield (entry 1). Allenene **18b**, having an oxygen atom on the alkyl tether, produced the corresponding tetrahydropyran compound **19b** in a rather low yield compared to the



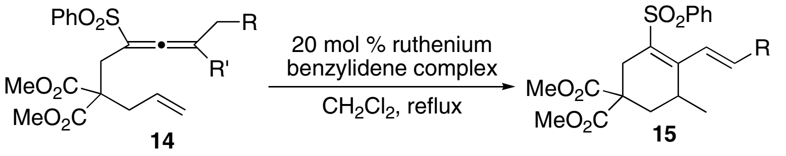
Scheme 2.



a: R=R'=H; **b**: R=Ph, R'=H; c: R=Me, R'=H; d: R=H, R'=Me; **e**: R+R'=-$(CH_2)_4$-

Scheme 3. Reagents and conditions: (a) LDA, THF, −78 °C, (40–76%); (b) PhSCl, Et_3N, THF, −78 °C; (c) *m*CPBA, CH_2Cl_2, 0 °C, (59–86%).

Table 1. Ruthenium benzylidene catalyst-mediated cycloisomerization of **14**

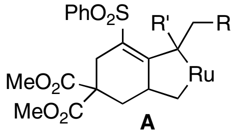


a: R=R'=H; **b**: R=Ph, R'=H; **c**: R=Me, R'=H; **d**: R=H, R'=Me; **e**: R+R'=-$(CH_2)_4$-

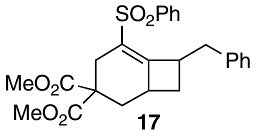
Entry	Allenene	Ru catalyst	R	R′	*t* (h)	Product (%)
1	**14a**	**5**[a]	H	H	10	**14a** (98)
2	**14a**	**5**	H	H	3.5	**15a** (41) + **14a** (54)
3	**14b**	**5**	Ph	H	0.5	**15b** (92)
4	**14c**	**5**	Me	H	0.5	**15c** (98)
5	**14d**	**5**	H	Me	2	**14d** (74)
6	**14e**	**5**	–$(CH_2)_4$–		5	**14e** (84)
7	**14c**	**4**	Me	H	4	**14c** (99)[b]
8	**14c**	**16**	Me	H	1	**15c** (21) + **14c** (59)

[a] Reaction was carried out in the presence of 5 mol % of **5**.

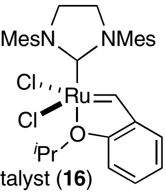
[b] Reaction was carried out in toluene at 40–80 °C.



A

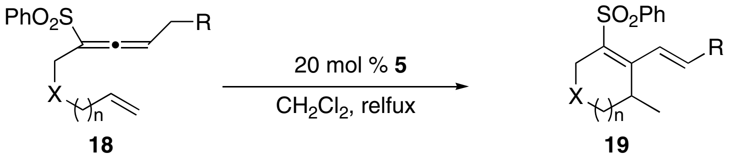


17



Hoveyda catalyst (**16**)

Table 2. Ruthenium benzylidene catalyst **5**-mediated cycloisomerization of **18**



a: n=1,R=Me, X=CH_2; **b**: n=1, R=Me, X=O; **c**: n=1, R=Me, X=NTs;
d: n=1, R=Ph, X=NTs; **e**: n=2, R=Me, X=$C(CO_2Me)_2$

Entry	Allenene	*n*	R	X	$Ti(OPr^i)_4$	Product (%)
1	**18a**	1	Me	CH_2	–	**19a** (77)
2	**18b**	1	Me	O	–	**19b** (33) + **18b** (50)
3	**18c**	1	Me	NTs	–	**19c** (50) + **18c** (11)
4	**18d**	1	Ph	NTs	–	**19d** (44) + **18d** (39)
5	**18b**	1	Me	O	+	**19b** (46) + **18b** (13)
6	**18c**	1	Me	NTs	+	**19c** (62) + **18c** (23)
7	**18d**	1	Ph	NTs	+	**19d** (62) + **18d** (34)
8	**18e**	2	Me	$C(CO_2Me)_2$	–	**18e** (82)[a]

[a] The desired **19e** could not be detected even at a higher reaction temperature (in toluene at 80 °C).

carbon analogue **14c** (entry 2). Similarly, the nitrogen congeners **18c** and **18d** underwent cycloisomerization to give the tetrahydropyridine derivatives **19c** and **19d** in moderate yields (entries 3 and 4). Improvement of the chemical yields for compounds **18b–d** were realized by the addition of 1 equiv of $Ti(OPr^i)_4$[16] as shown in entries 5–7, although the role of $Ti(OPr^i)_4$ is uncertain at this stage.[17] No consumption of the one-carbon homologated allenene **18e** was observed when exposed to the standard conditions for a prolonged time (entry 8). These results clarified that the newly developed second-generation Grubbs catalyst (**5**)-mediated cycloisomerization of allenenes cannot be used for the construction of seven-membered compounds.

In summary, we have described the novel ruthenium benzylidene catalyst-mediated cycloisomerization of allenenes having an alkyl appendage at the allenic terminus, leading to the formation of the cyclohexene derivatives. This method was shown to be applicable for the construction of heterocycles such as the tetrahydropyran and tetrahydropyridine derivatives. The determination of the scope and limitations of this method is now in progress.

Acknowledgements

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13. A mechanistic discussion is premature at this point, but we examined the following experiments to understand the reaction pathway. According to Arisawa and Nishda's procedure,[10a,d,e] trimethylsilyl vinyl ether was added to the reaction of **14b** with **5**, but no improvement on the chemical yield of **15b** could be attained. Furthermore, after consumption of the starting material in the reaction between **14b** and a catalytic amount of **5** (monitored by TLC), diethyl bis(allyl)malonate was added to the reaction mixture, which was then refluxed for one hour to give 4,4-bis(ethoxycarbonyl)cyclopent-1-ene (ring-closed metathesis product) together with **15b**. These results indicate that the actual active catalyst in the transformation of **14c** to **15c** might not be the newly generated species in situ, but **5** itself.
14. Allenenes **18** were prepared by conventional procedures.
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17. In order to confirm the effect of Ti(OPr^i)$_4$, the carbon analogues **14a** and **14b** were independently treated with **5** in the presence of Ti(OPr^i)$_4$ to afford **15a** and **15b**, respectively, in yields similar to those obtained in the absence of Ti(OPr^i)$_4$ (Table 1, entries 2 and 3).