Synthetic Methods

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Stereospecific and Stereoselective Rhodium(I)-Catalyzed Intramolecular [2+2+2] Cycloaddition of Allene-Ene-Ynes: Construction of Bicyclo[4.1.0]heptenes**

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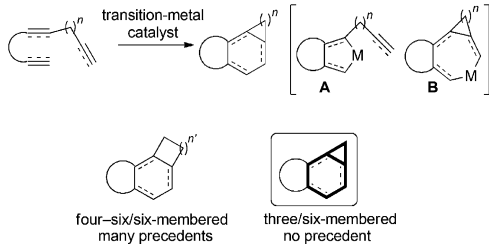
Abstract: *Treatment of the allene-ene-yne substrates with [{RhCl(CO)$_2$}$_2$] effected the intramolecular [2+2+2]-type ring-closing reaction to produce various of tri- and tetracyclic derivatives containing a cyclopropane ring. The reaction is highly stereoselective as well as stereospecific with good to excellent yields.*

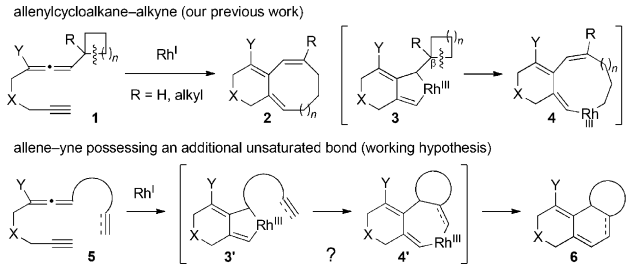
The transition-metal-catalyzed [2+2+2] cycloaddition reactions of unsaturated compounds provide a powerful step- and atom-economical methodology for the construction of various carbo- or heterocyclic six-membered rings.[1] Intramolecular variants straightforwardly enable the chemo- and regioselective construction of complex polycyclic skeletons from simple acyclic compounds. A number of transition-metal-catalyzed intramolecular [2+2+2] cycloadditions of the three C–C π bonds produce tricyclic skeletons (Scheme 1).[1] The



Scheme 1. Transition-metal-catalyzed intramolecular [2+2+2] cycloaddition: construction of various-sized tricyclic skeletons.

reaction is generally thought to proceed by 1) the formation of the metallabicyclic intermediate **A**, 2) the insertion of the remaining π bond into the C–metal bond of **A** to form the intermediate **B**, and 3) reductive elimination of the metal from **B**. There have been many examples regarding the intramolecular [2+2+2] cycloaddition of substrates ($n=3,4$) which affords the tricyclic compounds containing six/six-membered ($n=4$) or five/six-membered ($n=3$) frameworks.[1] The construction of four/six-membered frameworks ($n=2$) based on the intramolecular [2+2+2] cycloaddition have also been recorded by several groups.[1,2] However, there are no precedent available for the direct construction of three/six-membered frameworks ($n=1$) by the intramolecular [2+2+2] cycloaddition.[3] Thus, the direct construction of the highly strained three-membered ring seems to be hard because of the geometric requirement for the insertion step of the remaining π bond into the carbon–metal bond of **A** ($n=1$).[4] In contrast, the bicyclo[4.1.0]heptane ring system (three/six-membered framework) is found as a core structure in various natural products and biologically active compounds.[5]

We recently disclosed that the rhodium(I)-catalyzed intramolecular cycloaddition of the allenylcycloalkane-alkynes **1** ($n=1,2$) efficiently afforded the corresponding bicyclic compounds **2** ($n=1,2$; Scheme 2).[6,7] We presumed



Scheme 2. Rhodium(I)-catalyzed intramolecular cyclization of allene-ynes.

that these reactions would proceed by the initial formation of the rhodabicyclo[4.3.0] intermediate **3**,[6,8] followed by the β-carbon elimination to form the intermediate **4**,[9] which must collapse to the final products through reductive elimination. The plausible key intermediate **3** could accelerate the cleavage of the unfunctionalized C–C bond of cyclobutane ($n=1$) by relief of the high ring-strain energy (26.3 kcal mol^{-1}).[6a,10] This method was applied to the ring-opening of the normal-sized cyclopentane ($n=2$, ring-strain energy: 6.3 kcal mol^{-1}).[6b,10] We envisaged that the allene-alkyne derivatives **5**, possessing an additional π component instead of cycloalkane, would react with the rhodium(I) catalyst,[11] and in analogy to the conversion of **1** into **3**, form the intermediate **3′**. The insertion of the remaining π component to the C–Rh bond of the formed **3′** would produce the tricyclic rhodacycle **4′** if the β-hydride elimination from **3′** could be avoided. The resulting **4′** would then be transformed into the tricyclic product **6**.

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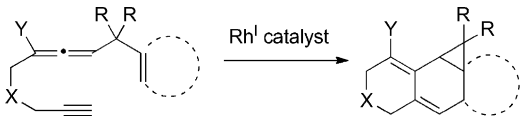
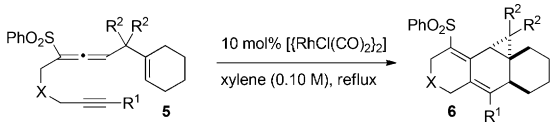
There are two examples dealing with the intramolecular [2+2+2] cycloaddition of allene derivatives. One is the report from Sato and Saito on the ruthenium-catalyzed intramolecular [2+2+2] cycloaddition of allene-ene-ynes,[12] thus resulting in the construction of the fused tricyclic skeletons in a highly stereoselective manner. The other is the rhodium(I)-catalyzed intramolecular [2+2+2] cycloaddition of bis-(allene)-ynes by Solà, Pla-Quintana, and co-workers.[13] We now describe the preliminary results of the rhodium(I)-catalyzed intramolecular [2+2+2] cycloaddition of allene-ene-ynes,[14–17] a reaction allows the preparation of the tri- and tetracyclic derivatives containing bicyclo[4.1.0]heptene skeletons (Scheme 3).



Scheme 3. This study: rhodium(I)-catalyzed intramolecular [2+2+2] cycloaddition of allene-ene-ynes.

Our initial study employed the phenylsulfonylallene-alkyne **5a**, having cyclohexenyl and dimethyl groups at the allenic terminus (Table 1, entry 1), the latter of which was introduced to avoid the unfavorable β-hydride elimination of the possible rhodacycle intermediate (e.g., **3′**; Scheme 2). After careful screening, we found that the use of $[\{RhCl(CO)_2\}_2]$ in refluxing xylene was suitable for our purpose to provide the expected tetracyclic derivative **6a** (72% yield; Table 1, entry 1).[18] The optimized reaction conditions were then applied to several other allene-internal alkyne species **5**. The ethynyl derivative **5b** gave the tetracyclic product **6b** in 89% yield (entry 2).[19] The reaction

Table 1: $[\{RhCl(CO)_2\}_2]$-catalyzed [2+2+2] cycloaddition of allene-ene-ynes **5**.

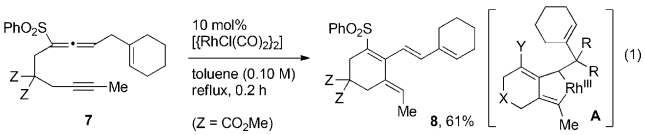


Entry	5	R^1	R^2	X	t [h]	Yield [%][a]
1	**5a**	H	Me	$C(CO_2Me)_2$	0.2	**6a**: 72
2	**5b**	Me	Me	$C(CO_2Me)_2$	0.3	**6b**: 89
3[b,c]	**5c**	*n*Bu	Me	$C(CO_2Me)_2$	1	**6c**: 99
4[b,c]	**5d**	CO_2Me	Me	$C(CO_2Me)_2$	1	**6d**: 99
5	**5e**	TMS	Me	$C(CO_2Me)_2$	0.3	**6e**: 78
6	**5f**	CH_2OH	Me	$C(CO_2Me)_2$	0.3	**6f**: 97
7	**5g**	Me	Me	$C(SO_2Ph)_2$	0.2	**6g**: 97
8[b]	**5h**	*n*Bu	Me	$C(CH_2O)_2CMe_2$	0.1	**6h**: 93
9[b]	**5i**	*n*Bu	Me	$C(CH_2OH)_2$	0.1	**6i**: 99
10	**5j**	*n*Bu	Me	NTs	0.5	**6j**: 77
11	**5k**	*n*Bu	Me	O	0.5	**6k**: 87
12	**5l**	Me	-$(CH_2)_5$- (R^2,R^2)	$C(CO_2Me)_2$	0.5	**6l**: 89

[a] Yield of the isolated product. [b] Toluene was used as solvent. [c] Reaction was performed at 80°C. TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

of a longer tethered 2-heptynyl analogue (**5c**) smoothly proceeded at a lower temperature (in toluene at 80°C) to afford the cycloadduct **6c** in 99% yield (entry 3). It was shown that the electron-withdrawing group did not interrupt this [2+2+2] cycloaddition. Indeed, the substrate **5d** furnished the cyclized product **6d** in 99% yield (entry 4), and both the TMS (**5e**) and hydroxymethyl (**5f**) groups at the alkyne terminus provided the corresponding cycloadducts **6e** (78% yield) and **6f** (97% yield; entries 5 and 6). The other three substrates **5g**, **5h**, and **5i** with *gem*-disubstitution[20] were exposed to the standard reaction conditions to furnish **6g** in 97% yield (entry 7), **6h** in 93% yield (entry 8), and **6i**[21] in 99% yield (entry 9). The nitrogen (**5j**) and oxygen (**5k**) congeners produced the corresponding aza-compound **6j** (77% yield) and oxa-compound **6k** (87% yield; entries 10 and 11). The substrate **5l** with a cyclohexyl group instead of a dimethyl group at the allenic position was successfully be converted into the pentacyclic adduct **6l** in 89% yield (entry 12).

As predicted on the basis of the mechanistic hypothesis described in Scheme 2, the unsubstituted simple cyclohexenylmethyl substrate **7** did not yield the desired tetracyclic product at all, but the tetraene compound **8** was obtained in 61% yield as a single *E* isomer [Eq. (1)]. This result

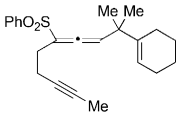
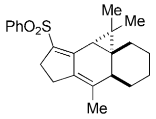
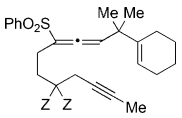
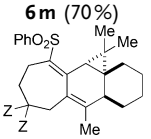
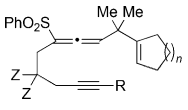
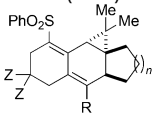


supported our hypothesis which includes the initial formation of **A** (R = H), which would be susceptible to β-hydride elimination,[11a,22] but **A** (R = Me) derived from substrate **5b** no longer has a β-hydrogen atom and undergoes the [2+2+2] ring-closing pathway. Thus, it became clear that the geminal disubstituent moiety at the allenic position of the substrates **5** is essential for this novel [2+2+2] cycloaddition.[23]

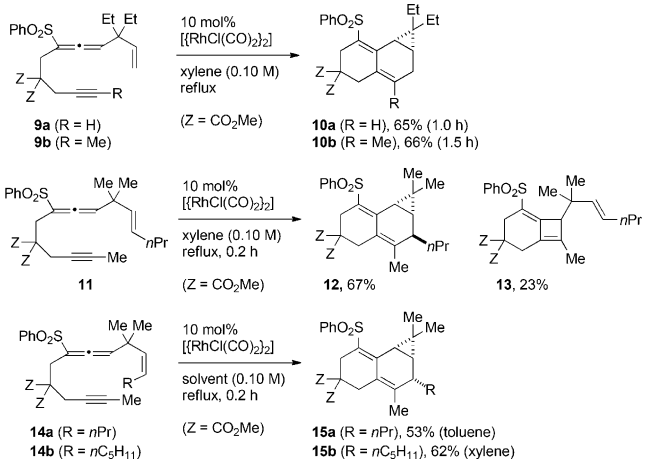
The substrate scope of this newly developed reaction was evaluated (Table 2). Treatment of the one-carbon-shortened substrate **5m** with $[\{RhCl(CO)_2\}_2]$ effected the formation of the five/six-membered framework to produce **6m** in 70% yield (entry 1). In contrast, the larger-sized tetracyclic product **6n**, containing a seven-membered ring, was obtained in 85% yield (entry 2). The substrates possessing a cyclopentenyl (**5o**) or cycloheptenyl (**5p**) ring instead of a cyclohexenyl group as alkene counterparts also underwent the cycloaddition to furnish the corresponding cycloadducts **6o** (80%) and **6p** (99%; entries 3 and 4).

We next examined the reactions of the substrates with acyclic alkenes (Scheme 4). Treatment of the substrates **9a** and **9b**, possessing simple vinyl groups as the alkene component, with $[\{RhCl(CO)_2\}_2]$ afforded the tricyclic compounds **10a** (65% yield) and **10b** (66% yield), respectively. Both the *E*- and *Z*-alkene derivatives were independently subjected to the ring-closing reaction conditions to determine whether the reactions occurred in a stereospecific manner and/or a stereoselective manner. Treatment of the *E*-alkene derivative **11** with $[\{RhCl(CO)_2\}_2]$ under the standard reaction

Table 2: [{RhCl(CO)$_2$}$_2$]-catalyzed [2+2+2] cycloaddition of other allene-ene-yne substrates **5**.[a,b]

Entry	5	t [h]	6 (yield[c])
			
1	**5m**	0.2	**6m** (70%)
			
2	**5n**	0.3	**6n** (85%)
			
3[d]	**5o**: $n=1$, R = H	0.3	**6o**: $n=1$, R = H (80%)
4[e]	**5p**: $n=3$, R = Me	0.5	**6p**: $n=3$, R = Me (99%)

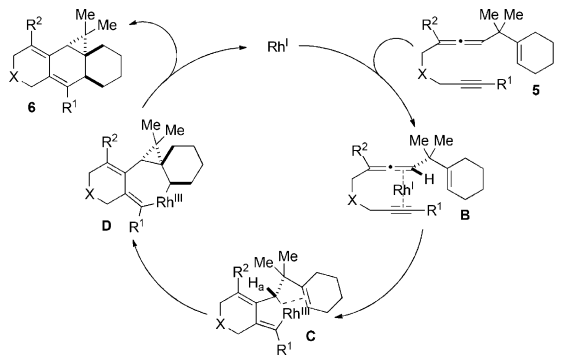
[a] Reaction conditions: 0.10 M solution of allene-ene-yne was treated with 10 mol% of [RhCl(CO)$_2$]$_2$ in refluxing toluene under nitrogen atmosphere. [b] Z = CO$_2$Me. [c] Yield of the isolated product. [d] Reaction was performed in refluxing xylene. [e] Reaction was performed at 80 °C.



Scheme 4. [{RhCl(CO)$_2$}$_2$}]-catalyzed [2+2+2] cycloaddition of acyclic alkene substrates **9**, **11**, and **14**.

conditions gave the [2+2+2] cycloadduct **12** with *trans* stereochemistry between the *n*-propyl residue and the cyclopropyl ring in 67% yield as a single diastereomer. The cyclobutene derivative **13** (23% yield) was obtained as a by-product. The formation of **13** was tentatively interpreted by the reductive elimination of the rhodium catalyst from the rhodabicyclo-[4.3.0] intermediate **3′** (Scheme 2).[24] In contrast, the (*Z*)-alkene derivative **14a** gave **15a**, which is a *cis*-isomer of **12**, in 53% yield as a single diastereomer.[25] Another *Z*-alkene derivative, **14b**, also afforded the corresponding *cis*-adduct **15b** in 62% yield.[26] Thus, it can be concluded that this intramolecular [2+2+2] cycloaddition is highly stereoselective as well as stereospecific.

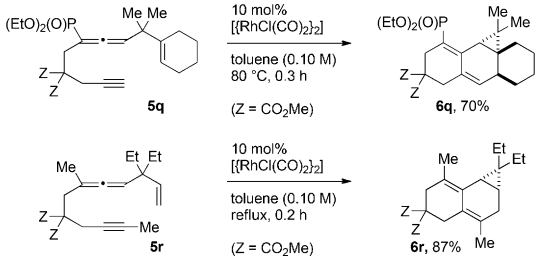
A plausible mechanism for this highly stereoselective and stereospecific [2+2+2] cycloaddition is proposed as shown for



Scheme 5. Plausible mechanism.

the conversion of **5** into **6** (Scheme 5). The initial coordination of **5** with rhodium(I) would occur between an allenic distal double bond and an alkyne to form the intermediate **B**, which should immediately collapse to the bicyclic rhodacyclopentene intermediate **C** by an oxidative ring-closing reaction. The insertion of the tethered alkene into the C(sp^3)–Rh^{III} bond would stereoselectively occur from the opposite face to the C–H$_a$ bond, thus resulting in the intermediate **D**. The reductive elimination of rhodium(III) from **D** would then give the product **6**.[27]

It should be mentioned that a phenylsulfonyl substituent on the allenyl moiety was not mandatory for this transformation (Scheme 6). In fact, upon exposure to the standard



Scheme 6. [{RhCl(CO)$_2$}$_2$]-catalyzed [2+2+2] cycloaddition of **5q** and **5r**.

reaction conditions, the [2+2+2] cycloaddition of the phosphonate derivative **5q** easily occurred to give **6q** in 70% yield. Furthermore, the ring-closing reaction of the methyl-substituted allene **5r** proceeded without any problems to provide the desired product **6r** in 87% yield. A phenylsulfonyl group on the allenyl moiety can be regarded as a surrogate of hydrogen atom and can be easily converted into a hydrogen atom by conventional means.[28,29]

In summary, we developed a novel rhodium(I)-catalyzed intramolecular [2+2+2] cycloaddition of allene-ene-ynes to produce either tri- or tetracyclic products, containing a cyclopropane ring as the core carbon skeleton with three contiguous stereogenic centers, in a stereoselective and stereospecific manner. To the best of our knowledge, this is the first example dealing with the construction of the bicyclo-[4.1.0]heptane derivatives by taking advantage of the [2+2+2] cycloaddition, which enables easy access to a variety

of the polycyclic skeletons from simple acyclic substrates. The scope and limitations of this method as well as application to the synthesis of natural products are now in progress.

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[14] The rhodium(I)-catalyzed intramolecular [2+2+2] cycloaddition of allene-yne-aldehydes was reported. See: Y. Oonishi, Y. Kato, Y. Sato, *Tetrahedron* **2013**, *69*, 7713 – 7718.

[15] For intramolecular [2+2+2] cycloaddition of allene-diynes with a stoichiometric amount of a cobalt complex, see: a) M. Petit, C. Aubert, M. Malacria, *Tetrahedron* **2006**, *62*, 10582 – 10593; for rhodium(I)-catalyzed reaction of allene-diynes, see: b) B. Bennacer, M. Fujiwara, S.-Y. Lee, I. Ojima, *J. Am. Chem. Soc.* **2005**, *127*, 17756 – 17767.

[16] For transition-metal-catalyzed intermolecular [2+2+2] cycloaddition of allene compounds, see: a) J.-C. Hsieh, D. K. Rayabarapu, C.-H. Cheng, *Chem. Commun.* **2004**, 532 – 533; b) T. Miura, M. Morimoto, M. Murakami, *J. Am. Chem. Soc.* **2010**, *132*, 15836 – 15838.

[17] For transition-metal-catalyzed partially intramolecular [2+2+2] cycloaddition of allene compounds, see: a) M. Shanmugasundaram, M.-S. Wu, M. Jeganmohan, C.-W. Huang, C.-H. Cheng, *J. Org. Chem.* **2002**, *67*, 7724 – 7729; b) P. Liu, S. Ma, *Org. Lett.* **2007**, *9*, 5319 – 5321; c) A. T. Brusoe, E. J. Alexanian, *Angew. Chem. Int. Ed.* **2011**, *50*, 6596 – 6600; *Angew. Chem.* **2011**, *123*, 6726 – 6730; d) N. N. Noucti, E. J. Alexanian, *Angew. Chem. Int. Ed.* **2013**, *52*, 8424 – 8427; *Angew. Chem.* **2013**, *125*, 8582 – 8585.

[18] The optimization of reaction conditions is summarized in Table S1 in the Supporting Information.

[19] We presumed that the somewhat lower yield of **6a** (72%), compared to that of **6b** (89%), might be due to the side reaction via the vinylidene-rhodium species generated from the terminal alkyne and the rhodium(I) complex. For selected examples of cyclization reactions via vinylidene rhodium intermediates, see: a) Y. Fukumoto, F. Kinashi, T. Kawahara, N. Chatani, *Org. Lett.* **2006**, *8*, 4641 – 4643; b) J. M. Joo, Y. Yuan, C. Lee, *J. Am. Chem. Soc.* **2006**, *128*, 14818 – 14819; and Ref. [11e].

[20] M. E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735 – 1766.

[21] X-ray analysis of the derivative of **6i** unambiguously established its structure having a tetracyclic structure containing the bicyclo[4.1.0]heptene skeleton (see the Supporting Information for details).

[22] a) C. Mukai, F. Inagaki, T. Yoshida, K. Yoshitani, Y. Hara, S. Kitagaki, *J. Org. Chem.* **2005**, *70*, 7159 – 7171; b) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* **2011**, *111*, 1954 – 1993.

[23] It was reported that $[Rh(dppp)]SbF_6$ was effective for avoiding undesired β-hydride eliminations in some rhodium(I)-catalyzed

cyclizations. For example, see: a) L. Jiao, M. Lin, Z.-X. Yu, *Chem. Commun.* **2010**, *46*, 1059 – 1061; b) L. Jiao, M. Lin, Z.-X. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 447 – 461; We carried out the reaction of **7** with 5 mol% of [Rh(dppp)]SbF_6, which resulted in the exclusive formation of **8** (94% yield).

[24] For transition-metal-catalyzed intramolecular [2+2] cycloaddition of allene-ynes, see: a) C. H. Oh, A. K. Gupta, D. I. Park, N. Kim, *Chem. Commun.* **2005**, 5670 – 5672; b) N. Saito, Y. Tanaka, Y. Sato, *Org. Lett.* **2009**, *11*, 4124 – 4126.

[25] The relative configurations of **12** and **15** were determined based on the NOE experiments (see the Supporting Information for details).

[26] In the cases of **14a** and **14b**, the cyclobutene derivatives with *Z*-alkene moiety were not obtained at all. However, negligible amounts of the cyclobutene derivatives with the *E*-alkene moiety (**13** and the *n*-pentyl analogue of **13**) were detected.

[27] The optical resolution of (±)-**5c** by HPLC provided (+)-**5c** (99% *ee*) and (−)-**5c** (99% *ee*), both of which were independently reacted under standard reaction conditions to produce (−)-**6c** (99% *ee*) and (+)-**6c** (99% *ee*), respectively, in quantitative yields. The absolute configurations of these four compounds have not yet been determined, but these two experiments unambiguously provided additional evidence that this ring-closing reaction must proceed in a stereospecific fashion.

[28] For reviews of the transformation of sulfones, see: a) C. Nájera, M. Yus, *Tetrahedron* **1999**, *55*, 10547 – 10658; b) N. S. Simpkins, *Sulfones in Organic Synthesis*, Pergamon, Oxford, **1993**.

[29] During our studies on the rhodium(I)-catalyzed ring-closing reaction, we have successfully shown that the phenylsulfonyl group on the allenyl moiety could be easily removed by conventional procedures. For example, see: a) F. Inagaki, S. Narita, T. Hasegawa, S. Kitagaki, C. Mukai, *Angew. Chem. Int. Ed.* **2009**, *48*, 2007 – 2011; *Angew. Chem.* **2009**, *121*, 2041 – 2045; b) T. Iwata, F. Inagaki, C. Mukai, *Angew. Chem. Int. Ed.* **2013**, *52*, 11138 – 11142; *Angew. Chem.* **2013**, *125*, 11344 – 11348.

