

# Rh-Catalyzed Triple Allene Approach to Bicyclo[4.4.0]decene Derivatives and Its Application for the Stepwise Synthesis of Steroid-Like Tetracyclic Skeletons

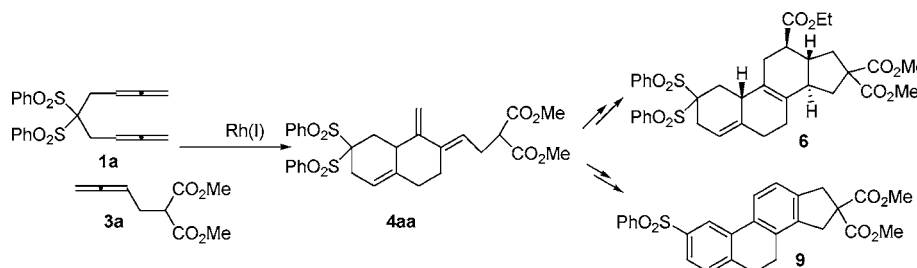
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## ABSTRACT



The construction of a new type of bicyclo[4.4.0]decene products with a conjugated exocyclic diene unit was developed using Rh-catalyzed cyclization of 1,5-bisallenes in the presence of monoallenes. The steroid-like tetracyclic products could be obtained by applying an alkylation–Diels–Alder process.

Transition-metal-catalyzed cyclization reactions have shown their power for the synthesis of complex organic skeletons in an often highly selective fashion from simple and readily available starting materials.<sup>1</sup> Nowadays, allenes have attracted extensive attention in these reactions due to their specific synthetic versatility.<sup>2,3</sup> Recently, we reported the bimolecular cyclometalation of bisallenes for one-step synthesis of steroid-like tetracyclic skeletons (eq 1).<sup>4</sup> Our continuing study showed that the bimolecular cyclization reaction of two different bisallenes provided a mixture of four products

leading to the isolation of two “cross” 18,19-norsteroid-like scaffolds formed from two different bisallenes after chromatographic separation.<sup>5</sup> Herein, we wish to report a Rh-catalyzed cyclization of 1,5-bisallenes in the presence of monoallenes for the efficient synthesis of fused 6,6-bicyclic

(1) (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, 96, 635. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, 102, 813. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, 104, 2127. (d) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, 100, 2901.

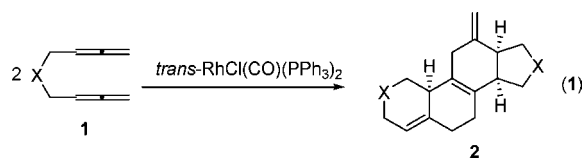
(2) For reviews, see: (a) Mandai, T. *Transition Metal-catalyzed Addition/Cycloaddition of Allenes*. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1 and 2 and references therein. (b) Ma, S. *Chem. Rev.* **2005**, 105, 2829 and references therein. (c) Wender, P. A.; Baryza, J. L.; Brenner, S. E.; Clarke, M. O.; Gamber, G. G.; Horan, J. C.; Jessop, T. C.; Kan, C.; Pattabiraman, K.; Williams, T. J. *Pure Appl. Chem.* **2003**, 75, 143. (d) Trost, B. M. *Acc. Chem. Res.* **2002**, 35, 695.

(3) For recent examples for cycloisomerizations of allenynes, see: (a) Brummond, K. M.; Painter, T. O.; Probst, D. A.; Mitasev, B. *Org. Lett.* **2007**, 9, 347. (b) Brummond, K. M.; McCabe, J. M. *Tetrahedron* **2006**, 62, 10541. (c) Lemièrre, G.; Gandon, V.; Agenet, N.; Goddard, J.; Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, 45, 7596. For recent examples for cycloisomerizations of allenenes, see: (d) Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, 69, 395. (e) Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, 6, 2161. For other examples for cyclometalations of allenes, see: (f) Wender, P. A.; Deschamps, N. M.; Sun, R. *Angew. Chem., Int. Ed.* **2006**, 45, 3957. (g) Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *Angew. Chem., Int. Ed.* **2006**, 45, 2459. (h) Barluenga, J.; Vicente, R.; Lopez, L. A.; Tomas, M. *J. Am. Chem. Soc.* **2006**, 128, 7050. (i) Trost, B. M.; Pinkerton, A. B.; Seidel, M. *J. Am. Chem. Soc.* **2001**, 123, 12466. (j) Chang, H.-T.; Jayanth, T. T.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, 129, 4166.

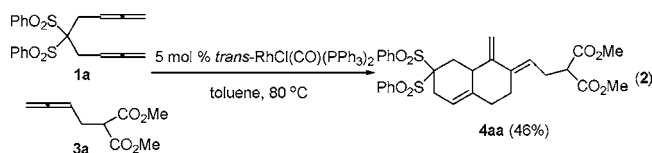
(4) Ma, S.; Lu, P.; Lu, L.; Hou, H.; Wei, J.; He, Q.; Gu, Z.; Jiang, X.; Jin, X. *Angew. Chem., Int. Ed.* **2005**, 44, 5275.

(5) Ma, S.; Lu, L. *Chem. Asian J.* **2007**, 2, 199.

products. In addition, with a sequential alkylation and cyclic Diels–Alder reaction, the steroid-like skeletons may be constructed in a stepwise manner diastereoselectively.

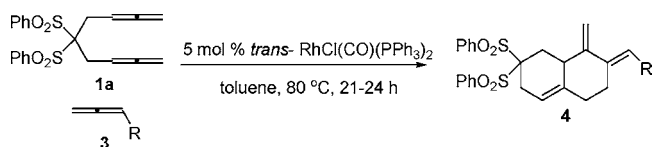


We initiated our study with *trans*-RhCl(CO)(PPh<sub>3</sub>)<sub>2</sub>-catalyzed cyclization between 1,5-bisallene **1a** and monoallene **3a** in toluene. Fortunately, after careful screening of the reaction conditions, the fused 6,6-bicyclic product **4aa** with two exocyclic carbon–carbon double bonds was isolated in 46% yield when the solution of bisallene **1a** in toluene was added via a syringe pump into the solution of rhodium catalyst and 2.5 equiv of monoallene **3a** in toluene at 80 °C (condition A) (eq 2).



Encouraged by the above result, we studied the scope of this cycloaddition reaction with different monoallenes **3** (Table 1). The reaction of **1a** and the freshly prepared

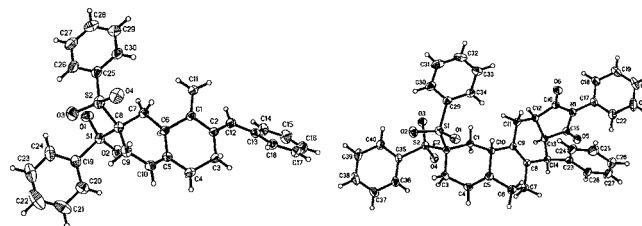
**Table 1.** Substrate Scope of Rh-Catalyzed Cyclization of Bisallene **1a** in the Presence of Monoallenes<sup>a</sup>



entry	R	conditions/ time (h)	yield of <b>4</b> (%)
1	Ph ( <b>3b</b> )	B <sup>b</sup> /22	55 ( <b>4ab</b> ) <sup>c</sup>
2	CH <sub>2</sub> NTsBoc ( <b>3c</b> )	A <sup>d</sup> /21	55 ( <b>4ac</b> ) <sup>c</sup>
3	CH <sub>2</sub> CH <sub>2</sub> NTsBoc ( <b>3d</b> )	A/24	50 ( <b>4ad</b> ) <sup>c</sup>
4	CH <sub>2</sub> CH <sub>2</sub> OH ( <b>3e</b> )	A/22	54 ( <b>4ae</b> ) <sup>c</sup>
5	CH <sub>2</sub> NX ( <b>3f</b> ) <sup>f</sup>	A/24	56 ( <b>4af</b> ) <sup>c</sup>
6	CH <sub>2</sub> CH <sub>2</sub> NX ( <b>3g</b> ) <sup>f</sup>	A/24	50 ( <b>4ag</b> ) <sup>c</sup>

<sup>a</sup> The reaction was carried out using **1a** (0.25 mmol), **3** (0.625 mmol), and 5 mol % of *trans*-RhCl(CO)(PPh<sub>3</sub>)<sub>2</sub> in toluene (12 mL) at 80 °C. <sup>b</sup> Conditions B: a solution of **1a** and **3** in toluene (10 mL) was added to a solution of *trans*-RhCl(CO)(PPh<sub>3</sub>)<sub>2</sub> in toluene (2 mL) via a syringe pump over ~10 h at 80 °C. <sup>c</sup> The byproduct **2a** was contaminated with other uncharacterized mixtures. <sup>d</sup> Conditions A: a solution of **1a** was added to a solution of *trans*-RhCl(CO)(PPh<sub>3</sub>)<sub>2</sub> and **3** in toluene (2 mL) via a syringe pump over ~10 h at 80 °C. <sup>e</sup> The yield of byproduct **2a** was less than 18%. <sup>f</sup> NX = phthalimide.

phenylallene **3b** efficiently afforded the cyclization product **4ab** in 55% yield under condition B (entry 1). The structure of **4ab** was unambiguously confirmed by X-ray diffraction

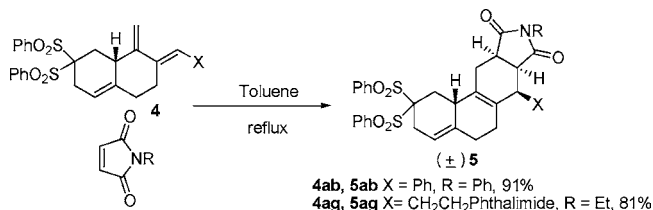


**Figure 1.** ORTEP representations of **4ab** (left) and **5ab** (right).

study (Figure 1, left).<sup>6</sup> The reaction of **1a** and *N*-Boc-protected buta-2,3-dienyl tosylamide **3c** provided the 2,4-dienylamide **4ac** in 55% yield (entry 2). Similarly, *N*-Boc-protected penta-3,4-dienyl tosylamide **3d** could also be used to afford **4ad** in 50% yield (entry 3). Interestingly, the reaction of the unprotected penta-3,4-dien-1-ol **3e** with **1a** afforded the alcohol **4ae** in good yield (entry 4). The reaction of buta-2,3-dienyl phthalimide **3f** or penta-3,4-dienyl phthalimide **3g** with **1a** both afforded corresponding products **4af** or **4ag** in moderate yields, respectively (entries 5 and 6).

Treatment of **4ab** with *N*-phenyl maleimide afforded the Diels–Alder product **5ab** in the yield of 91% (Scheme 1).

**Scheme 1**



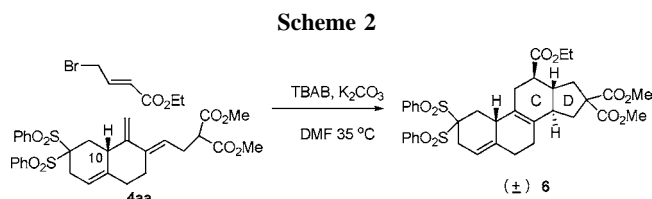
The diastereoisomeric ratio should be higher than 6.3:1. The structure of tetracyclic product **5ab** was unambiguously confirmed by X-ray diffraction study (Figure 1, right).<sup>7</sup> Treatment of **4ag** and *N*-ethyl maleimide also afforded the tetracyclic product **5ag** in the yield of 81%. The diastereoisomeric ratio is ≥93.5:6.5.

Encouraged by this highly selective intermolecular Diels–Alder reaction, the intramolecular reaction of the 1,3-diene unit in **4aa** with an activated alkene, e.g., α,β-unsaturated

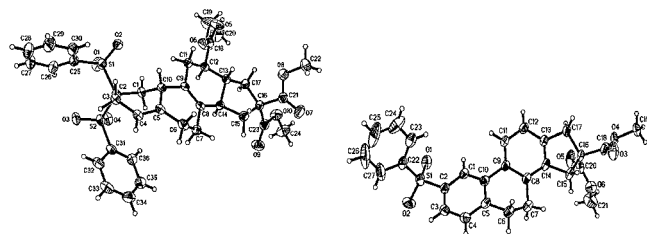
(6) Crystal data for **4ab**: C<sub>30</sub>H<sub>28</sub>O<sub>4</sub>S<sub>2</sub>, MW = 516.64, monoclinic, *P*2(1)/c. *a* = 13.4994(15) Å, *b* = 21.855(2) Å, *c* = 8.6424(10) Å, *V* = 2548.7(5) Å<sup>3</sup>, *T* = 293(2) K, *Z* = 4. *R* indices (all data), *R*<sub>1</sub> = 0.0844, *wR*<sub>2</sub> = 0.1379. Final *R* indices [*I* > 2σ(*I*)], *R*<sub>1</sub> = 0.0557, *wR*<sub>2</sub> = 0.1269. Reflections collected/unique: 14929/5553 (*R*<sub>int</sub> = 0.1088), number of observations [*I* > 2σ(*I*)] 3583; parameters, 329. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center, CCDC 651338.

(7) Crystal data for **5ab**: C<sub>40</sub>H<sub>35</sub>NO<sub>6</sub>S<sub>2</sub>, MW = 689.81, monoclinic, *P*2(1)/c. *a* = 16.4936(14) Å, *b* = 9.1500(8) Å, *c* = 23.709(2) Å, *V* = 3371.1(5) Å<sup>3</sup>, *T* = 293(2) K, *Z* = 4. *R* indices (all data), *R*<sub>1</sub> = 0.0754, *wR*<sub>2</sub> = 0.1276. Final *R* indices [*I* > 2σ(*I*)], *R*<sub>1</sub> = 0.0529, *wR*<sub>2</sub> = 0.1190. Reflections collected/unique: 17938/6631 (*R*<sub>int</sub> = 0.0940), number of observations [*I* > 2σ(*I*)] 4701; parameters, 442. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center, CCDC 651339.

enoate, was also studied. It was a surprise for us to observe that when product **4aa** was treated with ethyl 4-bromocrotonate,  $K_2CO_3$ , and TBAB in DMF at 35 °C, the cyclic Diels–Alder reaction followed the allylation reaction immediately to afford the steroid-like tetracyclic product **6** in the yield of 85% (Scheme 2).<sup>8</sup> The diastereoisomeric ratio



is  $\geq 10:1$ . The structure of the major diastereoisomer, obtained easily by recrystallization from  $CH_2Cl_2$  and petroleum ether, was unambiguously confirmed by X-ray diffraction study of **6** (Figure 2, left).<sup>9</sup> The C/D ring junction here



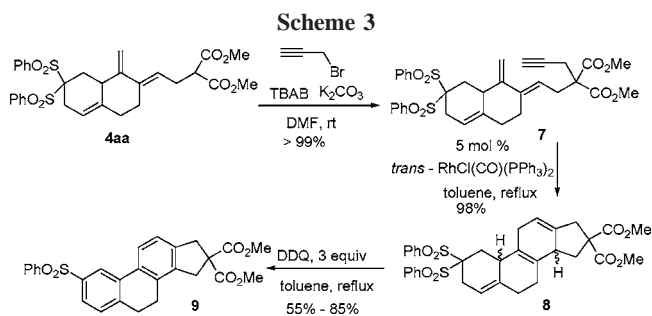
**Figure 2.** ORTEP representations of **6** (left) and **9** (right).

is *trans*, which is opposite to what was observed in our previous report.<sup>4</sup>

Furthermore, the intramolecular Diels–Alder reaction of the 1,3-diene unit in **4aa** and a terminal alkyne was also explored (Scheme 3). However, the reaction of **4aa**, the propargyl bromide,  $K_2CO_3$ , and TBAB in DMF afforded the alkylation product **7** in almost quantitative yield without further Diels–Alder reaction. Treatment of **7** with 5 mol %

(8) Crystal data for **6**:  $C_{36.5}H_{41}ClO_{10}S_2$ , MW = 739.26, triclinic,  $P-1$ ,  $a = 14.74(1)$  Å,  $b = 16.01(1)$  Å,  $c = 16.60(1)$  Å,  $V = 3550(5)$  Å<sup>3</sup>,  $T = 293(2)$  K,  $Z = 4$ . R indices (all data),  $R1 = 0.1107$ ,  $wR2 = 0.2031$ . Final R indices [ $I > 2\sigma(I)$ ],  $R1 = 0.0688$ ,  $wR2 = 0.1791$ . Reflections collected/unique: 18526/12890 ( $R_{int} = 0.0813$ ), number of observations [ $> 2\sigma(I)$ ] 7256; parameters, 898. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center, CCDC 651340.

(9) For recent examples for synthesis of steroid from an intramolecular Diels–Alder procedure, see: (a) Bear, B. R.; Parnes, J. S.; Shea, K. J. *Org. Lett.* **2003**, 5, 1613. (b) Nörret, M.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2001**, 40, 4074.



of *trans*- $RhCl(CO)(PPh_3)_2$  provided the Diels–Alder product **8** as a mixture of diastereoisomeric products. Aromatization of **8** with DDQ in toluene under reflux afforded the tetracyclic product **9** with two aromatic six-membered rings in 55–85% yield,<sup>10</sup> indicating a desulfonation reaction took place together with the dehydrogenation reaction.<sup>11</sup> The structure of aromatic product **9** was unambiguously confirmed by X-ray diffraction study (Figure 2, right).<sup>12</sup>

In conclusion, we have developed a Rh-catalyzed cyclization of a 1,5-bisallene in the presence of a monoallene affording a new type of fused 6,6-bicyclic products with a conjugated exocyclic diene unit, which may be applied as precursors for synthesis of tetracyclic skeletons with high diastereoselectivity efficiently via the alkylation and the subsequent cyclic Diels–Alder reaction. Further study in this area is being pursued in our laboratory.

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**Supporting Information Available:** Experimental procedures and characterization data of all new products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) The ring C in compound **8** may be somewhat aromatized in the solvent if exposed to air.

(11) (a) Adeva, M.; Sahagun, H.; Caballero, E.; Pelaez-Lamamie de Clairac, R.; Medarde, M.; Tome, F. *J. Org. Chem.* **2000**, 65, 3387. (b) Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, 103, 2108.

(12) Crystal data for **9**:  $C_{27}H_{24}O_6S$ , MW = 476.52, monoclinic,  $P2(1)/c$ ,  $a = 9.3539(11)$  Å,  $b = 8.0181(9)$  Å,  $c = 31.277(4)$  Å,  $V = 2326.9(5)$  Å<sup>3</sup>,  $T = 293(2)$  K,  $Z = 4$ . R indices (all data),  $R1 = 0.1305$ ,  $wR2 = 0.1621$ . Final R indices [ $I > 2\sigma(I)$ ],  $R1 = 0.0578$ ,  $wR2 = 0.1198$ . Reflections collected/unique: 13686/9561 ( $R_{int} = 0.0973$ ), number of observations [ $> 2\sigma(I)$ ] 4103; parameters, 618. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center, CCDC 651337.