Cycloaddition

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Rhenium-Catalyzed Synthesis of Stereodefined Cyclopentenes from β-Ketoesters and Aliphatic Allenes**

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Approaches to construct complex organic molecules, such as carbocyclic compounds, from simple starting materials as building blocks are of great interest. Five-membered carbocycles are especially important, and remarkable progress has been made in their syntheses.[1] Among them, [3+2] cycloaddition reactions have been studied intensively because the five-membered carbocycles can be derived from simpler molecules.[2] The synthesis of five-membered carbocycles starting from allenes have also been reported; for example (trimethylsilyl)cyclopentene annulation mediated by titanium complexes, gold-catalyzed [3+2] cycloaddition of enones/enals with allenyl methoxymethyl ethers, and cobalt-catalyzed reductive [3+2] cycloaddition of allenes and enones.[3] Herein, we report the unprecedented synthesis of polysubstituted cyclopentenes from β-ketoesters and aliphatic allenes.

Previous work on the use of rhenium complexes in organic synthesis, including our own studies on the reactions of acetylenes and olefins,[4,5] led us to envisage the reactivity of rhenium complexes towards allenes. By heating a mixture of β-ketoester **1a** and allene **2a** in toluene in the presence of rhenium complex [{ReBr(CO)$_3$(thf)}$_2$], the insertion of **2a** into either the C–H bond at the α-position[4a] or the carbon–carbon bond[4b] of **1a** was expected. After carrying out the above reaction, C–H insertion product **4a** was produced in 27% yield in addition to the unexpected formation of cyclopentene **3a** in 32% yield [Eq. (1)].[3] The structure of **3a** was determined by both NMR spectroscopy and single-crystal X-ray crystallographic analysis (Figure 1). For structure **3a**, both the regiochemistry and the stereochemistry at the three carbon centers was defined.

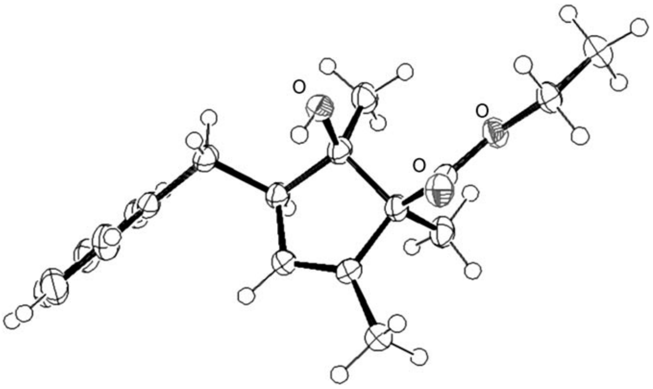
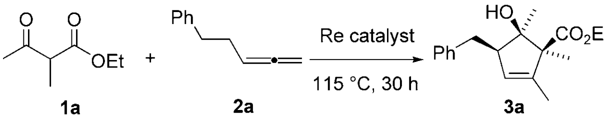
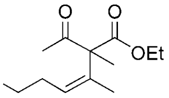


Figure 1. X-ray crystal structure of **3a**.[17] Thermal ellipsoids set at 50% probability.



1a **2a** **3a** (1)

	3a	4a
[{ReBr(CO)$_3$(thf)}$_2$] (2.5 mol%), toluene	32%	27%
[ReBr(CO)$_5$] (5.0 mol%), toluene	35%	10%
[Re$_2$(CO)$_{10}$] (2.5 mol%), toluene	76%	0%
[Re$_2$(CO)$_{10}$] (2.5 mol%), neat	85%	0%



4a

Additional investigation of the catalysts showed that treatment of β-ketoester **1a** and allene **2a** with [ReBr(CO)$_5$] (5.0 mol%) furnished the desired product in 35% yield. The yield of **3a** was improved to 76% by using [Re$_2$(CO)$_{10}$] (2.5 mol%) instead of [ReBr(CO)$_5$]. Gratifyingly, the yield was improved to 85% by heating **1a** and **2a** under solvent free conditions [Eq. (1)]. Notably, we detected another isomer peak in the GC-MS analysis, but it was less than 1% yield. Changing the electronic properties of the rhenium complexes by using phosphine ligands ([ReCl$_3$(PPh$_3$)$_2$(NCMe)], [ReCl$_3$(PMe$_2$Ph)$_3$], and [ReOCl$_3$(PPh$_3$)$_2$]) afforded decomposition products of allenes. Other metal complexes, such as [Mn$_2$(CO)$_{10}$], [MnBr(CO)$_5$], and [Ru$_3$(CO)$_{12}$] were also ineffective.

Once the optimal catalyst and reaction conditions were identified, we investigated the scope and limitations of this new synthetic method for making cyclopentenes using β-ketoesters and aliphatic allenes. Aliphatic allenes reacted with β-ketoesters in the presence of 2.5 mol% of the [Re$_2$(CO)$_{10}$] catalyst to furnish the corresponding cyclopentene derivatives in moderate to excellent yields (61–91%) (Table 1). Cyclopentene **3b** was isolated in 80% yield from the reaction of active methylene compound **1a** with allene **2b** (entry 1). Ester and silyloxy groups are tolerated under the reaction conditions as evidenced by the high yields of products, **3c** and **3d**, respectively (entries 2 and 3).[6] Active methylene compound **1b** also served as a good coupling partner to give cyclopentene **3e** in 61% yield. (entry 4). Changing the substituent from the ethyl group of the

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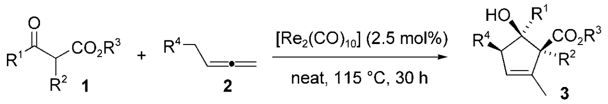
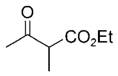
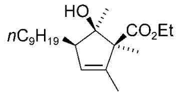
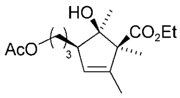
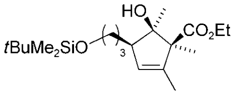
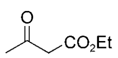
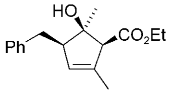
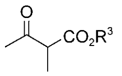
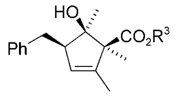
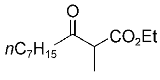
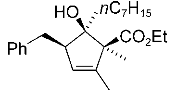
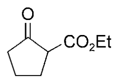
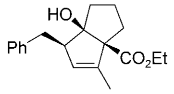
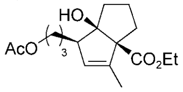
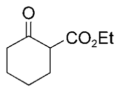
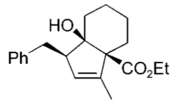
Table 1: Rhenium-catalyzed formation of cyclopentenes.[a]

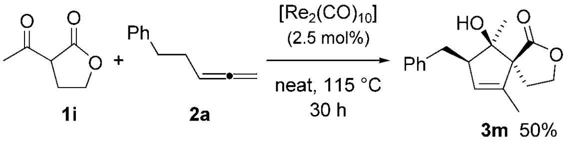


Entry	1	2 (R^4)	3	Yield [%][b]
1	 **1a**	**2b** (nC_9H_{19})	 **3b**	80
2	**1a**	**2c** ($AcO(CH_2)_3$)	 **3c**	73
3	**1a**	**2d** ($tBuMe_2SiO(CH_2)_3$)	 **3d**	74
4	 **1b**	**2a** ($PhCH_2$)	 **3e**	61
5	 **1c** $R^3 = tBu$	**2a**	 **3f** $R^3 = tBu$	68
6	**1d** $R^3 = CH_2CH{=}CH_2$	**2a**	**3g** $R^3 = CH_2CH{=}CH_2$	62[c]
7	**1e** $R^3 = (CH_2)_4CH{=}CH_2$	**2a**	**3h** $R^3 = (CH_2)_4CH{=}CH_2$	76[d]
8	 **1f**	**2a**	 **3i**	69
9	 **1g**	**2a**	 **3j**	76
10	**1g**	**2c**	 **3k**	91
11	 **1h**	**2a**	 **3l**	63[3]

[a] **1a** (1.0 equiv), **2** (1.2 equiv). [b] Yield of isolated product. [c] **1d** (1.2 equiv), **2a** (1.0 equiv). 48 h. [d] 48 h. [e] 48 h, see Ref. [7].

β-ketoester to a bulkier *tert*-butyl group (entry 5) did not affect the reaction significantly, and cyclopentene **3f** was obtained in 68% yield. The use of **1d** and **1e** as substrates indicated that the presence of an olefin within the ester group did not disrupt the reaction and cyclopentenes **3g** and **3h** were obtained in 62% and 76% yields, respectively (entries 6 and 7). Changing the substituent at the ketone part of the β-ketoester afforded a cycloadduct **3j** in 69% yield (entry 8). Interestingly, cyclic β-ketoesters, **1g** and **1h**, participated in the annulation reaction, and bicyclic compounds, **3j**, **3k**, and **3l**, were obtained in 76%, 91%, and 63% yields, respectively (entries 9–11).[7]

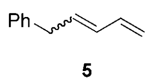
The utility of the present annulation reaction was demonstrated in the stereoselective synthesis of the spirocyclic compound **3m** as shown in Equation (2).[8]



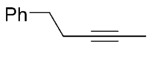
(2)

Transition-metal-catalyzed hydrocarbonation reactions of allenes with active methylene compounds have been reported,[9] and the reactions formally occur at three carbon atoms (α-, β-, and γ-positions) (Figure 2, left).[10] In contrast, the reaction in Equation (1) proceeded at the β, γ, and adjacent methylene positions of the allene (Figure 2, right).[11]

We conducted several experiments to obtain information on the reaction mechanism because the annulation occurs at an unusual site of the terminal allenes. Firstly, the possibility of a rhenium-catalyzed isomerization of aliphatic allenes to 1,3-dienes[12] at the initial step was examined. Treatment of allene **2a** with a catalytic amount of $[Re_2(CO)_{10}]$ (2.5 mol% or 25 mol%) at 115 °C in the absence of a β-ketoester, did not produce 1,3-diene derivative **5**. In addition, heating a mixture of **5** (*E*/*Z* 1:1.2) and **1a** in the presence of $[Re_2(CO)_{10}]$ (2.5 mol%) for 30 hours did not produce the corresponding cyclopentene derivative **3a**; the starting materials were recovered almost quantitatively.[13] These results clearly suggest that the present annulation reaction does not proceed by the isomerization of allene to 1,3-butadiene derivative **5**.



5



6

Since compound **4a** was obtained as a by-product, its role in the synthesis was investigated by

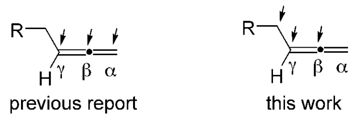
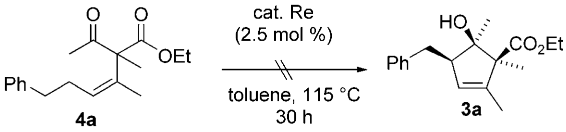


Figure 2. Reaction sites of terminal aliphatic allenes.

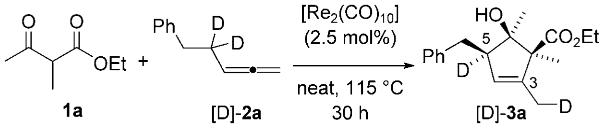
heating it in the presence of a catalytic amount of $[Re_2(CO)_{10}]$ or $[\{ReBr(CO)_3(thf)\}_2]$. Upon heating, the reaction did not proceed and the recovery of **4a** was almost quantitative [Eq. (3)]. This result indicates that the cyclopentene adduct **3a** was not generated by intramolecular cyclization of **4a**.



(3)

cat. Re = $[Re_2(CO)_{10}]$ or $[\{ReBr(CO)_3(thf)\}_2]$

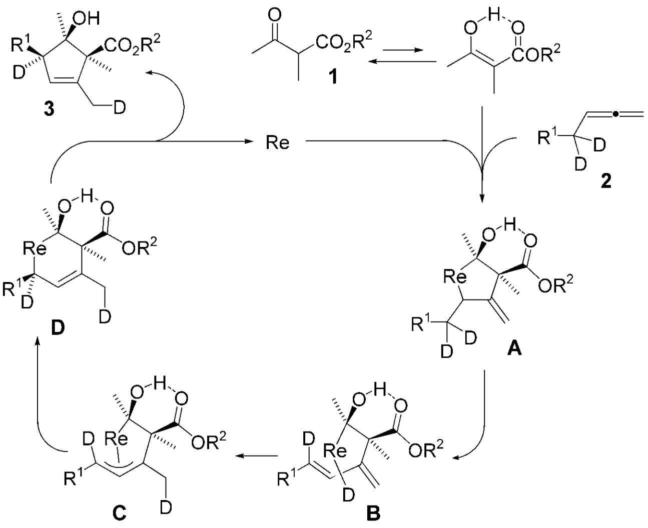
We performed a deuterium labeling experiment using (4,4-$^2H_2$)-phenethyl allenes ($[D_2]$-**2a**), which would enable us to determine where a proton of an adjacent methylene moiety of the allene is transferred [Eq. (4)]. Formation of cyclopentenes $[D_2]$-**3a** having a monodeuterated methyl group at C3 indicates that the proton of the methylene is transferred exclusively to the terminal carbon atom of the allene.



(4)

At present, we do not have enough experimental evidence to fully describe the reaction mechanism, especially in terms of the stereoselectivity at C5; however, we believe that the mechanism shown in Scheme 1 is operative.[14] Although the active rhenium species is not still clear,[15] we believe that the initial step in the reaction is the formation of rhenacyclopentane intermediate **A** from the rhenium catalyst, β-ketoester, and allene.[4a,b,16] At this stage, the *cis* stereochemical relationship between the hydroxy and ester groups of the product is controlled by hydrogen bonding between the two groups. β-Hydride elimination of **A** gives intermediate **B** having a diene moiety. Insertion of an *exo* double bond of **B** into the Re–D gives π-allyl rhenium intermediate **C**. The σ-allyl intermediate **D**, derived by rearrangement of **C**, undergoes a final reductive elimination to give the product and regenerate the rhenium catalyst.

In summary, we have developed a novel stereoselective annulation method for construction of cyclopentene frameworks containing multiple stereogenic centers. The reaction proceeds with a commercially available $[Re_2(CO)_{10}]$ catalyst, is operationally simple, and is atom economical. We hope the result provides new insights into the reactivity of unactivated allenes bearing an adjacent methylene moiety.



Scheme 1. Proposed mechanism.

Experimental Section

A mixture of **1a** (72.1 mg, 0.500 mmol), **2a** (87.0 mg, 0.600 mmol), and $[Re_2(CO)_{10}]$ (8.2 mg, 0.0125 mmol) was stirred in an oil bath heated to 115 °C for 30 h. After completion of the reaction, the mixture was purified by silica gel column chromatography using hexane/ethyl acetate (20:1→10:1) as the eluent to give **3a** (122 mg, 85 % yield).

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[1] For reviews on the synthesis of cyclopentanoid carbocycles, see: a) L. A. Paquette, *Chem. Rev.* **1989**, *89*, 1051–1065; b) T. Hudlicky, J. D. Price, *Chem. Rev.* **1989**, *89*, 1467–1486; c) G. Mehta, A. Srikhrisna, *Chem. Rev.* **1997**, *97*, 671–719; d) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1454–1457; *Angew. Chem. Int. Ed.* **2006**, *45*, 1426–1429, and references therein.

[2] For reviews, see: a) M. E. Welker, *Chem. Rev.* **1992**, *92*, 97–112; b) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92.

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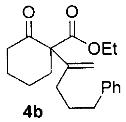
[5] For a review, see: R. Hua, J.-L. Jiang, *Curr. Org. Synth.* **2007**, *4*, 151–174.

[6] Internal allene, 1-phenyl-2,3-nonadiene, and 1,1-disubstituted allene, 3-pentyl-octa-1,2-diene, did not give the corresponding

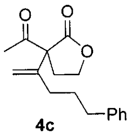
annulation products, and the allenes were recovered almost quantitatively.

[7] For the reaction in Table 1, entry 11, by-product **4b** was isolated in 7% yield.

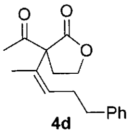


4b

[8] Inseparable by-product in Equation (2).



4c



4d

[9] For pioneering examples of hydrocarbonation reaction of allenes, see: a) Y. Yamamoto, M. Al-Masum, N. Asao, *J. Am. Chem. Soc.* **1994**, *116*, 6019–6020; b) B. M. Trost, V. J. Gerusz, *J. Am. Chem. Soc.* **1995**, *117*, 5156–5157.

[10] For reviews on the synthesis and reactions of allenes, see: a) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067–3125; b) *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**; c) S. Ma, *Chem. Rev.* **2005**, *105*, 2829–2871; d) K. M. Brummond, J. E. DeForrest, *Synthesis* **2007**, 795–818; e) S. Ma, *Aldrichimica Acta* **2007**, *40*, 91–102; f) H. H. A. M. Hassan, *Curr. Org. Synth.* **2007**, *4*, 413–439.

[11] For annulation reactions between activated allenes having an adjacent methylene moiety and imines under phosphine catalysis, see: a) X.-F. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc.* **2003**, *125*, 4716–4717; b) R. P. Wurz, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235.

[12] For a reaction of an aliphatic allene with carboxylic acid to form 1,3-butadiene derivatives, see: M. Al-Masum, Y. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 3809–3810.

[13] We could not detect other isomerization product that may be produced from the allene, such as methyl alkyne derivative **6**. Indeed, when aliphatic methyl alkyne **6** was treated with β-ketoester **1a** in the presence of $[Re_2(CO)_{10}]$ at 115°C, the reaction did not give the corresponding cyclopentene product **3a.**

[14] For a study on sigmatropic hydrogen shifts of allenes, see: F. Jensen, *J. Am. Chem. Soc.* **1995**, *117*, 7487–7492.

[15] For a discussion about photoreactions of $[Re_2(CO)_{10}]$ and their complexes with allenes, see: a) C. G. Kreiter, W. Michels, G. Heeb, *J. Organomet. Chem.* **1995**, *502*, 9–18, and references therein; b) H. Yang, P. T. Snee, K. T. Kotz, C. K. Payne, C. B. Harris, *J. Am. Chem. Soc.* **2001**, *123*, 4204–4210.

[16] The mechanism can explain the appearances of by-products in some cases, such as **4b**; β-hydride elimination and reductive elimination of intermediate **A** gives by-product **4b**.

[17] Crystal data for **3a:** The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. $C_{18}H_{24}O_3$, $M_r = 288.39$, 0.18x0.13x0.02 mm, triclinic, space group P-1 (#2), $a = 7.5638(4)$ Å, $b = 10.4887(5)$ Å, $c = 11.2406(7)$ Å, $\alpha = 70.915(3)^o$, $\beta = 75.657(3)^o$, $\gamma = 74.835(3)^o$, $V = 800.45(7)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.196$ g/cm^3, $\mu = 6.374$ cm^{-1}, $Mo_{K\alpha}$radiation ($\lambda = 1.54187$ Å) at 93(1) K, $2\theta_{max} = 136.3^o$, number of independent reflection 18099 ($R_{int} = 0.060$), $R = 0.0659$, $wR_2 = 0.1563$, $R_1 = 0.0565$. CCDC-706439 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.