Homogeneous Catalysis

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What Can a Metal Catalyst Do with Allenes? One-Step Formation of Steroid Scaffolds from Readily Available Starting Materials**

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The diversity of available transition metals and organic ligands for the formation of organometallic catalysts offers the possibility of excellent selectivity and tunability in homogeneous transformations.[1–4] Alkynes and alkenes are two classes of well-studied compounds in organic chemistry that have formed the basis of the petroleum industry and modern organic chemistry.[5] It should be noted that 1–1.5 % of allene exists in propylene produced by the cracking of hydrocarbons in petroleum.[6] The large amount of propylene consumed means that the production of propadiene in considerable quantities is thus possible. Although van't Hoff predicted the correct structures of allenes and higher cumulenes as early as 1874,[7] for a long period of time allenes were considered to be highly unstable, which retarded the demonstration of their synthetic potential. However, the situation has changed dramatically during the last 8 to 10 years, and many new reactions have been developed based on the chemistry of allenes.[8–13] Steroids are characterized by a carbon skeleton with four fused rings, and their presence in plants and animals illustrates their immense biological importance.[14–17] Steroids are used for the treatment of cancer, arthritis, allergies, and in birth control. Thus,

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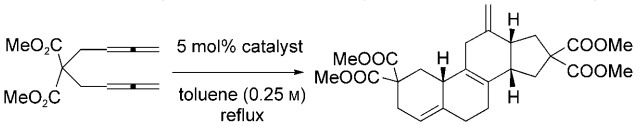
efficient catalytic approaches to new steroid derivatives are still of current interest.[18–25] Recently, during our study of allene chemistry,[26] we identified a very efficient one-step transition-metal-catalyzed transformation of simple 1,5-bisallenes to steroid skeletons.

We prepared 5,5-bis(methoxycarbonyl)-1,2,7,8-nonatetraene (**1a**)[27] from the bisallenylation of diethyl malonate with 2,3-butadienyl bromide.[28] The reaction of **1a** in the presence of a catalyst of 5 mol% $[RhCl(PPh_3)_3]$ and 10 mol% $AgSbF_6$[29] afforded a product with a complicated ^1H NMR spectrum (entry 1, Table 1). The structure of this product was unambiguously established by X-ray diffraction studies to be the 18,19-norsteroid derivative **2a** (Figure 1).[30]

Table 1: Dimeric cyclization of **1a** in the presence of different catalysts.



1a **2a**

Entry	Catalyst	*t* [h]	Yield of **2a** [%]
1	$[RhCl(PPh_3)_3] + AgSbF_4$[a]	3	10
2	$[\{RhCl(cod)\}_2] + P(OPh)_3$[b]	12.5	15
3[c]	$[RhH(CO)(PPh_3)_2]$	2.5	31
4	$[\{RhCl(cod)\}_2] + PPh_3$[d]	12	38
5	$[RhCl(PPh_3)_3]$	2	38
6	*trans*-$[RhCl(CO)(PPh_3)_2]$	2	42
7	$[Rh(cod)_2]BF_4$	12	–
8	$PtCl_2$	4	–

[a] 10 mol% $AgSbF_4$ was added. [b] 10 mol% $P(OPh)_3$ was added. [c] The reaction was conducted at 0.125 M **1a** in toluene. [d] 10 mol% PPh_3 was added.

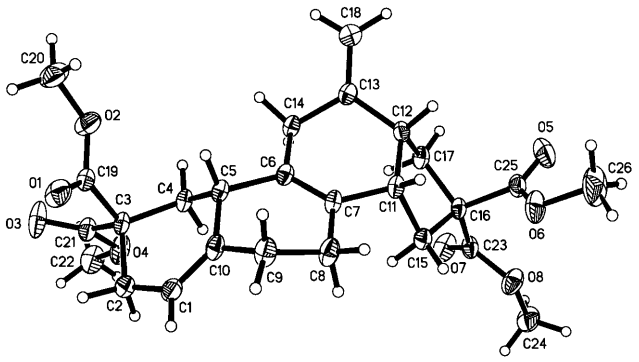
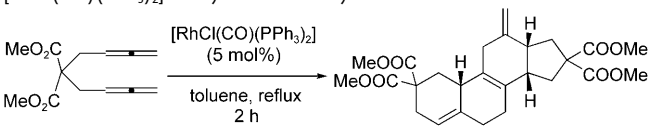


Figure 1. ORTEP representation of **2a**.

We screened a variety of catalysts using compound **1a** as the model, and some typical results are summarized in Table 1. The yields were improved when we used $[RhH(CO)(PPh_3)_2]$, $[RhCl(cod)]_2 + PPh_3$ (cod = cycloocta-1,5-diene), and $[RhCl(PPh_3)_3]$ without an Ag^+ salt (entries 3–5, Table 1). Further research showed that *trans*-$[RhCl(CO)(PPh_3)_2]$ was the best catalyst (entry 6, Table 1) while neither $[Rh(cod)_2]BF_4$ nor $PtCl_2$ showed any activity in this transformation (entries 7 and 8, Table 1).

Furthermore, a clear relationship between yields and concentrations was observed for this reaction (Table 2). It should be noted that the yield was greatly improved when a lower substrate concentration was used. We found that the reaction of **1a** at a concentration of 0.0417 M in toluene in the presence of 5 mol% *trans*-$[RhCl(CO)(PPh_3)_2]$ as the catalyst under reflux was very clean and afforded **2a** with a *cis* conjunction at the C/D rings in 73% yield as the only stereoisomer. It should be noted that no intermediate product was observed during the reaction process and no other stereoisomers were detected in the crude product by ^1H NMR spectroscopic analysis.

Table 2: Effect of the concentration of **1a** in toluene on the *trans*-$[RhCl(CO)(PPh_3)_2]$-catalyzed dimeric cycloisomerization of **1a**.[a]



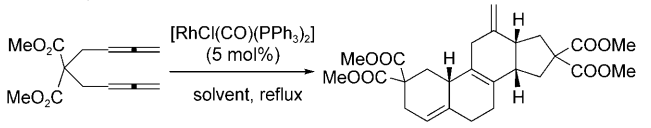
1a **2a**

Entry	Concentration of **1a** [M]	Yield of **2a** [%]
1	0.25	42
2	0.125	55
3	0.0625	69
4	0.0417	73
5	0.0313	72

[a] The reaction was carried out using **1a** (0.25 mmol) and *trans*-$[RhCl(CO)(PPh_3)_2]$ (5 mol%) in toluene under reflux.

The effect of the solvent on this reaction are summarized in Table 3. Among the solvents tested, the best results were obtained in toluene (entry 1, Table 3). Furthermore, the yield and reaction rate both dropped when the reaction was carried out at a lower temperature (compare entries 2 and 1, Table 3).

Table 3: Effect of the solvent on the *trans*-$[RhCl(CO)(PPh_3)_2]$-catalyzed dimeric cycloisomerization of **1a**.[a]



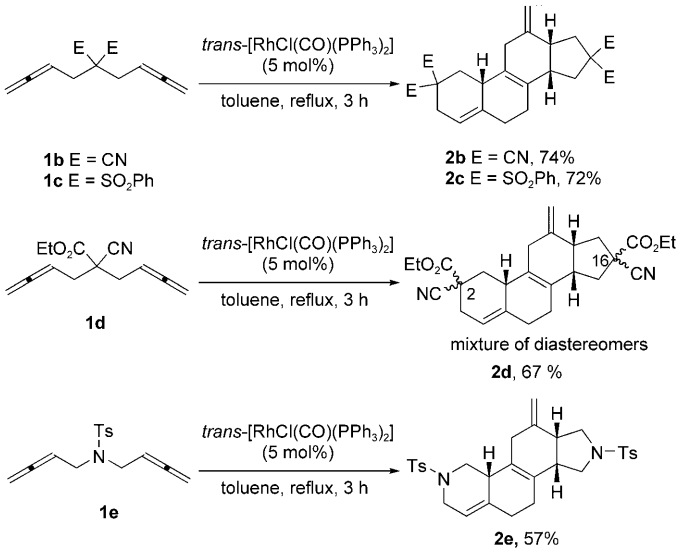
1a **2a**

Entry	Solvent	*t* [h]	Yield of **2a** [%][b]
1	toluene	2	73
2[c]	toluene	57	43
3	CH_3CN	9.6	17
4	THF	6	36
5[d]	DMF	2.5	28
6	dioxane	2.5	41
7	benzene	7	54
8	xylene	2	41

[a] The reaction was carried out using **1a** (0.0417 M, 0.25 mmol) and *trans*-$[RhCl(CO)(PPh_3)_2]$ (5 mol%) in the specified solvent under reflux. [b] Yields determined by NMR spectroscopy by using 1,3,5-trimethyl benzene as the internal standard. [c] The reaction was conducted at 60 °C. [d] The reaction was conducted at 110 °C.

The reaction was also slow and the yield was quite low when CH_3CN was used as the solvent (entry 3, Table 3), while the use of benzene, xylene, and dioxane led to the formation of **2a** in yields of 41–54% (entries 6–8, Table 3). It should be noted that the ^1H NMR spectrum of the crude products indicated that only one stereoisomer was observed in all these cases.

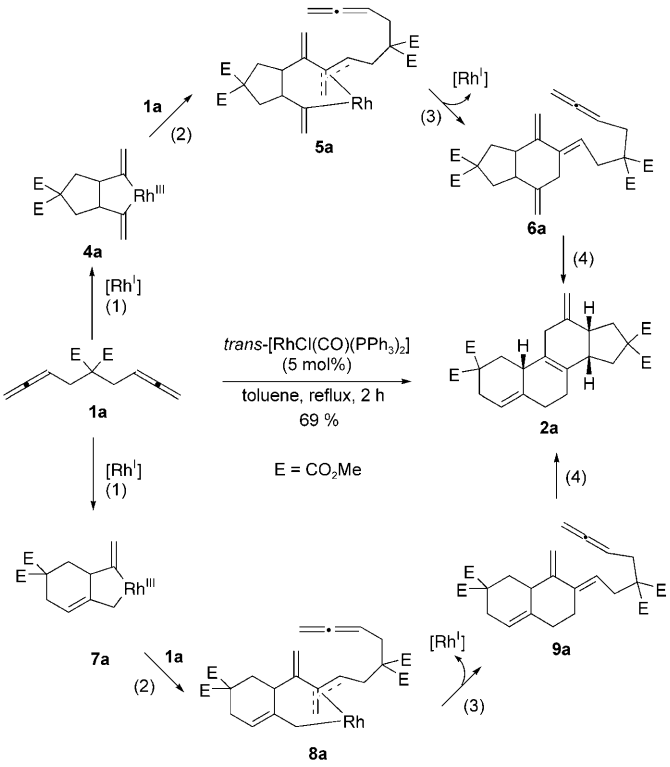
With the optimized conditions in hand, we studied the scope of this reaction, and found that it is general for differently substituted bisallenes. 18,19-Norsteroid derivative **2c** was readily prepared (1.086 g, 72%) from 1.5 g of bisallene **1c**, which was prepared from $CH_2(SO_2Ph)_2$, 2,3-butandienyl bromide,[28] and NaH in quantitative yield. The nitrogen analogue **2e** can be prepared from the bis(2,3-allenyl)amine **1e**. The dimeric cyclization of **1d** resulted in a mixture of 2,16 epimers **2d** in 67% yield (Scheme 1).



Scheme 1. Dimeric cyclization of bisallenes **1** with a *trans*-[RhCl(CO)-$(PPh_3)_2$] catalyst. Ts = toluene-4-sulfonyl.

A possible mechanism was postulated on the basis of the above results (Scheme 2). The reaction may proceed through the cyclometalation[31] of **1a** to afford **4a** or **7a**, which may then undergo carbometalation with one of the two allene moieties in **1a** to afford **5a** or **8a**, respectively. Subsequent reductive elimination would afford **6a** or **9a**, which could then undergo a Diels–Alder reaction to form the 18,19-norsteroid **2a** (Scheme 2). The results obtained illustrate that the intramolecular Diels–Alder reaction between an allene moiety and an alkene partner can proceed either in the presence[31a] or absence[32] of a metal catalyst. The reaction was conducted at a low temperature in an attempt to capture any possible intermediate(s), but the reaction was very fast and no intermediate product was detected.

In conclusion, we have reported an efficient route to 18,19-norsteroid derivatives from bisallenes by using a catalytic amount of *trans*-[RhCl(CO)$(PPh_3)_2$]. Although some steroids have been prepared from acyclic precursors by long synthetic routes,[18–25] the availability of the starting materials and the catalyst as well as the simplicity of the current procedure makes this methodology a very efficient route to steroids with new structural and steric features. Thus, this route may open up a new direction in steroid-related science.



Scheme 2. A possible mechanism for the transition-metal-catalyzed transformation of simple 1,5-bisallenes to steroid skeletons. (1) Cyclometalation, (2) carbometalation, (3) reductive elimination, (4) Diels–Alder reaction.

Experimental Section

Typical procedure: A solution of **1c** (1.509 g, 3.76 mmol) and *trans*-[RhCl(CO)$(PPh_3)_2$] (130 mg, 0.19 mmol, 5 mol%) in dry toluene (90 mL) was heated at reflux under Ar for 3 h. After the reaction was complete, as monitored by TLC (eluent: CH_2Cl_2/MeOH 40:1), removal of the solvent by rotary evaporation and flash chromatography of the product on silica gel (eluent: CH_2Cl_2/MeOH 100:1) afforded 1.086 g (72%) of **2c**. M.p. 143–145°C (dichloromethane/diethyl ether); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.18$–7.86 (m, 8H), 7.72–7.35 (m, 12H), 4.91 (br s, 1H), 4.75 (s, 1H), 4.71 (s, 1H), 3.02–2.50 (m, 9H), 2.42–2.20 (m, 3H), 2.15–1.90 (m, 4H), 1.70–1.62 ppm (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 26.1$, 28.5, 30.2, 30.5, 31.9, 34.3, 36.1, 37.5, 46.4, 47.4, 87.9, 93.5, 110.7, 114.1, 126.9, 128.6(×2), 128.7, 128.8, 131.0, 131.2, 131.4(×3), 131.5, 134.3, 134.5, 134.6, 135.8, 136.0, 136.4, 136.7, 139.8, 142.3 ppm; IR (KBr): $\tilde{\nu} = 3066$, 2906, 1447, 1328, 1309, 1144 cm^{-1}; MALDI: m/z: 839 $[M+K]^+$, 823 $[M^+ + Na]$; HRMS calcd for $C_{42}H_{40}O_8S_4Na$ $[M+Na]^+$: 823.1498; found: 823.1497. Elemental analysis calcd for $C_{42}H_{40}O_8S_4$: C 62.98, H 5.03; found: C 62.96, H 5.47%.

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[30] Crystal data for compound **2a**: $C_{26}H_{32}O_8$, $M_r = 472.52$, orthorhombic, space group $P2(1)2(1)2(1)$, 293 K, $Mo_{K\alpha}$, $a = 8.6778(12)$, $b = 9.7305(13)$, $c = 28.671(4)$ Å, $V = 2421.0(6)$ Å^3, $Z = 4$, final R indices $[I > 2\sigma(I)]$, $R1$ 0.0507, $wR2 = 0.1035$, no. of reflection measured/unique 14786/5647 ($R_{int} = 0.1486$). No. observations ($I > 2.00\sigma(I)$) 4180, no. variable 190, GOF = 0.898. Absolute structure parameter 0.1(10). CCDC-262016 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.

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