



Construction of tricyclic pyran derivatives through intramolecular [2+2+2] cycloaddition of allenynes with tethered aldehydes



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ARTICLE INFO

Article history:

Received 27 February 2013
Received in revised form 13 April 2013
Accepted 15 April 2013
Available online 27 April 2013

Keywords:

Rhodium
[2+2+2] cycloaddition
Allene
Alkyne
Aldehyde

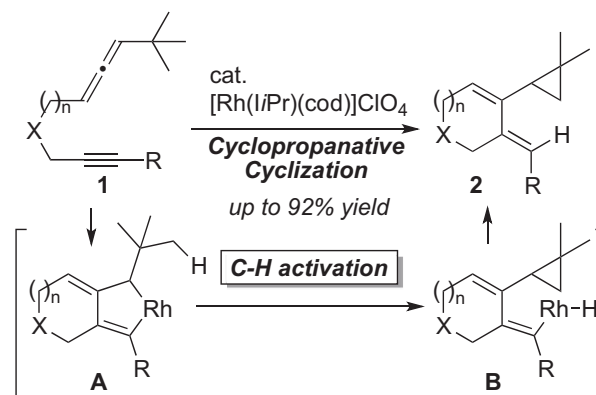
ABSTRACT

Rh(I)-catalyzed intramolecular [2+2+2] cycloaddition of allenynes with tethered aldehydes was investigated. The cyclizations proceeded smoothly under mild conditions to give various tricyclic compounds containing a pyran ring in good to high yields in a stereoselective manner.

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1. Introduction

Transition-metal-catalyzed [2+2+2] cycloaddition between three components of multiple bonds is a promising strategy for construction of complex polycyclic skeletons from simple starting materials.¹ In this context, our group has also reported a variety of [2+2+2] cycloadditions using various transition metals such as Ni, Pd, and Ru, and some applications of those cycloadditions to the synthesis of natural products have already been reported.² Herein we report a novel Rh-catalyzed [2+2+2] cycloaddition between alkyne, allene, and aldehyde, giving a tricyclic compound containing a pyran ring. The [2+2+2] cycloaddition was found during our ongoing investigation of a Rh(I)-catalyzed cyclopropanation/cyclization cascade between an allene having a *tert*-butyl substituent and tethered alkynes.³ That is, the reaction of **1** in the presence of a catalytic amount of [Rh(I^tPr)(cod)]ClO₄ provided cyclic compounds containing a cyclopropane ring in good to high yields, notably in which an sp³ C–H bond activation occurs at the stage of conversion of rhodacycle intermediate **A** to **B** along with the formation of a cyclopropane ring (Scheme 1). In this cyclization, the reaction of allenyne **1a** (*n*=4), having an aldehyde five carbons away from the terminus of alkyne in the chain, proceeded without any interference by the existence of the aldehyde moiety, giving the

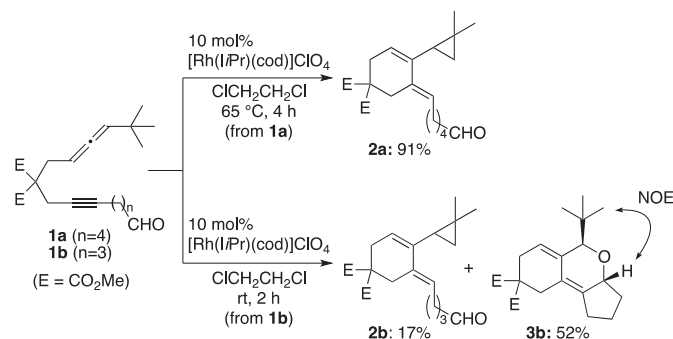


Scheme 1. Cyclization through C(sp³)-H bond activation.

expected cyclopropanation/cyclization product **2a** in 91% yield (Scheme 2). On the other hand, the reaction of **1b**, which has an aldehyde four carbons away from the terminus of alkyne in the chain (*n*=3), gave the tricyclic compound **3b** instead of **2b** as a major product.

The stereochemistry of **3b** with respect to the ring junction was determined to be *syn* by an NOE experiment, as shown in Scheme 2. This result means that a [2+2+2] cycloaddition between alkyne, allene, and aldehyde moieties in **1b** proceeded in a stereoselective manner through insertion of C=O bonds of the aldehyde moiety

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Scheme 2. Cyclization of allenynes with tethered aldehyde.

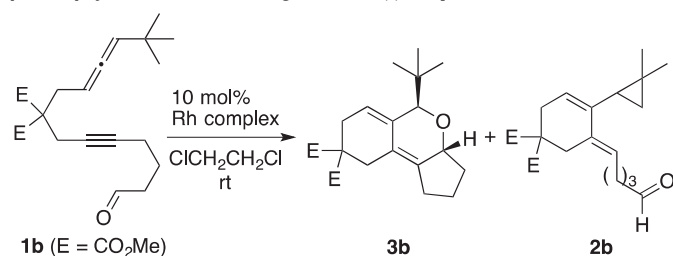
into the rhodacycle intermediate **A**.^{4,5} Although numerous examples of inter- or intramolecular [2+2+2] cycloaddition of alkynes or alkenes as a multiple bond component have been reported, [2+2+2] cycloaddition of substrates including an allene as a coupling partner is limited to several examples.^{6–11} Furthermore, there have been only a few reports on intramolecular [2+2+2] cycloadditions involving C=O bonds such as aldehydes and ketones.^{12–14} Thus, we investigated in detail the Rh-catalyzed [2+2+2] cycloaddition of allenynes **1** having an aldehyde moiety in the chain.

2. Results and discussion

We initially examined various Rh(I) complexes in this reaction in order to improve the yield of [2+2+2] cyclized product **3b** (Table 1). The reaction of **1b** using 10 mol % of cationic Rh complexes having phosphine ligands such as dppe and dppb instead of [Rh(IPr)(cod)]ClO₄ (cf. Scheme 2) provided no desired tricyclic compound **3b** and the starting material was recovered in 37 and 13% yields, respectively (runs 1 and 2). Also, the use of Wilkinson's catalyst (Rh(PPh₃)₃Cl) was not effective in this reaction, and the desired product was not obtained (run 3). Compared to the above Rh–phosphine catalysts, the Rh–NHC catalyst seemed to be effective in the reaction of **1b**.

Thus, the use of cationic Rh–NHC complexes including [Rh(I-Mes)(cod)]ClO₄, [Rh(IPr)(cod)]ClO₄, and [Rh(IME)(cod)]ClO₄ gave

Table 1
[2+2+2] Cycloaddition of **1b** using various Rh(I) complexes



Run	Rh complex	Time (h)	Yield (%)		
			3b	2b	SM rec.
1 ^a	[Rh(dppe)]ClO ₄	20	—	—	37
2 ^a	[Rh(dppb)]ClO ₄	23	—	—	13
3	Rh(PPh ₃) ₃ Cl	20	—	—	45
4 ^b	[Rh(IMEs)(cod)]ClO ₄	2	44	44	—
5 ^b	[Rh(IPr)(cod)]ClO ₄	1	34	12	—
6 ^b	[Rh(IME)(cod)]ClO ₄	24	66	16	—
7 ^c	[Rh(cod)]ClO ₄	2	69	16	—

^a [Rh(phosphine)]ClO₄ was prepared in situ by treatment of [Rh(cod)₂]ClO₄ and ligand with H₂.

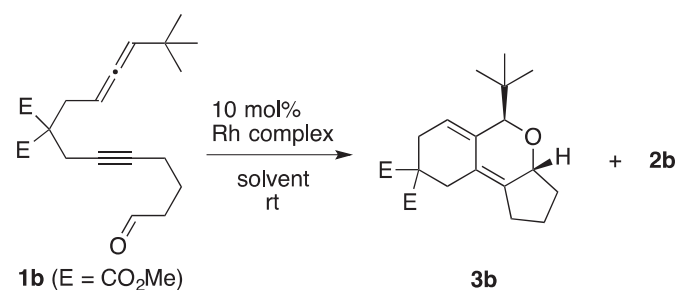
^b [Rh(NHC)(cod)]ClO₄ was prepared in situ from Rh(NHC)(cod)Cl and AgClO₄.

^c [Rh(cod)]ClO₄ was prepared in situ from [Rh(cod)Cl]₂ and AgClO₄.

the desired product **3b** in modest to good yields (runs 4–6). The yield of **3b** was improved to 66% in the reaction of **1b** using [Rh(IME)(cod)]ClO₄, but the reaction was very slow (run 6). Interestingly, it was found that the cyclization of **1b** with 10 mol % [Rh(cod)]ClO₄ in the absence of both phosphines and NHC ligands proceeded smoothly, giving the desired cyclic compound **3b** in 69% yield (run 7).

Next, the effects of both the counteranion parts of cationic Rh complexes and solvents were investigated (Table 2). Change in the counteranion of Rh cation complex from ClO₄⁻ to SbF₆⁻ did not influence the yield of **3b** but slowed down the reaction rate (run 1). The reaction of **1b** using [Rh(cod)]PF₆ was also slow, but the desired product **3b** was obtained in 77% yield (run 2). It was found that the use of [Rh(cod)]BF₄ greatly improved the yield of **3b** up to 83% (run 3). Change in the solvent from ClCH₂CH₂Cl to THF or toluene seemed to retard the reaction, and the product **3b** was obtained only in 10 or 20% yield along with the recovery of the starting material **1b** in 28 or 39% yield, respectively (runs 4 and 5).

Table 2
Effects of counteranions and solvents



Run	[Rh(cod)]X ^a	Solvent	Time (h)	Yield (%)		
				3b	2b	SM rec.
1	[Rh(cod)]SbF ₆	ClCH ₂ CH ₂ Cl	23	69	12	—
2	[Rh(cod)]PF ₆	ClCH ₂ CH ₂ Cl	23	77	9	—
3	[Rh(cod)]BF ₄	ClCH ₂ CH ₂ Cl	2	83	2	—
4	[Rh(cod)]BF ₄	THF	24	10	23	28
5	[Rh(cod)]BF ₄	toluene	24	20	15	39

^a [Rh(cod)]X complexes were prepared in situ from [Rh(cod)Cl]₂ and AgX.

Having established the optimal conditions for the [2+2+2] cycloaddition of allenynes with tethered aldehyde, we turned our attention to investigating the cycloaddition of various substrates (Table 3). The cyclization of **1c** and **1d** proceeded smoothly, giving the corresponding tricyclic products **3c** and **3d** in 59 and 80% yields, respectively (runs 1 and 2). The reaction of **1e**, having an oxygen atom in the chain, did not afford the corresponding product **3e** under the standard optimal conditions. However, the addition of 1.0 equiv of 2,2,2-trifluoroethanol (TFE) to the reaction mixture promoted the cycloaddition, giving the product **3e** in 25% yield (run 3).¹⁵ In the case of **1f**, containing a nitrogen atom in the chain, the corresponding heterocycle **3f** was obtained in a moderate yield without addition of TFE (run 4). The reactions of allenynes **1g** and **1h**, having an aromatic ring and a methyl group on the terminus of allene, respectively, afforded the corresponding [2+2+2] products **3g** and **3h** in good yields (runs 5 and 6). In those cases, however, the product **3g** was obtained as a single isomer, while the product **3h** was obtained as a mixture of isomers with respect to the ring junction (*syn/anti*=2.3:1). Each isomer of **3h** was separated into *syn-4h* and *anti-4h* after conversion of **3h** to **4h**, and those stereochemistries were unambiguously determined by NOESY spectra (Scheme 3). Notably, the [2+2+2] cycloaddition is applicable to construction of a 5–6–5 fused tricyclic ring system, and the corresponding product **3i** was obtained from **1i** in 81% yield (run 7).

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