

Rhodium(I)-Catalyzed [2+2], [2+2+2], and [2+2+2+2] Cycloadditions of Dienes or Alkynes with a Bis-ene

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Abstract:

A novel metal-catalyzed, all-alkene [2+2+2] cycloaddition reaction involving a strained and conformationally restricted bis-ene and a diene is reported. Modification of the catalyst leads to competition with a diene-ene [2+2] reaction, and when an alkyne was used in place of the diene, [2+2+2] and [2+2+2+2] cycloaddition reactions occurred involving the bis-ene and 1 or 2 equiv of the alkyne.

Keywords: cycloaddition reactions

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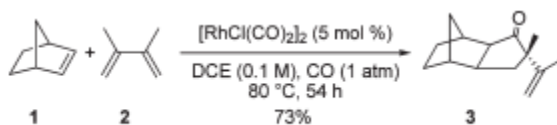
Summary: A novel metal-catalyzed, all-alkene [2+2+2] cycloaddition reaction involving a strained and conformationally restricted bis-ene and a diene is reported.¹ Modification of the catalyst leads to competition with a diene-ene [2+2] reaction, and when an alkyne is used in place of the diene, [2+2+2] and [2+2+2+2] reactions occur involving the bis-ene and 1 or 2 equiv of the alkyne, respectively.

To achieve more step-economical,² and therefore greener,³ syntheses, the optimal sequencing of known reactions and the introduction of new reactions are important. New reactions enable new ways of thinking about bond construction and thus fundamentally new strategic choices for making a target. Of special importance are complexity-increasing reactions that allow for the formation of multiple bonds and, where relevant, stereocenters in one synthetic operation.² We report herein a novel set of reactions including diene-ene [2+2], diene-bis-ene [2+2+2], and bis-yne-bis-ene [2+2+2+2] cycloadditions that were uncovered while studying the unusual reactivities of dienes (“the diene effect”) in an intermolecular diene-ene [2+2+1] cycloaddition reaction (Scheme 1).⁴

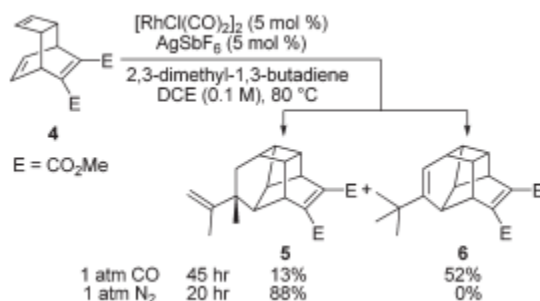
Concurrent with our study of the diene-ene [2+2+1] cycloaddition,⁴ Gibson and co-workers reported that tricycle **4**, the product of the thermal reaction of cyclooctatetraene (COT) and dimethylacetylene dicarboxylate (DMAD),⁵ can be used as a cyclobutadiene equivalent in Pauson-Khand reactions.⁶ Of further relevance to our work, Wilkinson previously isolated and characterized a complex with rhodium bound to tricycle **4** in a manner similar to norbornadiene,⁷

but, unlike norbornadiene,⁸ tricycle **4** has only recently been used in cycloadditions. On the basis of these reports, tricycle **4** was examined using conditions that we had optimized for the intermolecular diene-ene [2+2+1] cycloaddition (Scheme 1). However, instead of a cyclopentanone product, two structurally complex polycycles were isolated, with the major product incorporating a tert-butyl group (Scheme 2).⁹ After extensive 2D NMR analysis (see Supporting Information), the structure of polycycle **6** was determined, and it was hypothesized to be formed via an isomerization of isopropenyl product **5**. The structure of polycycle **5** was subsequently determined for the minor isomer, and the stereochemistry was analyzed using NOE analysis. Although tert-butyl product **6** was isolated as the major product, it was later found that isopropenyl product **5** initially forms and subsequently isomerizes under the reaction conditions to give thermodynamically more stable **6**.¹⁰ Since the reaction did not incorporate carbon monoxide (CO) into the ring, the reaction without CO was examined. A faster and more selective process was observed with the selective formation of **5** in 88% yield. Further optimization led to the exclusive formation of **5** in 99% yield (Table 1). Although [2+2+2] reactions involving at least one alkyne have been reported with a number of catalysts and substrates,¹¹ Scheme 2 describes an uncommon [2+2+2] cycloaddition involving three alkenes.¹²

Scheme 1. The Intermolecular Diene-ene [2+2+1] Reaction


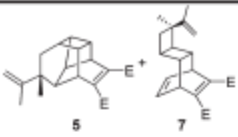

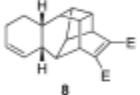

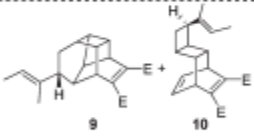

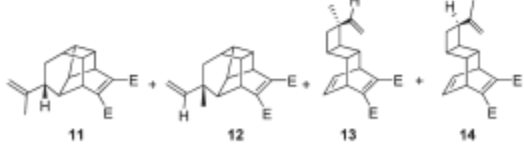


Scheme 2. Diene-Bis-ene [2+2+2] Reaction



While examining other catalysts with this diene-bis-ene [2+2+2] reaction, it was found that a different cationic Rh(I) catalyst, $[\text{Rh}(\text{COD})(\text{naphthalene})]\text{SbF}_6$,¹³ changed the course of the reaction of **4** with 2,3-dimethyl-1,3-butadiene. In addition to the diene-bis-ene [2+2+2] reaction, a dieneene [2+2] reaction had now occurred (Scheme 3). While less commonly encountered than mixed alkene-alkyne [2+2+2] reactions, [2+2] reactions of alkenes and alkynes have received noteworthy attention;¹⁴ however, there are few reported metal-catalyzed [2+2] reactions of two alkenes or of a diene and an alkene.¹⁵

Table 1. The [2+2] and [2+2+2] Cycloadditions of Dienes with 4^a

Entry	Diene	Catalyst	Catalyst	Time	Product, Isolated Yield
			Loading	(hr)	
					
1		[RhCl(CO) ₂] ₂	5 mol %	20	5 , 88%
2		[RhCl(CO) ₂] ₂	1 mol %	31	5 , 99%
3		[Rh(COD)(naphthalene)]SbF ₆	5 mol %	3.5	5 and 7 , 93% (1:2.3 ratio)
4 ^b		[Rh(COD)(naphthalene)]SbF ₆	10 mol %	3.5	5 and 7 , 50% (10:1 ratio, 45% 4)
<hr/>					
					
5		[RhCl(CO) ₂] ₂	5 mol %	0.5	8 , 81%
6		[RhCl(CO) ₂] ₂	1 mol %	47	8 , 48% (47% 4)
7 ^c		[RhCl(CO) ₂] ₂	1 mol %	3.5	8 , 96%
<hr/>					
					
8		[RhCl(CO) ₂] ₂	1 mol %	47	9 , 63% (25% 4)
9		[Rh(COD)(naphthalene)]SbF ₆	10 mol %	1.25	9 and 10 , 65% (1:2 ratio)
<hr/>					
					
10		[RhCl(CO) ₂] ₂	1 mol %	47	11 , 12 , and 13 , 56% (3.8:1.4:1 ratio; 26% 4)
11 ^d		[RhCl(CO) ₂] ₂	1 mol %	15	11 , 12 , and 13 , 37% (3.8:2.6:1 ratio; 52% 4)
12		[Rh(COD)(naphthalene)]SbF ₆	10 mol %	1	13 and 14 , 82% (1:1.6 ratio)

^a Reaction conditions: DCE (0.1 M), 10 equiv of diene unless otherwise noted, N₂ atmosphere, 80 °C. ^b Catalyst solution was flushed with CO for 10 min, followed by nitrogen before substrates were added. ^c Addition of 1.7 equiv the diene over 3 h. ^d Addition of 8 equiv of diene over 15 h.

As given in Table 1, other dienes and conditions were screened using the catalyst systems from Schemes 2 and 3. With 2,3-dimethyl-1,3-butadiene, it was found that the catalyst loading of [RhCl(CO)₂]₂ can be lowered to 1 mol % while maintaining an excellent yield of polycycle **5** (entry 2). Other dienes were not as efficient at lower catalyst loadings of [RhCl(CO)₂]₂ (entries 6, 8, and 10), which could be due to polymerized diene sequestering the catalyst. To slow the rate of polymerization of the diene relative to the desired reaction, slow addition of 1,3-cyclohexadiene to tricycle **4** in the presence of the catalyst solution was performed. Gratifyingly, a 96% yield of **8** resulted (entry 7). Unfortunately, slow addition of isoprene was not as effective

as found for 1,3-cyclohexadiene (entry 11), presumably due to the volatility and more facile polymerization of isoprene.

Although CO is not incorporated into the product of either of the reactions discussed, it appears that the CO ligand on the catalyst, or lack thereof, is important in determining the ratio of the [2+2+2]/[2+2] reaction products. This was deduced by pretreatment of a solution of [Rh(COD)(naphthalene)]SbF₆ with CO prior to addition of **4** and a diene, which resulted in almost exclusive formation of [2+2+2] cycloadduct **5** (entry 4).

For the diene-ene [2+2] cycloaddition, the product stereochemistry indicates that the rhodium catalyst is bound in an *exo*-fashion to only one olefin of triene **4**. This bears significance and suggests that other strained alkenes should work with this cycloaddition. To test this hypothesis, 1,4-epoxy-1,4-dihydronaphthalene (**15**) was reacted with 2,3-dimethyl-1,3-butadiene using the [(COD)Rh(naphthalene)]SbF₆ catalyst. As envisioned, vinylcyclobutane **16** was produced, although in only moderate yield (Scheme 4).¹⁶

Since the diene reacts as a two-carbon component in the [2+2] and [2+2+2] reactions, a few alkynes were tried for comparison. In particular, it was found that 3-hexyne worked well under the [2+2+2] reaction conditions, providing polycycle **17** and cyclobutene **18** in 73% and 5% yield respectively (Scheme 5). When the product of the [2+2+2] reaction (**17**) was resubjected to the reaction conditions, no further reaction occurred, implying that cyclobutene **18** results from a novel four-component [2+2+2+2] reaction. When [Rh(COD)(naphthalene)]SbF₆ was used as the catalyst, the complete consumption of starting material was over an order of magnitude faster and only the [2+2+2] reaction cycloadduct **17** was observed (Scheme 5).

On the basis of the experimental results from this study, a general mechanism for the [2+2], [2+2+2], and [2+2+2+2] reactions is proposed (Figure 1). Of mechanistic importance, the [2+2] reaction occurs via rhodium coordination to the *exo*-face of the cyclobutene π -system, while the [2+2+2] and [2+2+2+2] reactions are derived from *endo*-face coordination. Interestingly, reductive elimination of 4-A to form the vinylcyclobutane occurs instead of ring expansion to 4-B and reductive elimination to form a putatively less strained cyclohexene. For example, similar cationic rhodium(I) catalysts react with dienes and alkynes in a [4+2] pathway to provide six-membered-ring products.¹⁷ A rationale for this result is that the pendant olefin can coordinate the rhodium center during reductive elimination for the [2+2] reaction, but not for the [4+2] cycloaddition, thereby providing a lower energy barrier for the former.

In summary, we have discovered novel [2+2+2] and [2+2] cycloaddition reactions involving a bis-ene and dienes. By using an alkyne in place of the diene, [2+2+2] and [2+2+2+2] reactions were observed in which 1 or 2 equiv of the alkyne reacted with the bis-ene. Significantly, the conversion of COT and DMAD to tricycle **4** and the subsequent incorporation of a diene or alkyne via the [2+2], [2+2+2], or [2+2+2+2] cycloadditions (i.e., two-, three-, and four-component processes) create molecular complexity in the form of multiple rings (including fused four-membered rings); seven, nine, and 10 stereocenters, respectively; and five, six, and seven carbon-carbon bonds, respectively. While such complexity-increasing, multicomponent catalytic cascades are uncommon now, they provide a mechanistic and synthetic framework for uncovering other new reactions and reactivities and for achieving greater step economy in accessing targets of functional value.

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Supporting Information Available: Experimental procedures and characterization data for the products of the reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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