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Rhodium(I)-Catalyzed [4+2+2] Cycloadditions of 1,3-Dienes, Alkenes, and Alkynes for the Synthesis of Cyclooctadienes

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In 1989, we reported the first transition metal-catalyzed, intramolecular [4+2] cycloadditions of dienes and alkynes, representing a mechanistically novel and synthetically useful route to cyclohexadienes (**a** to **f**, Scheme 1) that works effectively often at room temperature, even when the corresponding Diels−Alder reaction requires forcing conditions or is ineffective.[1] This reaction was subsequently shown to work with dienes and alkenes[2] or allenes.[3] We anticipated that the metallacyclic intermediates (**b** and **d**) presumably involved in these reactions could be intercepted with various 1- to *n*-carbon trapping agents to produce higher order [2+2+*n*] and [4+2+*n*] cycloadducts. Subsequent studies showed that the [4+2] cycloaddition of dienes and alkynes could indeed be diverted with CO to produce a three-component [4+2+1] product (cycloheptadienone **e**) as well as [2+2+1] product (cyclopentenone **c**).[4] In 2002, the Gilbertson group creatively showed that the metallacycles involved in these processes could also be captured by alkynes to give a [4+2+2] cyclooctatriene product **g**.[5] An equally impressive, alternative [4+2+2] process for eight-membered ring synthesis based on enynes and dienes was also reported by the P. A. Evans group.[6]

In our studies on the [2+2+1] reactions of dienes, alkynes, and CO (**a** to **c**), we observed that dienes accelerate the reaction relative to alkenes, providing a new route to alkenyl-substituted cyclopentenones **c**, a dienyl Pauson−Khand reaction. This observation suggested that dienes, unlike alkenes, might react with a tethered alkene in the presence of CO to produce cyclopentanones **c**, a previously unknown process. This led to the first examples of a catalytic [2+2+1] route to cyclopentanones.[4] Given the enhanced reactivity of dienes observed in these studies, we have now examined the reaction of dienes as 4-carbon components tethered to alkenes in the presence of alkynes as trapping agents. We report herein the first examples of this combination in a metal-catalyzed [4+2+2] cycloaddition, producing cyclooctadienes often in high yields and with regiocontrol.[7] In preliminary studies, we have also established the first fully intermolecular example of this three-component process.

The results of a preliminary screen of several rhodium(I) catalysts are shown in Table 1. It is noteworthy that these catalysts favor the [4+2+2] reaction over the otherwise facile intramolecular [4+2] process, even when only 1.1 equiv of an alkyne trapping agent is used. $[RhCl(CO)_2]_2$ modified with $AgSbF_6$ results in the highest combined yield of [4+2+2] cycloadducts under the conditions described in Table 1 (85%, entry 2). Lower temperatures (60 to 40 °C) were also found to favor the three-component process. Further optimization studies showed that increasing the reaction concentration from 0.01 to 0.10 M also leads to overall higher yields of the desired products. It should be noted that only trace amounts (<5%) of the intramolecular [4+2] product are ever observed under the optimized conditions.

Scheme 1. Trapping of Metallacycles with π-Components

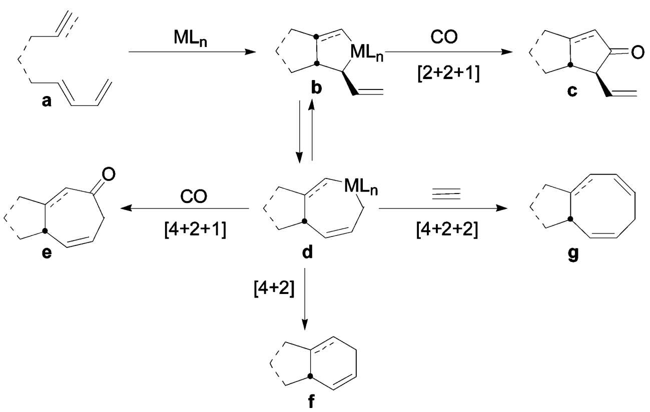
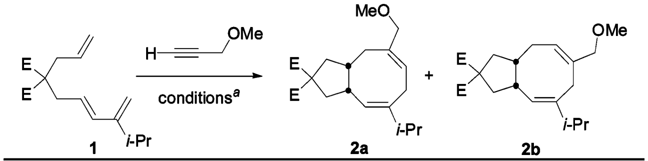


Table 1. Initial Catalyst Screen with Diene-ene **1** and Methyl Propargyl Ether



entry	catalyst[b]	additive[c]	yield[d]	ratio[f] (2a:2b)
1	$[RhCl(CO)_2]_2$	none	12%	5.0:1
2[e]	$\mathbf{[RhCl(CO)_2]_2}$	$\mathbf{AgSbF_6}$	**85%**	**4.2:1**
3	$RhCl(PPh_3)_3$	$AgSbF_6$	22%	1.1:1
4	$[Rh(NBD)Cl]_2$	$AgSbF_6$	55%	1.1:1
5	$[(C_{10}H_8)Rh(COD)]^+SbF_6^-$	none	31%	0.63:1

[a] Conditions (unless otherwise noted): DCE (0.01 M), 65 °C, 1.1 equiv of methyl propargyl ether. [b] 5 mol %. [c] 5 mol %. [d] GC yield. [e] DCE (0.10 M), 40 °C, 1.2 equiv of methyl propargyl ether. [f] Determined by ^1H NMR.

The [4+2+2] reaction has been found to proceed efficiently with a variety of terminal alkynes having ether, alkyl, ester, or ketone substituents (Table 2). Reaction times ranged from minutes to 5 h. Internal alkynes such as 1,4-dimethoxybut-2-yne and hex-3-yn-2-one react inefficiently under the reaction conditions. The regioselectivity of the alkyne insertion is influenced by both steric and electronic features of the alkyne. Both methyl and *tert*-butyldimethylsilyl (TBS) propargyl ethers give comparable yields and regioselectivities (entries 1 and 2). Replacing the methylenemethoxy group with a bulkier cyclopropyl group increases the regioselectivity from 4.2:1 to 11.7:1 (entry 1 versus 3). When ethyl propiolate is used, cycloadducts **5a** and **5b** are formed in 72% yield (ratio 6.4:1, entry 4). Additionally, when the reaction is run with 3-butyn-2-one the regioselectivity is reversed, favoring the **6b** isomer (ratio 1:1.9, combined yield 81%, entry 5). Significantly, the [4+2+2] reaction can also be carried out under one atm of acetylene, yielding cycloadduct **7** in 75% yield (entry 6). The scope of the reaction with respect to diene-ene substitution and tether type is shown in Table 3. Substitution in the 2-position of the diene results in higher yields and accelerated reaction rates relative to those obtained with the unsubstituted diene (entries 1−3). This is similar to the substituent effects observed in dienyl [2+2+1] cyclo-

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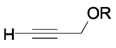
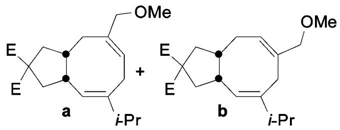
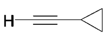
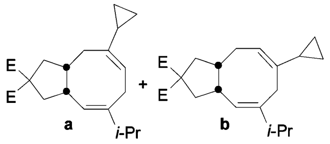
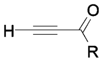
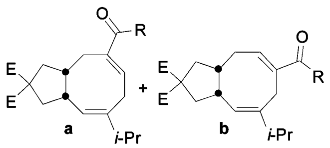
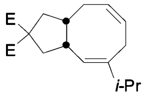
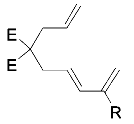
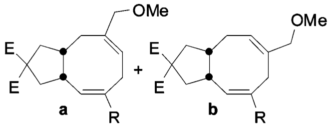
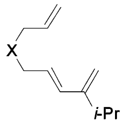
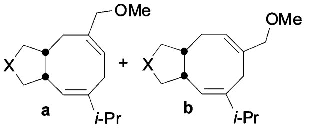
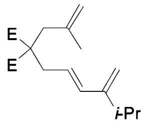
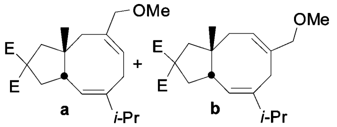
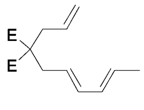
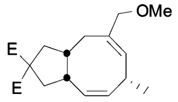
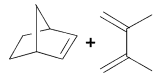
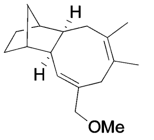
Table 2. Alkyne Scope of the [4+2+2] Reaction[a]

entry	substrate	t (h)	product, isolated yield (ratio[d])
			
1	R=Me	3	**2a,b** 85% (4.2:1)
2[b]	R=TBS	3.5	**3a,b** 76% (2.4:1)
3[c]		2	 **4a,b** 88% (11.7:1)
			
4	R=OEt	1.5	**5a,b** 72% (6.4:1)
5	R=Me	0.5	**6a,b** 81% (1:1.9)
6		5	 **7** 75%

[a] Conditions (unless otherwise noted): 5 mol % [RhCl(CO)$_2$]$_2$, 10 mol % AgSbF$_6$, DCE (0.10 M), 40 °C, 1.2 equiv of alkyne. [b] 2.0 equiv of alkyne. [c] 80 °C. [d] Determined by ^{1}H NMR.

Table 3. Diene-ene Scope of the [4+2+2] Reaction[a]

entry	substrate	t (h)	product, isolated yield (ratio[f])
			
1	**1** R=*i*-Pr	3	**2a,b** 85% (4.2:1)
2[b]	**8** R=Me	3	**14a,b** 76% (3.4:1)
3[c]	**9** R=H	24	**15a,b** 70% (2.8:1)
			
4[b]	**10** X=O	4	**16a,b** 79% (4.0:1)
5[d]	**11** X=N-Ts	2	**17a,b** 74% (5.1:1)
6[b,d]	 **12**	27	 **18a,b** 68% (1.5:1)
7[b,d]	 **13**	20	 **19a** 37%
8[e]		24	 **20** 56%

[a] Conditions same as in Table 2 (unless otherwise noted), methyl propargyl ether (1.2 equiv). [b] 2.0 equiv of alkyne. [c] 3.0 equiv of alkyne. [d] 60 °C. [e] 5.0 equiv of diene, 6.0 equiv of norbornene. [f] Determined by ^{1}H NMR.

additions.[4] With R = *i*-Pr the reaction was complete in 3 h, providing cycloadducts **2a** and **2b** in 85% combined yield (entry 1).

Substrates containing heteroatoms were also tolerated and allowed for the efficient formation of the corresponding heterocycles (entries 4 and 5). Significantly, substitution at the 2-position of the alkene moiety results in the formation of cycloadducts **18a** and **18b** (68% combined yield), a noteworthy result due to its stereoselectivity (cis-fusion) and its creation of an angular quaternary center (entry 6). Methyl substitution at the terminal position of the diene (entry 7) results in regio- and stereoselective formation of **19a** (37% yield). Replacing the allyl group with a crotyl group or a homoallyl group to produce bicyclo[6.4.0] systems results thus far in only trace conversions, even when the reaction is heated (60 °C) for 24 h (not shown).

Remarkably, the [4+2+2] cycloaddition can be carried out *inter*molecularly, as demonstrated by the chemo-, diastereo-, and regioselective conjunction of three different π-systems (norbornene, 2,3-dimethyl-1,3-butadiene, and methyl propargyl ether) to produce cycloadduct **20** (entry 8). This is the first example of a nontethered, three-component [4+2+2] cycloaddition.

In summary, initial examples of rhodium(I)-catalyzed [4+2+2] cycloadditions between diene-enes and terminal alkynes are described along with studies on substituent effects and the regio- and the diastereoselectivity of the reaction. Additionally, the first example of a three-component [4+2+2] cycloaddition is reported. These processes allow for the rapid and efficient construction of a wide variety of eight-membered ring systems.

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Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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