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Metal-Catalyzed [2+2+1] Cycloadditions of 1,3-Dienes, Allenes, and CO**

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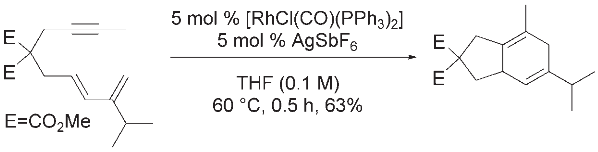
Step economy is a preeminent goal of synthesis.[1] It influences the length, efficiency, cost, time, separation, and environmental impact of a synthesis. Step economy is favored by the use of single, serial, or multicomponent reactions that proceed in one operation with a great increase in target revelant complexity. The design or discovery of such reactions is thus critical to extending the practical reach of organic synthesis. Toward this end, we have directed effort at the identification of new metal-catalyzed reactions, especially those which are forbidden or difficult to achieve in the absence of a catalyst. This program has thus far produced several new two-, three-, and four-component reactions, including [4+4],[2] [4+2],[3] [5+2],[4] [6+2],[5] [5+2+1],[6] [2+2+1],[7] [4+2+1],[7a] and [5+1+2+1][8] cycloadditions. Herein, we report the first examples of the [2+2+1] cycloaddition reaction of diene–allenes and CO and preliminary examples of acceleration of this process by Brønsted acids.

This investigation originated from our studies on the first metal-catalyzed intramolecular [4+2] cycloadditions of dienes and alkynes [Eq. (1)].[3,9] We recognized that the metallacyclic intermediates in this process could be intercepted by an additional component to produce three-component cycloadducts. With CO as the trapping agent, this approach indeed proved effective, thus resulting in the first examples of an intramolecular dienyl Pauson–Khand reaction [Eq. (2)] and a new [4+2+1] cycloaddition (not shown).[7a,10] Significantly, the diene was found to facilitate the reaction relative to an alkene [cf. Eqs. (2) and (3)].[7a,b] In the case of



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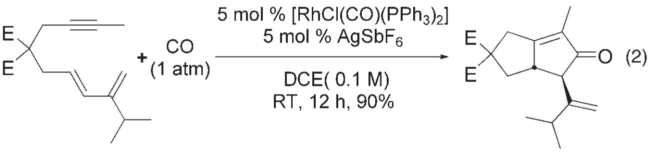
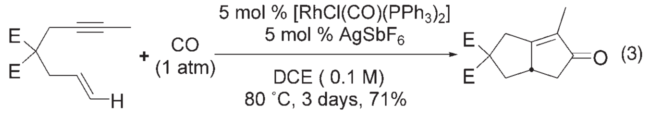
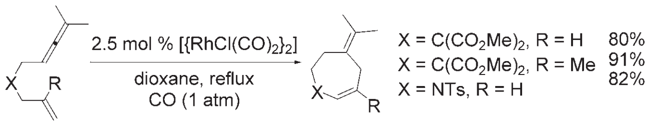


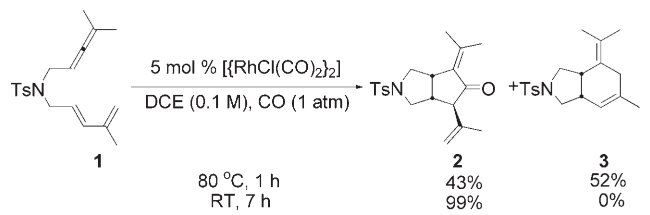


the [2+2+1] cycloaddition reaction of diene-enes, the presence of the diene enabled the reaction to occur, as these reactions do not proceed with simple bisalkenes.[7c] We expected that dienes could be used as two-carbon-atom components to enhance or enable other reactions because of their special reactivity. For example, although many impressive cases of the [2+2+1] cycloaddition reaction of alkyne–allenes (the allenic Pauson–Khand reaction) have been reported,[11] there have been no analogous reactions described for simple alkene–allenes. In fact, Brummond[12] and Itoh[13,14] found independently that simple alkene–allenes prefer to undergo efficient Rh^I-catalyzed cycloisomerizations to seven-membered rings rather than [2+2+1] cycloaddition reactions (even in the presence of CO; Scheme 1).[13,14] We have now found that if a diene–allene is used instead of an alkene–allene, a new [2+2+1] cycloaddition reaction is achievable, often in high yield.



Scheme 1. Rh^I-catalyzed cycloisomerization reaction of alkene–allenes. Ts = tosyl.

Under the optimal conditions found for the analogous [2+2+1] cycloaddition reaction of diene-enes,[7c] diene–allene **1** provides the [2+2+1] and the [4+2] cycloadducts **2** and **3** upon treatment with a catalytic amount of a Rh^I complex in 1,2-dichloroethane (DCE) at 80 °C under one atmosphere of CO (Scheme 2). It is noteworthy that diene–allenes give high yields of the [4+2] product in the absence of CO.[15] Exploration of the reaction conditions revealed that a decrease in reaction temperature from 80 °C to room temperature led to the exclusive formation of the [2+2+1] product **2**, which was structurally assigned by X-ray crystallographic analysis.



Scheme 2. Initial results and temperature effects for the competing [2+2+1] and [4+2] cycloaddition reactions.

A brief survey of different Rh^I complexes indicated that [{RhCl(CO)$_2$}$_2$] is the best catalyst of those examined (Table 1, entries 1–3). The nature of the solvent had a substantial effect on the efficiency of the reaction. Poor-to-moderate yields were obtained and long reaction times were required when toluene, dioxane, and acetonitrile were used, whereas excellent yields were obtained when the reaction was carried out in either DCE, methanol, or 2,2,2-trifluoroethanol (TFE; entries 1, 4–8). Significantly, a dramatic increase in the reaction rate was observed with TFE.[16] Gratifyingly, when the catalyst loading was lowered to 0.1 mol% and the concentration in TFE was increased to 0.5 M, an excellent yield of **2** was obtained (entry 9).

Table 1: Optimization of the [2+2+1] cycloaddition of **1**.[a]

Entry	Catalyst	Solvent	t [h]	Yield of **2** [%][b]
1	[{RhCl(CO)$_2$}$_2$]	DCE	7	99
2	[Rh(naph)(cod)]SbF$_6$	DCE	1.5	32
3	[{RhCl(dppb)}$_2$]	DCE	32	80
4	[{RhCl(CO)$_2$}$_2$]	toluene	24.5	38
5	[{RhCl(CO)$_2$}$_2$]	dioxane	21.5	64
6	[{RhCl(CO)$_2$}$_2$]	CH$_3$CN	45	77
7	[{RhCl(CO)$_2$}$_2$]	MeOH	12	96
8	[{RhCl(CO)$_2$}$_2$]	TFE	0.25	92
9	[{RhCl(CO)$_2$}$_2$]	TFE[c]	8	97

[a] Rhodium (10 mol%), 0.1 M, RT, 1 atm CO. [b] Yield of isolated product. [c] Catalyst (0.1 mol%), 0.5 M. cod = 1,5-cyclooctadiene, naph = napthalene, and dppb = 1,4-bis(diphenylphosphino)butane.

Intrigued by the rate enhancement observed with TFE, we wondered whether this effect could be due to the acidity of the solvent, as the observed trend correlates poorly with the corresponding dielectric constants or dipole moments of the solvents used. To test this hypothesis, the effect of adding acids to the [2+2+1] cycloaddition reaction of **1** was investigated (Table 2).[17] This study revealed that the addition of acid provides a rate enhancement and, with the exception of *para*-toluenesulfonic acid (TsOH; the most acidic of the acids surveyed), has a negligible effect on the yield of the [2+2+1] cycloaddition reaction. The fastest reactions were obtained when the reaction was carried out in DCE in the presence of 14 equivalents of phenol (entry 7) or in TFE (entry 2). For practical reasons, including avoiding the need to

Table 2: Effect of acid on reaction time for diene–allene **1**.[a]

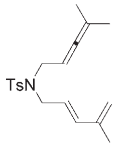
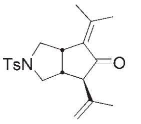
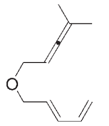
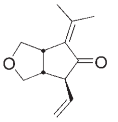
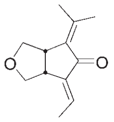
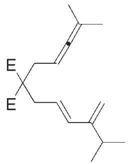
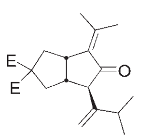
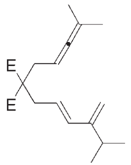
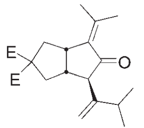
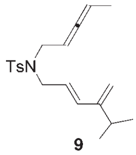
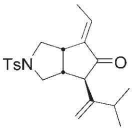
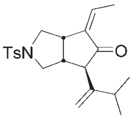
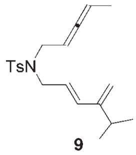
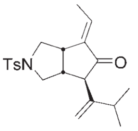
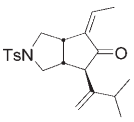
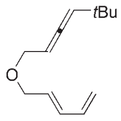
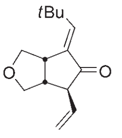
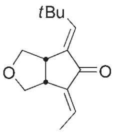
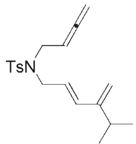
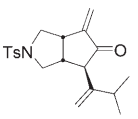
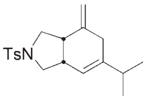
Entry	Solvent	Acid (equiv)	t [h]	Yield [%]
1	DCE	none	7	99
2	TFE	none	0.25	92
3	DCE	TsOH (0.05)	1.3	81
4	DCE	AcOH (6)	4	93
5	DCE	AcOH (100)	2.5	96
6	AcOH	none	2	93
7	DCE	PhOH (14)	0.25	94
8	DCE	TFE (14)	2	95

[a] [{RhCl(CO)$_2$}$_2$] (5 mol%), 0.1 M, RT, CO (1 atm).

separate phenol from the product at the end of the reaction, TFE was chosen as the solvent in the initial studies on the scope of this new [2+2+1] cycloaddition.

The [2+2+1] cycloaddition reaction of diene–allenes that vary in diene and allene substitution and type of tether was examined next (Table 3). In all cases, reaction at the proximal double bond of the allene was observed. Me, H, and *i*Pr substitution at the 2-position of the diene is well tolerated; however, approximately 10–25 % of the olefin isomer was observed for H substitution.[18] Entries 1–3 indicate that the presence of heteroatoms in the tether has no deleterious effect on the efficiency of the reaction. The [2+2+1] cycloaddition reaction of substrate **9**, which has a terminally methyl-substituted allene, gave both diastereomers **10** and **11**. When this reaction was carried out in TFE, only a 39 % overall yield was obtained (entry 5); however, a much cleaner and higher-yielding process (81 %) was obtained when the reaction was carried out in DCE at a concentration of 0.05 M (entry 6). The [2+2+1] cycloaddition reaction of **12**, which is substituted with the larger *t*Bu group, can be carried out in TFE in an excellent overall yield of 94 % (entry 7). Initial attempts to carry out the [2+2+1] cycloaddition reaction of diene–allene **15** in either TFE or DCE were unsuccessful. It was found that when the temperature and CO pressure were increased and the concentration in DCE was decreased, a 43 % yield of the [2+2+1] product and a 19 % yield of the [4+2] product (entry 8) were obtained.

Table 3: Substrate scope for the diene–allene [2+2+1] cycloaddition reaction.

Entry	Diene–allene	Conditions[a]	*t* [h]	Product	Yield
1	 **1**	A	8	 **2**	97
2	 **4**	B	1.5	 **5** +  **6**	97 (2.9:1)
3	 **7**	C	0.3	 **8**	92
4	 **7**	D	1.5	 **8**	81
5	 **9**	E	16	 **10**  **11**	39 (4.6:1)
6	 **9**	F	24	 **10**  **11**	81 (1.2:1)
7	 **12**	B	24	 **13** +  **14**	94 (7.5:1)
8	 **15**	G	1.5	 **16**  **17**	62 (2.3:1)

[a] Conditions: A: [{RhCl(CO)$_2$}$_2$] (0.1 mol%), TFE (0.5 M), RT, CO (1 atm); B: [{RhCl(CO)$_2$}$_2$] (2.5 mol%), TFE (0.1 M), RT, CO (1 atm); C: [{RhCl(CO)$_2$}$_2$] (1 mol%), TFE (0.1 M), RT, CO (1 atm); D: [{RhCl(CO)$_2$}$_2$] (5 mol%), DCE (0.1 M), RT, CO (1 atm); E: [{RhCl(CO)$_2$}$_2$] (2.5 mol%), TFE (0.5 M), RT, CO (1 atm); F: [{RhCl(CO)$_2$}$_2$] (1 mol%), DCE (0.05 M), RT, CO (1 atm); G: [{RhCl(CO)$_2$}$_2$] (5 mol%), DCE (0.01 M), 60 °C, CO (4 atm).

In conclusion, the first examples of the diene–allene [2+2+1] cycloaddition reaction are reported, thus providing an efficient, selective, and operationally facile route (room temperature, 1 atm CO) to highly substituted alkylidenyl cyclopentanones. The reaction is chemoselective with respect to the allene as the proximal olefin is targeted. The use of the diene leads exclusively to the [2+2+1] cycloadduct instead of the product from the carbocyclization reaction, which has been reported with alkene–allenes (Scheme 1), thus resulting in a process of mechanistic and synthetic utility. An additional point of significance is that the reaction is accelerated in several cases when performed in TFE or in the presence of certain Brønsted acids, thus suggesting cocatalysis possibly involving CO protonation in the migratory-insertion step. Further investigations on this and other [*m*+*n*+o] cycloaddition reactions of dienes are ongoing.[19]

Experimental Section

Typical procedure: Preparation of the catalyst solution: $[\{RhCl(CO)_2\}_2]$ was weighed into an oven-dried test tube equipped with a magnetic stir bar, and TFE was added by syringe to make a 0.005 M solution. The test tube was capped with a septum, and the solution was stirred under a balloon of CO vented to a bubbler for 45 min.

Diene–allene **1** (21 mg, 0.063 mmol) was weighed into an oven-dried test tube equipped with a magnetic stir bar, TFE (0.114 mL) was added by syringe, and the test tube was capped with a rubber septum. The solution was stirred under a balloon of CO vented to a bubbler for 30 min. The catalyst solution ($[\{RhCl(CO)_2\}_2]$; 0.0127 mL, 0.000063 mmol) was added by syringe, and the reaction mixture was stirred under a balloon of CO for 8 h. The solution was concentrated by rotary evaporation, and the residue was purified by column chromatography on silica gel ($EtOAc/CH_2Cl_2$ 2:98). The product-containing fractions were combined and concentrated to give **2** (20.6 mg, 97 %) as a white solid; the compounds were chromatographically homogeneous.

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Keywords: allenes · cycloaddition · dienes · Pauson–Khand reaction · rhodium

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[2] a) P. A. Wender, N. C. Ihle, *J. Am. Chem. Soc.* **1986**, *108*, 4678–4679; b) P. A. Wender, N. C. Ihle, C. R. D. Correia, *J. Am. Chem. Soc.* **1988**, *110*, 5904–5906.

[3] For the first examples, see: a) P. A. Wender, T. E. Jenkins, *J. Am. Chem. Soc.* **1989**, *111*, 6432–6434; b) P. A. Wender, T. E. Jenkins, S. Suzuki, *J. Am. Chem. Soc.* **1995**, *117*, 1843–1844.

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[6] a) For the first report with alkynes, vinylcyclopropanes, and CO; see: P. A. Wender, G. G. Gamber, R. D. Hubbard, L. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 2876–2877; b) for the first report with allenes, vinylcyclopropanes, and CO; see: H. A. Wegner, A. de Meijere, P. A. Wender, *J. Am. Chem. Soc.* **2005**, *127*, 6530–6531.

[7] a) For the first report of a diene-yne [4+2+1] and dienyl Pauson–Khand reaction, see: P. A. Wender, N. M. Deschamps, G. G. Gamber, *Angew. Chem.* **2003**, *115*, 1897–1901; *Angew. Chem. Int. Ed.* **2003**, *42*, 1853–1857; b) for the first intermolecular dienyl Pauson–Khand reaction, see: P. A. Wender, N. M. Deschamps, T. J. Williams, *Angew. Chem.* **2004**, *116*, 3138–3141; *Angew. Chem. Int. Ed.* **2004**, *43*, 3076–3079; c) for the first [2+2+1] cycloaddition reaction of diene-enes and CO, see: P. A. Wender, M. P. Croatt, N. M. Deschamps, *J. Am. Chem. Soc.* **2004**, *126*, 5948–5949; d) Y. K. Chung, S. I. Lee, J. H. Park, S.-G. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 10190 (Y. K. Chung, S. I. Lee, J. H. Park, S.-G. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 2714–2715).

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[10] For a [4+2+2] cycloaddition reaction of diene-ynes and alkynes, see: S. R. Gilbertson, B. DeBoef, *J. Am. Chem. Soc.* **2002**, *124*, 8784–8788.

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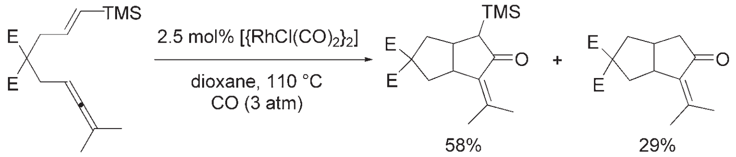
[13] T. Makino, K. Itoh, *J. Org. Chem.* **2004**, *69*, 395–405.

[14] Only the vinylsilane substrate below reacted in a [2+2+1] fashion:



[15] For the first example of a metal-catalyzed intramolecular diene–allene [4+2] cycloaddition reaction, see: P. A. Wender, T. E. Jenkins, S. J. Suzuki, *J. Am. Chem. Soc.* **1995**, *117*, 1843–1844.

[16] A similar rate enhancement was observed for the intermolecular [5+2] cycloaddition reaction of vinyl cyclopropanes and alkynes, see: P. A. Wender, C. M. Barzilay, A. J. Dyckman, *J. Am. Chem. Soc.* **2001**, *123*, 179–180.

[17] Although protic acids accelerate the [2+2+1] cycloaddition reaction, the Lewis acid $MgBr_2(OEt_2)$ does not have the same effect in this case.

[18] Similar isomerizations are observed in the [2+2+1] cycloaddition reaction of diene-enes and CO; ref. [7c].

[19] Full procedural details and characterization data are given in the Supporting Information.