Cycloaddition Reactions

Intermolecular Dienyl Pauson–Khand Reaction**

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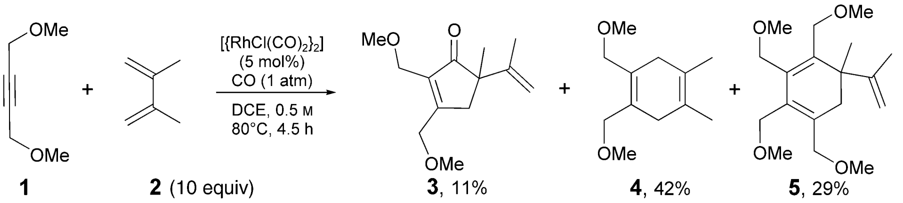
The design and discovery of new reactions that produce molecular complexity and value with step economy are preeminent goals of organic synthesis.[1] Our studies toward this objective have thus far resulted in new metal-catalyzed [4+4],[2] [4+2],[3] [5+2],[4] and [6+2][5] cycloadditions and three-component [5+2+1],[6] [4+2+1], and [2+2+1] reactions.[7] In the course of our studies on the rhodium(I)-catalyzed intramolecular dienyl [2+2+1] Pauson–Khand reaction, we observed that when a diene is used in place of an alkene the reaction rate is significantly accelerated.[7] The present study was aimed at determining whether this enhanced reactivity would enable the use of dienes in a catalyzed intermolecular [2+2+1] Pauson–Khand reaction.

The intermolecular Pauson–Khand reaction is a powerful complexity-increasing process for the construction of cyclopentenones, in which three carbon–carbon bonds and two stereocenters are produced in one operation. Although this reaction originally required stoichiometric amounts of cobalt,[8] catalytic versions based on Co^0,[9] Rh^I,[10] Ir^I,[11] and Ru^0[12] have recently emerged. The catalyzed intermolecular reaction often requires a reactive alkene. For example, Narasaka and co-workers reported that attempts to conduct a Rh^I-catalyzed intermolecular Pauson–Khand reaction with simple alkenes (styrene or 1-phenyl-3-butene) and 1-phenylpropyne (1 atm CO, dibutyl ether, 130 °C) were unsuccessful. Only more activated alkenes (norbornene and ethylene) gave [2+2+1] cycloaddition products, and then in only low to moderate yields.[10a] We now report that dienes can be used in an intermolecular [2+2+1] process to produce alkenyl cyclopentenones, often in high yields and from commercially or readily available starting materials.



1 **2** (10 equiv) **3**, 11% **4**, 42% **5**, 29%

Scheme 1. Competing [2+2+1], [4+2], and [2+2+2] cycloadditions.

Table 1: Studies of the [2+2+1] cycloaddition reaction of **1**, **2**, and CO.[a]

Entry	*T* [°C]	Solvent[b]	*c* [M][c]	CO [atm]	Equiv. of **2**	*t* [h]	Yield of **3** [%][d]
1	80	DCE	0.5	1	10	6	(11)[e]
2	60	DCE	0.5	1	10	6	> 99 (98)
3	60	TCE	0.5	1	10	7	96
4	60	dioxane	0.5	1	10	23	65
5	60	toluene	0.5	1	10	23	85
6	60	neat	–	1	10	9	86
7	60	DCE	0.5	2	10	22	51
8	60	DCE	0.5	0.5	10	6	(54)[f]
9	60	DCE	0.5	1	2	6	> 99
10	60	DCE	0.5	1	1.1	7	54
11	60	DCE	1	1	2	3	85

[a] [{RhCl(CO)$_2$}$_2$]: 5 mol%. [b] DCE = 1,2-dichloroethane; TCE = 1,1,2,2-tetrachloroethane. [c] Alkyne concentration. [d] Indicated yields were measured by GC; yields of the isolated product are denoted with parentheses. Unless otherwise specified, < 5% of **4** was observed by GC, and **5** was not observed. [e] Compounds **4** and **5** were obtained in 42% and 29% yield, respectively. [f] Compounds **4** and **5** were obtained in 14% and 9% yield, respectively.

Our initial investigation of the intermolecular reaction of alkyne **1** and diene **2** was marginally encouraging; it provided the [2+2+1] cycloadduct **3** as a single regioisomer but in only 11% yield along with the [4+2] cycloadduct **4** and the [2+2+2] cycloadduct **5** (Scheme 1). Studies to control the selectivity of the reaction explored the effect of variations in temperature, solvent, CO pressure, diene equivalents, and concentration (Table 1). A decrease in temperature resulted in a remarkable increase in the selectivity of the reaction, which now provided **3** in nearly quantitative yield (Table 1, entry 2). Under similar conditions (in accord with prior work),[10a] the use of norbornene in place of the diene gave the corresponding [2+2+1] adduct in only 4% yield (see Supporting Information). Other solvents studied afforded **3** in acceptable yields (Table 1, entries 3–5) but were not as efficient as DCE. Significantly, the reaction can be run successfully in the absence of solvent (Table 1, entry 6), thus avoiding atom-uneconomical solvent waste. Increasing the CO pressure to 2 atm resulted in a longer reaction and a decrease in yield, whereas lowering the CO pressure to 0.5 atm resulted in a shorter, less selective reaction (Table 1, entries 7 and 8). Decreasing the amount of diene to 2 equiv-

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[**] This research was supported by a grant (CHE-9800445) from the National Science Foundation. High-resolution mass spectra were provided by the University of California, San Francisco. X-ray crystallographic data was collected at the University of California, Berkeley (CHEXRAY). Fellowship assistance from Eli Lilly and Co. (N.M.D. and T.J.W.) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

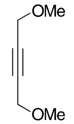
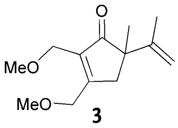
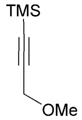
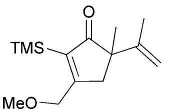
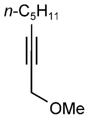
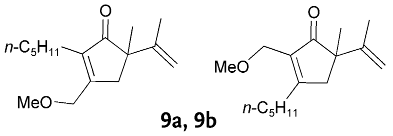
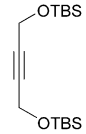
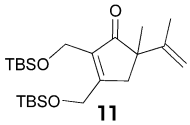
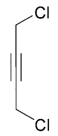
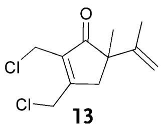
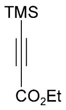
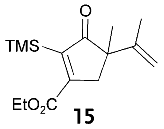
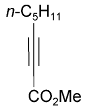
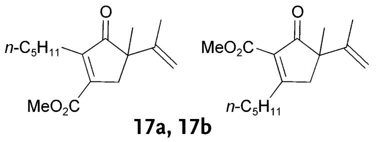
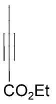
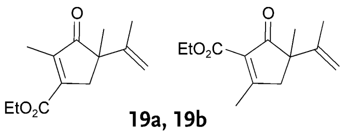
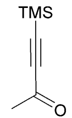
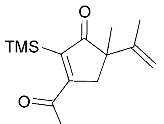
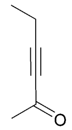
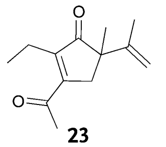
DOI: 10.1002/ange.200454117

alents had no affect on the yield; however, only a 54% yield was observed when 1.1 equivalents of **2** were used (Table 1, entries 9 and 10). Finally, an increase in the concentration of the reaction resulted in a slight decrease in yield (Table 1, entry 11).

Table 2 summarizes the effect of alkyne structure on the reaction. Various functionalities are tolerated, and under optimal conditions several alkynes underwent the desired reaction to provide the corresponding [2+2+1] cycloadducts in excellent yields (> 85%; Table 2, entries 1–4, 6). The reaction of the differentially substituted alkyne **6** proceeded in a completely regioselective fashion (Table 2, entry 2), whereas the reaction of the *n*-pentyl-substituted alkyne **8** gave a 1:1.6 mixture of regioisomeric products **9a** and **9b** (Table 2, entry 3). Replacement of the methyl ether groups with more synthetically versatile TBS ethers resulted in a slight decrease in yield (see Table 2, entries 1 and 4). The reaction of 1,4-dichlorobutyne (**12**) afforded the cycloadduct **13** in only a modest 38% yield (Table 2, entry 5). Ethyl trimethylsilylpropynoate (**14**) proved to be an excellent substrate for this reaction, which afforded the cycloadduct **15** in 95% yield with complete regioselectivity. Methyl 2-octynoate (**16**) and methyl 2-butynoate (**18**) reacted to give the corresponding mixtures of regioisomers in moderate yields. Ynones, such as **20** and **22**, were less effective substrates under the current conditions. A striking difference was also noticed between the reactions of the silylated ynone **20** and ynoate **14** (Table 2, entries 6 and 9); in the latter reaction the yield of the product was more than twice that in the former. Although not a problem in most cases, the cycloadduct **23** exhibited product-inhibitory behavior, thus accounting for the longer reaction time required for its formation (see Supporting Information for more details).

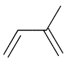
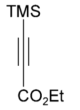
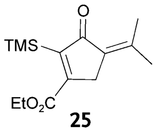
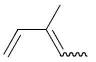
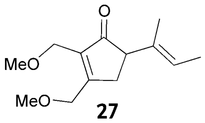
Variation in the substitution of the diene was next examined. Other methyl-substituted dienes did not react as efficiently as 2,3-dimethyl-1,3-butadiene under the optimized conditions described above. Isoprene and (*E*)-3-methyl-1,3-pentadiene reacted at the less substituted double bond to give the cyclopentenones **25** and **27** in moderate yields (Table 3), the former arising through isomerization of the initially formed product. 1,3-Butadiene did not undergo reaction, whereas the reactions of piperylene (1,3-pentadiene) and 2-methyl-1,3-pentadiene gave complex mixtures of products under

Table 2: Intermolecular dienyl Pauson–Khand reaction of various alkynes with **2** and CO.[a]

Entry	Alkyne	*t* [h]	Solvent[b]	Product(s)	Yield [%]
1	 **1**	6	DCE	 **3**	98[c]
2	 **6**	30	DCE	 **7**	93
3	 **8**	30	DCE	 **9a, 9b**	55, 35
4	 **10**	6	DCE	 **11**	87
5	 **12**	5	1:1 DCE/TCE	 **13**	38
6	 **14**	24	1:1 DCE/TCE	 **15**	95[c]
7	 **16**	28	DCE	 **17a, 17b**	31, 22
8	 **18**	28	DCE	 **19a, 19b**	18, 39
9	 **20**	32	TCE	 **21**	39
10	 **22**	72	TCE	 **23**	63

[a] [{RhCl(CO)$_2$}$_2$] (5 mol%), CO (1 atm), 60 °C, **2** (10 equiv). [b] Concentration of alkyne: 0.5 M. [c] Yield > 99% by GC analysis. TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

Table 3: Reactions of alkyl-substituted dienes.[a]

Entry	Diene	Alkyne	t [h]	Solvent[b]	Product	Yield [%]
1	 **24**	 **14**	68	1:1 TCE/DCE	 **25**	31
2	 (E)-**26**, (Z)-**26** (2.4:1)	 **1**	22	DCE	 **27**	37

[a] [{RhCl(CO)$_2$}$_2$] (5 mol%), CO (1 atm), 60°C, diene (10 equiv). [b] Concentration of alkyne: 0.5 M.

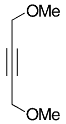
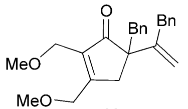
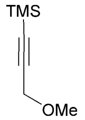
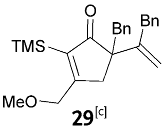
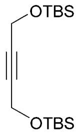
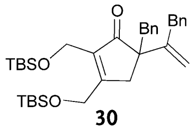
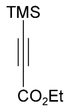
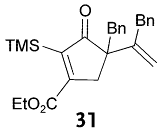
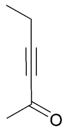
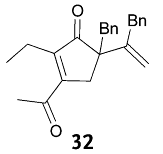
our previously optimized reaction conditions. Adjustment of the steric bulk of the diene, however, was well tolerated. Table 4 shows the results of some reactions of 2,3-dibenzyl-1,3-butadiene. Gratifyingly, these reactions were high yielding with only 2 equivalents of the diene.

Although the reaction of the free diol 2-butyne-1,4-diol led to no cycloadduct, the desired diol product can be readily obtained by desilylation of **11** (see Supporting Information). Moreover, although terminal alkynes did not undergo cyclization under the present conditions, the desilylation of silylated surrogates provides access to these cycloadducts (Scheme 2).

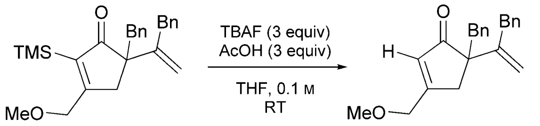
Since the process is biphasic, there is a possibility that if it were run on a larger scale complications could arise. As shown in Table 5, scale changes over two orders of magnitude did not significantly affect the outcome.

In summary, the first examples of a metal-catalyzed, intermolecular dienyl Pauson–Khand reaction have been reported. For many alkynes and 2,3-disubstituted 1,3-dienes, the reaction leads to the regioselective formation of alkenyl cyclopentenones under mild conditions and often in excellent yields from commercially or readily available starting materials. Further studies on this and other novel multicomponent processes are in progress.

Table 4: Reactions of 2,3-dibenzyl-1,3-butadiene.[a]

Entry	Alkyne	t [h]	Solvent[b]	Product	Yield [%]
1	 **1**	9	DCE	 **28**[c]	81
2	 **6**	24	DCE	 **29**[c]	98
3	 **10**	6	DCE	 **30**	75[d]
4	 **14**	24	1:1 DCE/TCE	 **31**	99[e]
5	 **22**	27	TCE	 **32**	61[f]

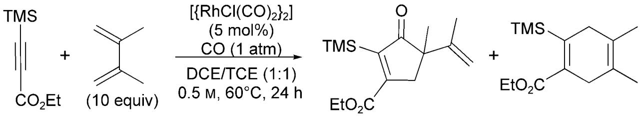
[a] [{RhCl(CO)$_2$}$_2$] (5 mol%), CO (1 atm), 60°C, diene (10 equiv). [b] Concentration of alkyne: 0.5 M. [c] Structure verified by X-ray crystallographic analysis.[13] [d] With 1.2 equivalents of the diene: 63% yield. [e] With 1.2 equivalents of the diene: 82% yield. [f] The [4+2] adduct was also obtained in 10% yield.



29 → **33**, 75%

Scheme 2. Desilylation of **29**. TBAF = tetrabutylammonium fluoride, RT = room temperature.

Table 5: Scalability of the reaction.



14 + **2** → **15** + **34**

Entry	**14** [mmol]	Yield of **15** [%][a]	Yield of **34** [%][a]
1	0.10	95	0
2	1.0	91	0
3	10.0	81	6

[a] Yield of isolated product.

Experimental Section

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

Typical procedure: Ethyl 3-trimethylsilylpropiolate (**14**; 180 μL, 170 mg, 1.00 mmol), 2,3-dimethyl-1,3-butadiene (1.13 mL, 822 mg, 10.0 mmol), 1,1,2,2-tetrachloroethane (distilled, 1.00 mL), and 1,2-dichloroethane (distilled, 1.00 mL), were mixed in an oven-dried 16 × 150-mm test tube with a stir bar. Chlorodicarbonylrhodium(I) dimer (19.4 mg, 50.0 μmol) was then added to the mixture. The test tube was capped with a septum and was evacuated and refilled with CO three times. The resulting solution was stirred at 60°C for 24 h under a CO atmosphere and then purified by flash column chromatography on silica gel (eluant: 2% diethyl ether in pentane). Product-containing fractions were identified and concentrated by rotary evaporation to yield the alkenyl cyclopentenone **15** (254 mg, 91%) as a yellow oil.

Received: February 26, 2004 [Z54117]

Keywords: cycloaddition · dienes · multicomponent reactions · Pauson–Khand reaction · rhodium

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[1] P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind.* **1997**, 765–769.

[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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