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Cyclopentadienone Synthesis by Rhodium(I)-Catalyzed [3 + 2] Cycloaddition Reactions of Cyclopropenones and Alkynes

Paul A. Wender,* Thomas J. Paxton, and Travis J. Williams

Departments of Chemistry and of Molecular Pharmacology, Stanford University, Stanford, California 94305-5080

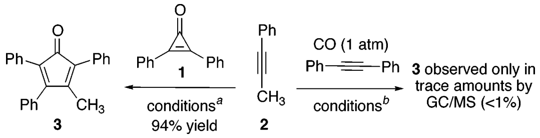
Received August 12, 2006; E-mail: email: wenderp@stanford.edu

Cyclopentadienones[1] (CPDs) are members of a diverse class of fascinating molecules with demonstrated value and even broader potential in synthesis, biology, materials science, and nanotechnology. They have been used as 2π or 4π components in cycloaddition approaches to highly substituted arenes,[2] as ligands in a range of coordination complexes,[3a] including ruthenium catalysts for reversible reductions of π systems,[3b,c] and as polymer cross-linking agents.[4] CPDs have been proposed as biosynthetic intermediates[5] and have been used as building blocks in the synthesis of natural products (e.g., hirsutic acid),[6a] molecules of theoretical interest (e.g., cubane and tetrahedrane),[6b,c] therapeutic leads,[7] and a remarkable variety of novel polymers, dendrimers, and devices.[8]

The synthesis of CPDs has been achieved in various ways: elimination reactions of substituted cyclopentenones,[9] condensations of propanones with α-diketones[10] and carbonylations of metallacyclopentadienes.[11] An approach of historical and contemporary significance involves the metal mediated or catalyzed formal [2 + 2 + 1] cycloaddition of 2 equiv of one alkyne and carbon monoxide (CO).[12] The use of two different alkynes in the catalyzed three-component process is not known and is complicated by the potential formation of up to 10 hetero- and homocoupled products. Many creative strategies have been developed to address these inherent chemo- and regioselectivity problems. Tethering two different alkynes has proven effective, and the use of temporary silicon tethers by Pearson simplifies the problem of post cycloaddition tether removal.[13] Boger and Nakamura have reported that cyclopropenone ketals, either thermally (via dipolar cycloaddition)[14a] or with a $Pd(OAc)_2$ catalyst,[14b] undergo cycloaddition with various π systems to provide CPDs after ketal hydrolysis. As part of our studies on metal-catalyzed cycloadditions, we have found that cyclopropenones serve as excellent 3-carbon components in Rh(I)-catalyzed [3 + 2] cycloadditions with a wide range of alkynes, providing CPDs selectively and in high yield.

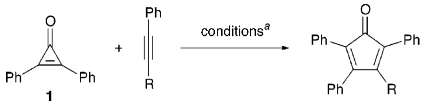
The essence of this new approach to CPDs is shown in Scheme 1. When commercially available diphenylcyclopropenone (**1**, 1.5 equiv) and alkyne **2** (1 equiv) are heated in toluene for 2 h at 80 °C with 1 mole percent $[RhCl(CO)_2]_2$, the [3 + 2] cycloadduct **3** is obtained in 94% yield. Significantly, only one regioisomer is produced, and its structure was established by X-ray crystallography. Moreover, the reaction is scalable by 2 orders of magnitude: ***3** can be prepared in 85% yield on a multigram scale.* In contrast, attempts to produce **3** through a [2 + 2 + 1] cycloaddition by heating alkyne **2**, diphenylacetylene, and $[RhCl(CO)_2]_2$ (5 mole percent) in toluene under an atmosphere of CO for a prolonged period at higher temperature (24 h, 110 °C) produced only trace amounts of **3** (<1% by GC/MS) along with traces of tetracyclone (**12**) and various quinones. Lower catalyst loading (0.1 mole percent) in the reaction of **1** and **2** is possible, but the yield is lower and the reaction time longer (69%, 9 h at 80 °C). In the absence of catalyst, the reaction of **1** and **2** does not occur. Other transition metal catalysts [$Pd(OAc)_2$, *trans*-$IrCl(CO)(PPh_3)_2$], Lewis acids [$Ti(O^iPr)_4$, $MgBr_2{\cdot}Et_2O$], or Brønsted acids (TsOH) afford at most trace quantities of **3**.

Scheme 1. The [3 + 2] and [2 + 2 + 1] Cycloadditions to Form CPDs



[a] Reaction run using 1 mol % $[RhCl(CO)_2]_2$, toluene (0.3 M), 80 °C, 2 h. [b] Reaction run using 5 mol % $[RhCl(CO)_2]_2$, toluene (0.3 M), 110 °C, 24 h.

Table 1. [3 + 2] Reactions of **1** with Substituted Phenylacetylenes



entry	R	conditions	product	yield[b]
1	CH_3	2 h, 80 °C	**3**	94%
2	CH_2OCH_3	4 h, 110 °C	**4**	97%
3	$C(O)CH_3$	18 h, 110 °C	**5**	91%
4	Cl	6 h, 110 °C	**6**	71%
5	$C(O)NH_2$	12 h, 80 °C	**7**	99%
6[c]	$CH(OH)CH_3$	23 h, 110 °C	**8**	64%
7[d]	CN	11 h, 110 °C	**9**	37%
8	CHO	3 h, 110 °C	**10**	42%
9[e]	C≡C−Ph	21 h, 60 °C	**11**	35%
10[f]	Ph	65 h, 80 °C	**12**	17%

[a] Reaction run using 1.5 equiv **1**, 1 mol % $[RhCl(CO)_2]_2$, toluene (0.3 M). [b] Isolated yields. [c] $[RhCl(CO)_2]_2$, 2 mol %. [d] $[RhCl(CO)_2]_2$, 5 mol %. [e] $[RhCl(CO)_2]_2$, 10 mol %. [f] Compound **1**, 1 equiv.

This Rh(I)-catalyzed [3 + 2] cycloaddition tolerates a broad range of aryl alkyne substituents (Table 1): methyl-, methoxymethyl-, methyl ketone-, chloride-, and amide-functionalized phenylacetylenes all react efficiently and regioselectively (entries 1−5). Free alcohol, nitrile, aldehyde, and even 1,3-diyne moieties also react to provide CPDs with high regioselectivity (entries 6−9). In the case of diphenyl-1,3-butadiyne, formation of **11** is accompanied by formation of its decarbonylative [4 + 2] dimer (**11a**, not shown) and higher oligomers (Supporting Information). In each case, the observed regiochemistry is consistent with observations of Pauson−Khand reactions of analogous aryl alkynes.[15] Diphenylacetylene reacts slowly with **1** (entry 10). Terminal alkynes (phenylacetylene, 1-octyne, and acetylene) and dimethyl acetylene dicarboxylate do not afford CPDs under these conditions. In these cases, only decarbonylation of **1** and trimerization of the alkyne are observed.

Functionalized aryl alkynes also react efficiently (Table 2). The electron-rich alkyne **13** selectively provides **14** in 94% yield (entry 1). Similarly, electron-deficient alkynes **15**, **17**, and **19** afford cycloadducts **16**, **18**, and **20**, respectively, in high yields (entries

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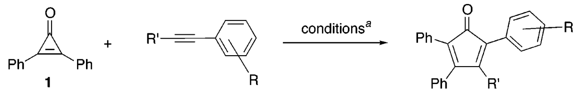
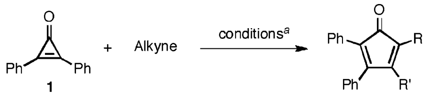
Table 2. [3 + 2] Reactions of **1** with Substituted Arylacetylenes

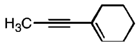
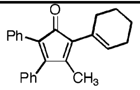
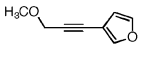
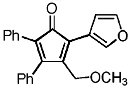
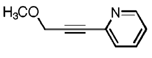
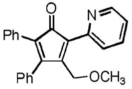
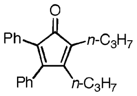
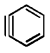
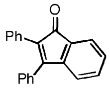


entry	R, R′	conditions	product	yield^b
1	*p*-OCH$_3$, CH$_3$ (**13**)	2.5 h, 80 °C	**14**	94%
2	*p*-C(O)CH$_3$, CH$_2$OCH$_3$ (**15**)	5 h, 110 °C	**16**	78%
3	*p*-CF$_3$, CH$_3$(**17**)	6.5 h, 110 °C	**18**	91%
4	*o*-F, CH$_3$(**19**)	20 h, 80 °C	**20**	77%
5	*o*-CH$_3$, CH$_3$(**21**)	5 h, 110 °C	**22**	98%

[a] Reaction run using 1.5 equiv **1**, 1 mol % [RhCl(CO)$_2$]$_2$, toluene (0.3 M). [b] Isolated yields.

Table 3. [3 + 2] Reactions of **1** with Other Alkynes



entry	alkyne	conditions	product	yield^b
1	 **23**	3 h, 80 °C	 **24**	88%
2	 **25**	17.5 h, 110 °C	 **26**	52%
3	 **27**	20 h, 80 °C	 **28**	52%
4	$n\text{-}C_3H_7C\equiv C\text{-}n\text{-}C_3H_7$ **29**	7.5 h, 80 °C	 **30**	65%
5^c	 **31**	3.5 h, 120 °C	 **32**	69%

[a] Reaction run using 1.5 equiv of **1**, 1 mol % [RhCl(CO)$_2$]$_2$, toluene (0.3 M). [b] Isolated yields. [c] [RhCl(CO)$_2$]$_2$, 3 mol %; benzyne is prepared in situ from 1,2-diiodobenzene and zinc in ethanol (1.7 M).

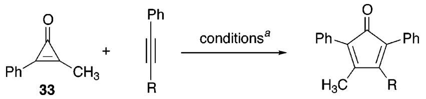
2−4). It is noteworthy that ortho-substituted aryl alkynes (**19** and **21**, entries 4−5) are well tolerated.

Importantly, the reaction is not limited to aryl alkynes. Enynes, heteroaryl alkynes, benzyne, and even 4-octyne all undergo selective [3 + 2] cycloadditions (Table 3). For example, enyne **23** can be converted to **24** in 88% yield (entry 1). Furan **25** and pyridine **27** both react to give CPDs **26** and **28**, respectively (entries 2−3). 4-Octyne gives **30** in 65% yield, and benzyne (prepared from the in situ reduction of 1,2-diiodobenzene, see Supporting Information) reacts to provide indenone **32** in a 69% yield (entries 4−5).

The reaction also works with arylalkylcyclopropenones. For example, methylphenylcyclopropenone (**33**), prepared in two steps from 1-phenyl-2-butanone, reacts regioselectively with alkynes to give the corresponding CPDs (Table 4). **33** reacts with diphenylacetylene to give **3** in 57% yield (entry 1) and alkynes **2** and **35** react with **33** to give cycloadducts **34** and **36** in 44% and 61% yields, respectively (entries 2−3).

In summary, the Rh(I)-catalyzed [3 + 2] cycloaddition of cyclopropenones and alkynes is shown to provide an efficient and regioselective route to CPDs. Diaryl- and arylalkylcyclopropenones can be used as the 3C component in combination with aryl-, heteroaryl-, and dialkyl-substituted alkynes as 2C components providing CPDs often in high yields and in multigram quantities.

Table 4. [3 + 2] Reactions of **33** with Alkynes



entry	R	conditions	product	yield^b
1^c	Ph	17.5 h, 110 °C	**3**	57%
2^c	CH$_3$ (**2**)	7.5 h, 110 °C	**34**	44%
3^d	C(O)CH$_3$ (**35**)	5 h, 110 °C	**36**	61%

[a] Toluene (0.3 M). [b] Isolated yields. [c] 1.1 equiv **33**; 1 mol % [RhCl(CO)$_2$]$_2$. [d] 1.1 equiv **33**; 5 mol % [RhCl(CO)$_2$]$_2$.

The functional group tolerance observed among alkynes and the broad range of alkynes highlight important distinctions between reactions of cyclopropenones and cyclopropenone ketals. This [3 + 2] cycloaddition offers a unique and versatile route to a range of CPDs and novel CPD-derived scaffolds, polycycles, and materials. Further studies will be reported in due course.

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Supporting Information Available: Experimental details and characterization data for all cycloadducts, including X-ray information for **3**, **11a**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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