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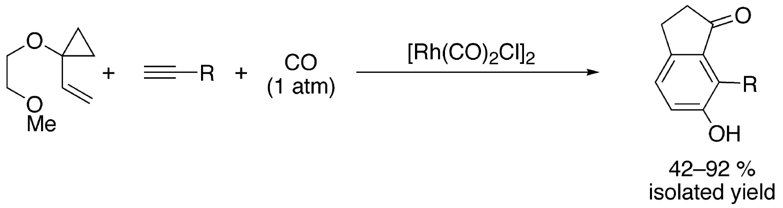

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Multicomponent Cycloadditions: The Four-Component [5+1+2+1] Cycloaddition of Vinylcyclopropanes, Alkynes, and CO

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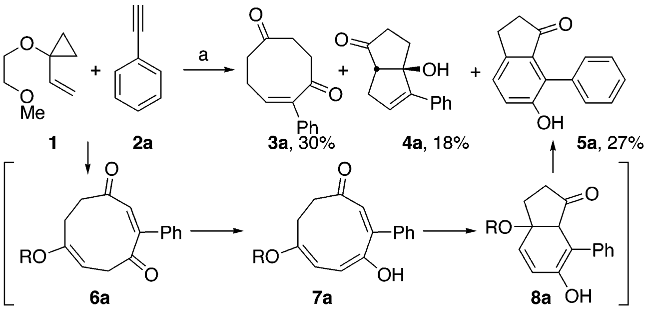
A preeminent goal of organic synthesis is to achieve structural complexity and function with step economy.[1,2] Multicomponent cycloadditions provide a means to realize these ends.[3] We previously reported the first examples of metal-catalyzed [4+4] cycloadditions of bis-dienes,[4] [4+2] cycloadditions of diene-ynes and diene-allenes,[5] [5+2] cycloadditions of vinylcyclopropanes (VCPs) and π-systems,[6] and [6+2] cycloadditions of vinylcyclobutanones and π-systems.[7] More recently, we have begun to explore whether these and other two-component processes[8] could be converted to new multicomponent [$m + n + o$...($+x$)] cycloadditions through the trapping of metallacyclic intermediates with one or more additional components. These studies have, thus far, produced the first [5+2+1] cycloadditions,[3k] a novel dienyl Pauson−Khand-like ([2+2+1]) reaction[3l−n] and a new [4+2+1] cycloaddition,[3l] based on the capture of intermediates in [5+2] and [4+2] cycloadditions. We report herein the first examples of a four-component cycloaddition involving VCPs, terminal alkynes and CO.

In the course of our studies on the [5+2+1] cycloaddition of VCPs, alkynes, and CO, it was found that reaction of VCP **1**[6h] and phenylacetylene (**2a**) with [Rh(CO)$_2$Cl]$_2$ under 1 atm CO (Scheme 1) produced the expected three-component cycloadduct cyclooctenedione **3a** (30%) and its transannular closure product bicyclo[3.3.0]-octenone **4a** (18%), along with a new product **5a** (27%). Spectroscopic analysis of **5a** led to its assignment as a phenylhydroxyindanone, which was confirmed by X-ray crystallography. Significantly, **5a** is a four-component product, putatively arising through the cycloaddition of a VCP, an alkyne, and two CO units to give the nine-membered ring intermediate **6a**. Tautomerization of **6a** to triene **7a**, followed by electrocyclic closure to **8a** and elimination driven by aromatization provides a novel, albeit plausible, route to **5a**.

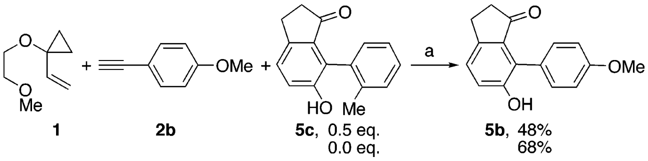
The significant complexity increase generated by this new reaction, and the usefulness of biaryl and indanone derivatives as ligands for metal complexes and catalysts,[9] sensors,[10] scaffolds for drug discovery and libraries,[11] and building blocks for synthesis,[12] prompted further investigation of this process. During the course of these studies a beneficial effect of using solvent systems from which the hydroxyindanone products **5** precipitate during the course of the reaction was observed. This suggested that yields of the four-component process might be lowered by product interference in reactions in which the products remained soluble throughout. Control experiments indeed showed that interference by the product hydroxyindanone **5** influences the efficiency of the four-component process (Scheme 2). Additional controls indicated that VCP **1** is unstable to the reaction conditions in the presence of the hydroxyindanones **5** (see Supporting Information). In accordance with these observations, use of excess VCP in conjunction with solvent systems favoring in situ precipitation of the products **5** afforded conditions that allowed for efficient four-component reactions with a variety of terminal alkynes (Table 1, 14 examples).

Scheme 1 Initial Results with Phenylacetylene **2a**[a]



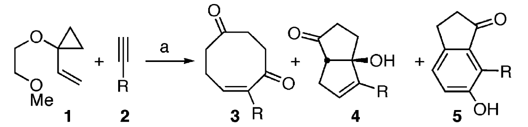
[a] Conditions: a) CO (1 atm), [Rh(CO)$_2$Cl]$_2$ (2.5 mol %), 1,4-dioxane (0.5 M, **1**), 60 °C; H$_3$O$^+$. Isolated yields; R = −CH$_2$CH$_2$OCH$_3$.

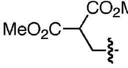
Scheme 2. Product Interference in the Four-Component Process[a]



[a] Conditions: a) CO (1 atm), [Rh(CO)$_2$Cl]$_2$ (5 mol %), **2b** (1.5 equiv) toluene (0.1 M in **1**), 60 °C; silica gel.

Table 1. Four-Component Reactions of Terminal Alkynes[a]



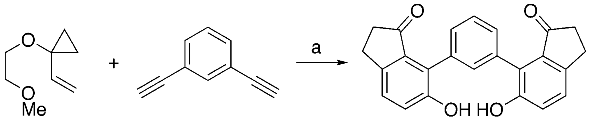
	alkyne R =	solvent[b]	t	3	4	5
1.	*p*-Ph-Ph–, **2d**	toluene	24h	0%	0%	92%
2.	*m*-Ph-Ph–, **2e**	1:3 tol:dec	48h	3%	8%	83%
3.	*p*-MeO-Ph–, **2b**	1:3 tol:dec	48h	0%	5%	75%
4.	*m*-MeO-Ph–, **2f**	toluene	48h	0%	9%	59%
5.[c]	*o*-MeO-Ph–, **2g**	toluene	48h	16%	0%	42%
6.	*p*-Me-Ph–, **2h**	1:3 tol:dec	48h	0%	4%	65%
7.	Ph–, **2a**	toluene	48h	0%	7%	57%
8.	*p*-CF$_3$-Ph–, **2i**	1:3 tol:dec	48h	0%	8%	71%
9.	*p*-F-Ph–, **2j**	1:3 tol:dec	48h	0%	7%	81%
10.	*m*-F-Ph–, **2k**	1:3 tol:dec	48h	0%	4%	65%
11.	*p*-Br-Ph–, **2l**	1:1 tol:dec	48h	0%	10%	74%
12.	*p*-(TBSCC)-Ph–, **2m**	1:3 tol:dec	36h	0%	0%	78%
13.[c]	 $(MeO_2C)_2CHCH_2$– **2n**	toluene	24h	6%	0%	50%
14.[c]	PhCH$_2$CH$_2$–, **2o**	toluene	24h	0%	12%	43%

[a] Conditions: a) CO (1 atm), [Rh(CO)$_2$Cl]$_2$ (2.5 mol %), **1** (2.0 equiv), 0.1 M in **2**, 60 °C; H$_3$O$^+$. [b] Toluene:decane mixtures. [c] [Rh(CO)$_2$Cl]$_2$ (5 mol %).

While para substituted aryl alkynes generally gave good to excellent yields, substitutents at the meta or ortho positions led to attenuated yields, presumably due to the increased solubility of the four-component products **5**. Halogen groups are tolerated (Table

10.1021/ja042728b CCC: $30.25

Scheme 3. Bidirectional, Seven-Component Reaction[a]

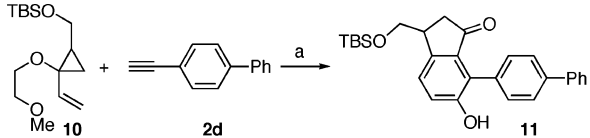


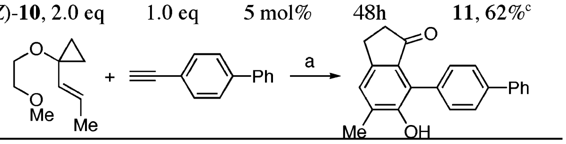
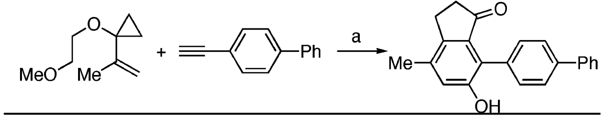
1 **2p** (0.5 eq) **9**, 56%

[a] Conditions: a) CO (1 atm), 5 mol % $[Rh(CO)_2Cl]_2$, toluene (0.1 M, **1**), 60 °C, 48 h; silica gel.

1, entries 9−11), allowing for the possibility of further diversification following the [5+1+2+1] cycloaddition. Aliphatic alkynes also can be used as substrates in the four-component process (entries 13, 14), although under these conditions they are generally less efficient. The four-component reaction is completely chemoselective for terminal alkynes over internal alkynes, as illustrated by the good yield with di-yne **2m**, with complete selectivity for the terminal alkyne. Bis-ethynylbenzene **2p** (Scheme 3) was shown to be effective in a bi-directional [5+1+2+1] cycloaddition producing the bridged bis-indanone **9** in an overall yield of 56%, *with the creation of ten C−C bonds from seven components in a single operation*.

Table 2. Four-Component Reactions of Substituted VCPs[a]



	VCP	**2d**	$[Rh]_2$	*t*	Yield
1.	(*E*)-**10**, 2.0 eq	1.0 eq	5 mol%	96h	**11**, 52%[b]
2.	(*Z*)-**10**, 2.0 eq	1.0 eq	5 mol%	48h	**11**, 62%[c]
					
3.	**12**, 1.0 eq	1.5 eq	10 mol%	60h	**13**, 74%
					
4.	**14**, 2.0 eq	1.0 eq	10 mol%	96h	**15**, 64%

[a] Conditions: (a) CO atm), $[Rh(CO)_2Cl]_2$ (x mol %), toluene (0.1 M), 60 °C; silica gel. [b] Regioselectivity 33:1. [c] Regioselectivity 9:1.

Substitution of the VCP is also tolerated, leading predictably to substituted hydroxyarylindanone products in good yields (Table 2). As observed in our previous work, these reactions proceed with selective cleavage of the less substituted cyclopropane bond.[13]

In conclusion, a new four-component cycloaddition reaction of VCPs, terminal alkynes and CO has been developed, yielding hydroxyindanone products in generally good to excellent yields, putatively through an initially formed nine-membered ring intermediate. Further studies on this unique process and applications of the hydroxyindanone products as molecular scaffolds and novel ligands are underway.

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Supporting Information Available: Representative procedure and characterization data for products **5**, **9**, **11**, **13**, **15**. X-ray data for compound **5a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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