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Cobalt Octacarbonyl-Catalyzed Scalable Alkyne Cyclotrimerization and Crossed [2 + 2 + 2]-Cycloaddition Reaction in a Plug Flow Reactor

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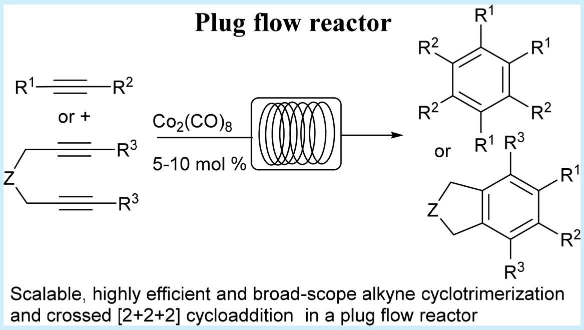
Supporting Information

ABSTRACT: Cobalt-catalyzed alkyne cyclotrimerization and crossed [2 + 2 + 2] cycloadditions are developed in a plug flow reactor. The protocol generally uses 5 mol % of $Co_2(CO)_8$ and is scalable at least at multigram scale. Efficient and scalable use of $Co_2(CO)_8$ for crossed reactions of diynes and alkynes has hardly any precedent.



Metal-catalyzed [2 + 2 + 2] cycloadditions are an atom-economical and efficient way to produce highly functionalized carbo- and heterocycles. Starting from various unsaturated substrates, such as alkynes, nitriles, alkenes, cumulenes, and heterocumulenes, it allows the synthesis of a great variety of aromatic and nonaromatic cycles. This process is catalyzed by complexes of more than 17 different metals.[1] Cobalt complexes have proven to be versatile reagents in the field of [2 + 2 + 2] chemistry.[2] The cobalt-mediated reactions produce cobalt-complexed products that can undergo further transformations. Vollhardt et al. reported the use of $CpCoL_2$ ($L = CO$ or $CH_2{=}CH_2$) to effect cyclotrimerizations of alkynes,[3] including the use of alkynylboronates.[4] Double bonds forming part of the aromatic heterocycles were used as unsaturated partners in [2 + 2 + 2] cycloadditions.[5] In addition, catalytic uses of these cobalt catalysts were reported,[6] including intermolecular alkyne cyclotrimerizations using simple catalytic systems based on CoX_2[7] and, more recently, pyridine synthesis.[8] Asymmetric reactions were first reported by Heller et al. using a molecularly defined Co(I) precatalyst, a chiral menthyl-substituted indenyl Co(I) complex.[9] Recently, an in situ formed catalytic system based on cobalt(II) salts and chiral P,N-ligands was developed by Hapke et al. for the asymmetric cyclization of triynes.[10] $Co_2(CO)_8$ is a proven versatile reagent for the selective formation of multiple carbon−carbon bonds in a single chemical step. In addition to its main synthetic application, the Pauson-Khand reaction, some [2 + 2 + 2] reactions are catalyzed by this unexpensive and easy to handle reagent.[11] Thus, cycloalkenes were used in crossed cyclizations with diynes, giving tandem [2 + 2 + 2]/[4 + 2] cyclizations using cobalt carbonyl as the catalyst.[12] Some examples of cyclotrimerization of alkynes have been reported.[13]

Continuous technology has shown great advantages compared with batch flask conditions, in particular, for scaled-up processes.[14] The environmental benefits of flow chemistry over traditional batch chemistry, such as the excellent heat and mass transfer or the efficiency in mixing in small volumes, have attracted much attention.[15] In addition, these methodologies allow process intensification, for instance, running reactions under extreme process windows and using high temperatures and elevated pressures.[16] Various metal-catalyzed reactions using a flow microreactor and continuous systems have been described.[17] We have recently shown a general protocol for both inter- and intramolecular Pauson-Khand reaction in a microreactor.[18]

Herein, we present the first scalable end efficient cobalt octacarbonyl-catalyzed [2 + 2 + 2] cycloadditions performed in a plug flow stainless steel reactor. The scope includes cyclotrimerizations of terminal and internal alkynes with high selectivity and crossed reactions between diynes and alkynes.

We first explored the trimerization of phenylacetylene. When terminal alkynes are used, achieving intermolecular reactions in a highly regioselective manner is difficult. The formation of a mixture of 1,2,4- and 1,3,5-regioisomers, being the first the major product, is common.[19] Table 1 (entries 1−9) shows the optimization study with this substrate. Total conversion was achieved with reaction temperatures greater than 90 °C and

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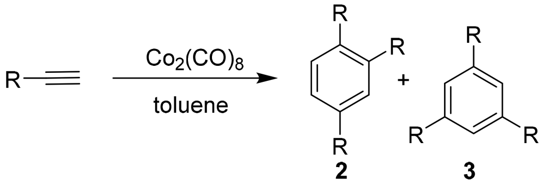
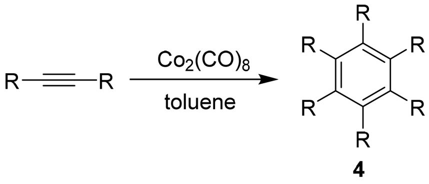
Table 1. Cyclotrimerizations of Terminal Alkynes



entry[a]	R	prod.	temp (°C)	rt (min)	cat. (mol %)	conv[b]	yield (%)[c]	ratio **2**/**3**[d]
1	Ph	**2a**	90	15	5	>99	88	95:5
2	Ph	**2a**	90	10	5	85	70	95:5
3	Ph	**2a**	110	10	5	>99	98	98:2
4	Ph	**2a**	130	10	2	93	78	98:2
5	Ph	**2a**	150	5	2	99	90	99:1
6	Ph	**2a**	180	3.5	2	>99	98	99:1
7	Ph	**2a**	180	1.5	2	>99	94	99:1
8[e]	Ph	**2a**	180	60	5	>99	80	90:10
9[f]	Ph	**2a**	150	60	5	70	55	92:8
10[g]	Ph	**2a**	180	3.5[h]	2	>99	92	99:1
11	C_4H_9	**2b**	180	3.5	2	>99	93	95:5
12	4-MeC_6H_4	**2c**	180	3.5	2	>99	94	99:1
13	4-FC_6H_4	**2d**	180	3.5	2	>99	99	100:0
14	4-BrC_6H_4	**2e**	180	3.5	2	>99	96	100:0
15	4-$Me_2NC_6H_4$	**2f**	180	3.5	2	15		
16	4-$Me_2NC_6H_4$	**2f**	230	5	5	>99	87	97:3
17	4-$NO_2C_6H_4$	**2g**	230	5	5	95	83	100:0
18	4-$NO_2C_6H_4$	**2g**	280	5	5	decomp.		
19	Cy	**2h**	180	3.5	2	50	39	95:5
20	Cy	**2h**	230	5	5	>99	84	96:4

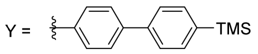
[a] Conditions for all experiments: 0.4–0.5 mmol/mL substrate concentration (1.6 mL used in each experiment), 20 bar system pressure, 8.1 mL reactor volume. [b] By NMR. [c] In **2**/**3** mixtures after chromatography. [d] Determined by GC–MS. [e] Batch test in sealed tube. No conversion was observed in a reaction in refluxing toluene after 8 h. [f] Batch test under MW heating in a 4:1 toluene/MeOH mixture. [g] Scale-up experiment with 10 g of substrate. [h] Total reaction time: 105 min. When the purification was achieved using a metal scavenger cartridge, total time was 108 min, yield was 96%, purity of **2a** 96% by NMR with duroquinone as the internal standard.

Table 2. Cyclotrimerizations of Internal Alkynes



entry[a]	R	prod.	temp (°C)	rt (min)	cat. (mol %)	conv[b]	yield (%)[c]
1	$(CH_2)_2CH_3$	**4a**	180	3.5	5	79	60
2	$(CH_2)_2CH_3$	**4a**	180	10	5	86	73
3	$(CH_2)_2CH_3$	**4a**	200	5	5	>99	86
4	$(CH_2)_2CH_3$	**4a**	230	5	5	>99	96
5	$(CH_2)_2CH_3$	**4a**	230	10	2	86	78
6[d]	$(CH_2)_2CH_3$	**4a**	230	5[e]	5	>99	87
7	Ph	**4b**	230	5	5	80	68
8	Ph	**4b**	230	10	5	>99	94
9	CH_2OCH_3	**4c**	230	5	5	>99	99
10	$COOCH_3$	**4d**	230	15	7.5	>99	82
11[f]	$COOCH_3$	**4d**	270	20	5	>99	79
12	Y[g]	**4e**	230	20	10	85	71

[a] Conditions for all experiments: 0.5–0.3 mmol/mL substrate concentration (1.6 mL used in each experiment), 20 bar system pressure, reactor volume: 8.1 mL. [b] By NMR. [c] In pure product. [d] Scale-up experiment with 10 g of substrate. [e] Total reaction time: 116 min. When the purification was achieved using a metal scavenger cartridge total time was 119 min, yield 91%, purity of **4a** 97%. [f] 30 bar system pressure. [g]



catalyst loadings of 2–5 mol %. Yields were excellent under conditions of entries 3 and 6, the first with lower temperature and the latter with shorter resident time and only 2 mol % of catalyst. Batch tests were carried out for comparison. Under refluxing toluene, no conversion was observed after 8 h, whereas in a sealed tube at 180 °C, the reaction was completed in 1 h (entry 8); when using MW heating and after 60 min, the conversion achieved was 70% (entry 9). Once the best conditions were found, entry 10 shows the result of a scaled-up reaction where 10 g of phenylacetylene was efficiently transformed into **2a** in 92% yield after a total reaction time of 105 min. For this reaction, connecting a cartridge with a metal scavenger at the end of the system allowed us to obtain **2a** in 96% purity. The procedure was applied to seven terminal alkynes (entries 11–20). We could reach good yields (83–99%) in all cases. However, with some substrates (entries 16, 17, and 20), we had to increase the reaction temperature to 230 °C and the residence time to 5 min. The 1,2,4-isomer **2** was the exclusive product in some examples, or was the greatest majority, as shown by GC–MS analysis. The method is highly efficient and

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selective under low catalyst loadings. These are among the highest regioselectivities reported to date for this reaction. It has been proposed that the intensification conditions used in microreactors, in particular, the high pressures used, may have an impact not only on the reaction kinetics but also on the selectivity.[16a]

In Table 2, we summarize the reactions with internal alkynes. 4-Octyne was used to optimize conditions (entries 1−5). Using 5 mol % of catalysts, 5 min of residence time, and 230 °C, we could reach a 96% yield of the final hexapropylbenzene **4a** (entry 4). There was no observable conversion in the batch tests, both under reflux (8 h) or under MW heating (150 °C) after 1 h. Under the conditions of entry 4, 10 g of the alkyne was transformed after 116 min total reaction time into the final product with an 87% yield (entry 6). The procedure was applied to four more internal alkynes (entries 7−12), achieving yields between 71 and 99%. In some cases, the residence time was increased to a maximum of 20 min, and catalyst loading needed to be increased up to 10 mol % (entry 12). These reactions are known to give solubility problems as in the case of entries 8 and 12. The plug flow reactor (PFR) allows installation of a thermostated line at the exit of the reactor to solubilize the product, avoiding precipitation and obstructions. Product **4e** is an interesting representative of a star-shaped product and was described as a polyphenylene dendrimer precursor.[12]

We applied our conditions to two nonsymmetric alkynes (Scheme 1). Products **4f** have been previously described as

Scheme 1. Regioselective Synthesis of Hexasubstituted Benzenes

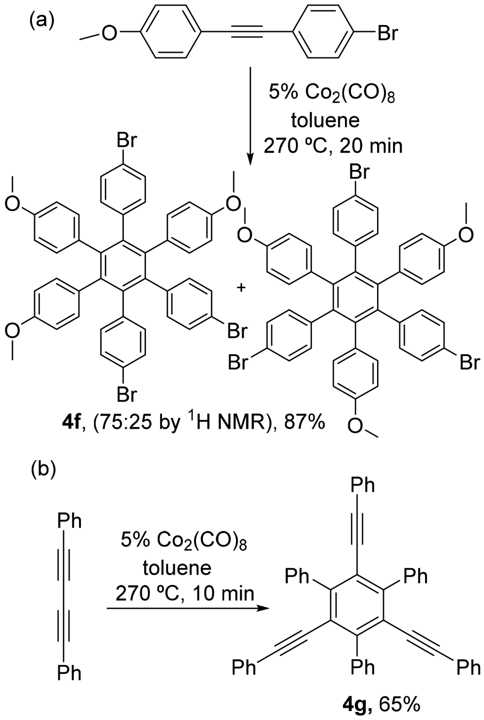
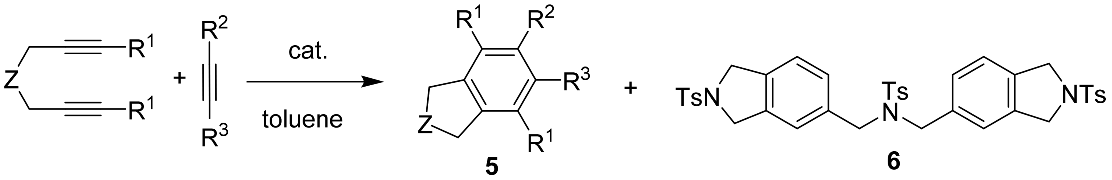


Table 3. Crossed [2 + 2 + 2] Cycloadditions of Diynes and Alkynes



5 **6**

entry[a]	Z	R^1	R^2	R^3	prod.	cat.	cat. (mol %)	temp (°C)	rt (min)	alkyne equiv	conv[b]	yield (%)[c] of **5** (**6**)
1	TsN	H	Ph	H	**5a**	$Co_2(CO)_8$	10	130	10	3	62	38
2	TsN	H	Ph	H	**5a**	$Co_2(CO)_8$	10	150	10	5	>99	72
3	TsN	H	Ph	H	**5a**	$Co_2(CO)_8$	10	180	3.5	3	>99	68
4	TsN	H	Ph	H	**5a**	$Co_2(CO)_8$	10	230	5	5	>99	20 (30)
5	TsN	H	Ph	H	**5a**	$Mo(CO)_6$	10	180	3.5	3	6	
6	TsN	H	Ph	H	**5a**	$Co_3(CO)_9\mu^3CH$	10	180	3.5	3	>99	28 (35)
7	TsN	H	Ph	H	**5a**	$Co_4(CO)_{12}$	10	180	3.5	3	>99	67
8	TsN	H	Ph	H	**5a**	$Rh_2(CO)_4Cl_2$	10	180	3.5	3	98	71 (10)
9	TsN	H	Ph	H	**5a**	$Ru_3(CO)_{12}$	10	180	3.5	3	61	28
10	TsN	H	Ph	H	**5a**	$CpCo(CO)_2$	10	180	3.5	3	45	21
11	TsN	H	Ph	H	**5a**	$Cr(CO)_6$	10	180	3.5	3	<5	
12[d]	TsN	H	Ph	H	**5a**	$Co_2(CO)_8$	10	180	60	3	70	35
13[e]	TsN	H	Ph	H	**5a**	$Co_2(CO)_8$	10	150	30	3	35	26
14	TsN	H	$(CH_2)_3CH_3$	H	**5b**	$Co_2(CO)_8$	10	150	10	3	>99	35
15	TsN	H	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	**5c**	$Co_2(CO)_8$	10	230	20	3	>99	51
16	TsN	CH_3	Ph	H	**5d**	$Co_2(CO)_8$	10	230	5	5	>99	70
17	TsN	CH_3	$(CH_2)_3CH_3$	H	**5e**	$Co_2(CO)_8$	10	230	10	5	>99	54
18	TsN	CH_3	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	**5f**	$Co_2(CO)_8$	10	230	10	3	>99	61
19	$(EtO_2C)_2C$	H	Ph	H	**5g**	$Co_2(CO)_8$	10	200	10	3	>99	85
20[f]	$(EtO_2C)_2C$	H	Ph	H	**5g**	$Co_2(CO)_8$	10	200	10	3	>99	68
21	$(EtO_2C)_2C$	H	$(CH_2)_3CH_3$	H	**5h**	$Co_2(CO)_8$	10	180	10	3	>99	82
22	$(EtO_2C)_2C$	H	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	**5i**	$Co_2(CO)_8$	10	230	10	3	>99	58
23	$(EtO_2C)_2C$	CH_3	Ph	H	**5j**	$Co_2(CO)_8$	10	230	10	5	>99	78
24	$(EtO_2C)_2C$	CH_3	$(CH_2)_3CH_3$	H	**5k**	$Co_2(CO)_8$	10	230	10	5	>99	75

Table 3. continued

entry[a]	Z	R^1	R^2	R^3	prod.	cat.	cat. (mol %)	temp (°C)	rt (min)	alkyne equiv	conv[b]	yield (%)[c] of **5** (**6**)
25	$(EtO_2C)_2C$	CH_3	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	**5l**	$Co_2(CO)_8$	10	230	10	3	>99	70

[a] Conditions for all experiments: 0.13 mmol/mL substrate concentration, 20 bar system pressure, 8.1 mL reactor volume. [b] By NMR. [c] In pure product. [d] Batch test in a sealed tube. [e] Batch test under MW heating in a 4:1 toluene/MeOH mixture, 25% of starting diyne was recovered. [f] Scale-up experiment with 5 g of substrate, total reaction time 210 min.

precursors of covalent organic capsules.[20] They were prepared in ca. 30% yield by heating the starting alkyne in dioxane at 110 °C for 2 weeks. We obtained an 87% yield under the conditions described in Scheme 1a. Product **4g** was prepared as a single 1,3,5-product in 65% yield (Scheme 1b).

Cobalt carbonyl has hardly been used[11] for crossed cyclotrimerization reactions between diynes and alkynes, possibly because it gives alkyne cyclotrimerization over the crossed products. However, as with the PFR conditions, the reaction mixture is continuously loaded into the reactor, and we envisioned the possibility of using this catalyst for this variation of the [2 + 2 + 2] reaction. Thus, *N*,*N*-dipropargyltosylamide was reacted with phenylacetylene under different conditions (Table 3, entries 1−9). A careful selection of reaction temperature, alkyne equivalents, and residence time was necessary to favor the crossed product over the alkyne or the diyne trimer **6**. The best result (72−86% yields) was achieved at 150−180 °C, with 5−3 equiv of alkyne, 10−3.5 min of residence time, and 10 mol % of catalyst (entries 2 and 3, respectively). Different metal carbonyls were used under these conditions (entries 5−11). $Rh_2(CO)_4Cl_2$ and $Co_4(CO)_{12}$ gave results similar to those of $Co_2(CO)_8$ (entries 7 and 8), leading the others to complex mixtures of decomposition products. Two batch reactions were carried out, giving poor results both in a sealed tube or under MW heating (entries 12 and 13). The method was applied to four different diynes (two of them substituted at the alkyne end) and three different alkynes (entries 14−25). Yields were variable, with better performance of phenylacetylene over 1-hexyne and 4-octyne. Entry 20 shows the result of a 5 g scale reaction giving **5g** in 68% yield after 210 min of total time.

In summary, we show a general protocol for alkyne cyclotrimerization and crossed [2 + 2 + 2] cycloadditions of diynes with alkynes in a PFR. The method uses inexpensive $Co_2(CO)_8$, is highly efficient, has a broad scope, and is easily scalable. We believe the applicability to crossed reactions is remarkable and novel. This procedure opens a new alternative that can lead to novel scaled-up applications of this powerful transformation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02168.

> Complete experimental procedures and spectroscopic data of products; description of the equipment; copies of ^1H NMR spectra of known products and ^1H and ^{13}C NMR spectra of new products (PDF)

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Notes

The authors declare no competing financial interest.

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