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Catalytic scalable Pauson-Khand reaction in a plug flow reactor.

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Abstract A catalytic, scalable intra- and intermolecular Pauson-Khand reaction protocol using 5 mol % of $Co_2(CO)_8$ as the catalyst in a plug flow reactor (PFR) is shown.

The Pauson–Khand reaction (PKR) is a formal [2+2+1] cycloaddition of an alkyne, an alkene and a carbonyl unit to give a cyclopentenone. Until the late nineties it was mediated by a stoichiometric amount of metal, generally cobalt.[1] Many catalytic protocols that use different cobalt and other metal complexes have appeared, some of them lacking a general scope.[2] In particular, there are few examples of intermolecular catalytic reactions. With the focus on green chemistry, it is actually impossible to think on an industrial chemical reaction, which involves transition metal complexes, that is not efficiently catalytical. In thinking on the synthetic applications of the PKR more efforts are necessary to improve the current available catalytic methodologies.

Most catalytic PKR are currently being performed under rhodium catalysis. However, cobalt still is a non expensive and efficient alternative. In addition there is a key safety issue with scalable PKR which is the use of CO gas. A limited, controllable use of this component as well as the use of low catalyst loadings is a challenge that we envisioned could be addressed through the use of flow chemistry.

Over the past two decades, continous technology has evolved quickly and many reactions have shown great advantages when performed under flow conditions with regard to batch flask conditions.[3] In the case of gas–liquid biphasic reactions, the large gas–liquid interfacial area may allow using small amounts of gas that can be exactly measured. In addition, 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.[4]

Various carbonylation reactions using a flow microreactor and continous systems have been described.[5] These include transition-metal catalyzed aminocarbonylations,[6] carbonylative Heck[7] and Sonogashira[8] reactions among others. In 2013 Yoshida's group reported the only example of a Pauson-Khand reaction in a photochemical flow microreactor. They preformed a stoichiometric reaction using previously prepared and purified cobalt hexacarbonyl-alkyne complexes.[9]

Herein we present an efficient protocol to perform catalytic, scalable intra- and intermolecular Pauson-Khand reactions using 5 mol % of $Co_2(CO)_8$ as the catalyst in a PFR.

We used substrate **1a** to optimize conditions (Table 1). The cobalt catalyzed PKR has been described in the literature using 3-10 mol % of $Co_2(CO)_8$ under 1-7 atm of CO and with the aid of additives such as phosphites,[10] phosphines,[11] tributylphosphinesulfide,[12] dimethoxyethane,[13] or a cobalt-TMTU complex.[14] These are used to substitute in situ one or more CO ligands with different coordinating groups in order to form a more stable complex that could re-enter a catalytic cycle before decomposing into unactive species.[15] We described a catalytic protocol using CO adsorbed in molecular sieves (zeolites).[16] The initial alkyne hexacarbonyl complex previously prepared and purified has been used as the catalysts.[17] Our interest was to do the reaction without additives using only 3 equiv of CO. Low residence times and the possibility of working at high pressures would allow high efficiency on this process. The scheme of the system used in this work is depicted in figure 1. We first performed the reaction in batch. Entry 1 shows the best result achieved in a stainless reactor. Optimization of conditions in the PFR (entries 2-8) revealed the need to elevate the temparature up to 120 ºC to achieve total conversion. Catalyst loading was fixed at 5 mol% as with lower loadings conversions decreased (entries 7 and 9). Entry 6 shows the best conditions leading to 99% yield which were 9 min of residence time, 120 ºC with 3 equiv of CO. In entry 10 we show the results of a scaled up reaction where 5 g of **1a** were efficiently transformed into **2a** in 91% yield. The

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Electronic Supplementary Information (ESI) available: *Spectra of new compounds. See DOI: 10.1039/x0xx00000x* total time for this experiment was 38 min. The optimized conditions were applied to subtrates **1b-h** giving products **2b-h** in excellent yields (91-99% except **2c**). Some of these substrates are known for not giving good results in PKR. Substitution at the internal position of the olefin as in **1b**, gives generally poor yields which is not the case with our methodology (98%, entry 11). Electron poor olefins are many times uneffective.[18] However substrate **1c** gave a moderate yield (56%) of **2c** with a longer residence time (17 min, entry 13) as an only distereomer. This product kept the *trans* stereochemistry of the starting material (see Table 1 scheme). Substrates **1d-g** reacted readily giving the corresponding cyclopentenones in excellent yields (91-95%, entries 15-18). Finally, the presence of a bulky substituent at the alkyne as in **1h** required stronger conditions (entry 21) to achieve nearly quantitative yields of product **2h**.

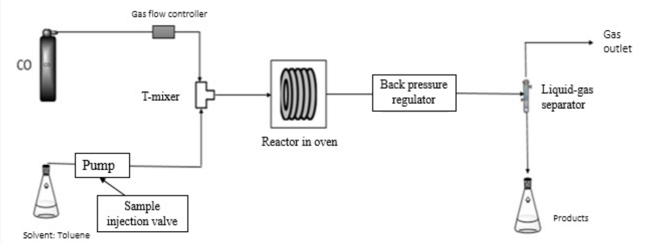
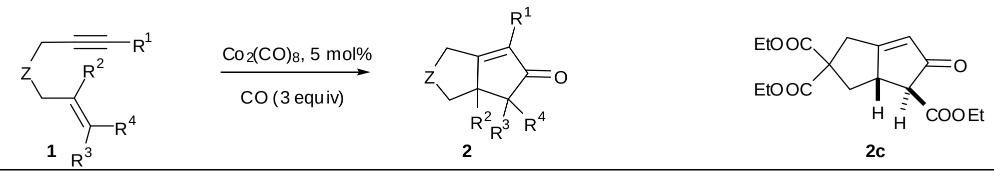
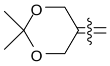


Figure 1. Scheme of the flow system used for the catalytic PKR

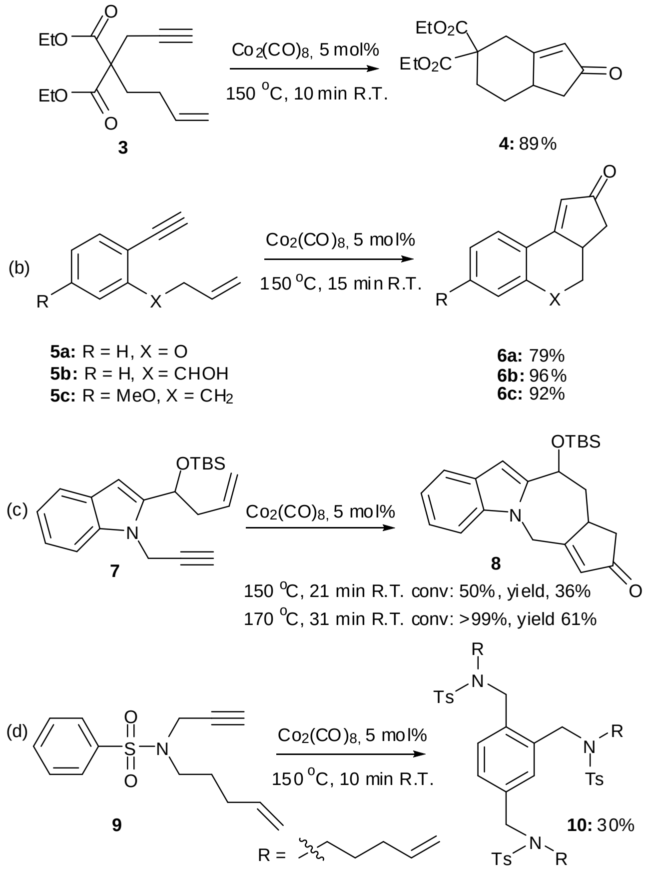


entry	Starting	Z	R¹	R²	R³,R⁴	Product	temp (°C)	Residence time (min)	cat. (mol %)	Conversion[b]	yield (%)[c]
1[d]	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	120	4 h[e]	5	>99	78
2	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	90	11.2	5	51	35
3	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	90	10.8	5	48	34
4	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	105	10.8	5	>99	68
5	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	120	10	5	>99	87
6	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	120	9	5	>99	99
7	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	120	9	2	80	70
8	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	150	9	5	>99	51
9	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	120	11	2	85	57
10[f]	**1a**	$(EtO_2C)_2C$	H	H	H,H	**2a**	120	9	5	>99	91
11	**1b**	$(EtO_2C)_2C$	H	Me	H,H	**2b**	120	9	5	>99	98
12	**1c**	$(EtO_2C)_2C$	H	H	CO_2Et,H	**2c**	120	9	5	60	20
13	**1c**	$(EtO_2C)_2C$	H	H	CO_2Et,H	**2c**	120	17	5	85	56
14	**1c**	$(EtO_2C)_2C$	H	H	CO_2Et,H	**2c**	150	17	5	>99	42
15	**1d**	TsN	H	H	H,H	**2d**	120	9	5	>99	94
16	**1e**	TsN	Me	H	H,H	**2e**	150	11	5	97	91
17	**1f**	TsN	H	H	Me,Me	**2f**	120	10	5	>99	91
18	**1g**		H	H	H,H	**2g**	120	10	5	>99	95
19	**1h**	O	Ph	H	H,H	**2h**	120	9	5	18	7
20	**1h**	O	Ph	H	H,H	**2h**	150	15	5	88	87
21	**1h**	O	Ph	H	H,H	**2h**	170	21	5	>99	99

[a] Conditions for all experiments: 0.4 mmol/mL substrate concentration (0.8 mL used in each experiment), 20 bar system pressure, 3 equiv of CO (0.61 mmol/mL), reactor volume: 60.63 mL. [b] by NMR. [c] in pure product. [d] Control experiment in batch. [e] Reaction time. [f] Scale-up experiment with 5 g of starting material. Total time 38 min.

In view of these good results we switched to a group of substrates precursors of 6 and 7 membered rings (Scheme 1). Both with linear substrate **3** and aromatic-ring templated compounds **5** we reached 79-96% yields in products **4** and **6** (Scheme 1, a,b). The synthesis of 7 membered rings on the other hand is a known limitation of the PKR. Only certain indolic-templated substrates[19] or allenynes[20] have produced these rings. We show the synthesis of compound **8** which was obtained in 61% yield when we carried out the reaction at 170 °C and with a residence time of 31 min. On the contrary, under all the conditions tested with substrate **9** we did not detected the desired PKR product but isolated a moderate yield of a [2+2+2] product (**10**, 30%), as a result of a cyclotrimerization of the alkyne.

Finally we showcase some examples of intermolecular PKR under flow conditions in Scheme 2. These results are particularly important as the catalytic intramolecular version of the PKR has found less development. High pressures of CO and the use of additives are common procedures that work well only with terminal akynes.[1,2] In our hands, from norbornene and only 3 equiv of CO, we prepared different final products in a totally diastereoselective manner. The terminal alkynes (phenylacetylene and 1-hexyne) gave good yields of **11a** and **11c** respectively under the standard reaction conditions. Internal alkynes reacted moderately and needed higher temperatures and residence times but gave the disubstituted cyclopentenones **11b** and **11d** in 42 and 66% yield respectively. In addition to product **11b**, the reaction of norbornene with 1-phenylpropyne gave a 40% yield of a [2+2+2] product **12**, as a result of a cyclotrimerization process of three units of the alkyne.



Scheme 1. Synthesis of 6- and 7-membered ring containing PK aducts.

In summary we show a general protocol for both inter-and intramolecular PKR in a PFR. The use of a minimum amount of CO, the efficiency of the process, low catalysts loadings, broad scope and scalability of this method opens a new alternative that can lead to novel applications of this powerful transformation.

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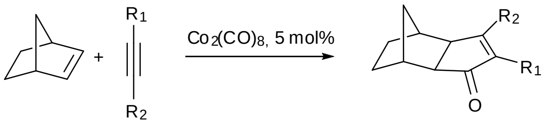
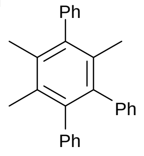


Product	temp (°C)	R.t (min.)	Yield[a]
11a: R_1 = Ph, R_2 = H	120	9	79%
11b: R_1 = Ph, R_2 = CH_3	170	20	42%[b,c]
11c: R_1 = Bu, R_2 = H	120	10	85%
11d: R_1 = R_2 = CH_2OCH_3	170	15	66%[b]

[a] In pure product
[b] No reaction observed at lower temperature
[c] 40% of [2+2+2] product **12** isolated



12

Scheme 2. Catalytic intermolecular PKR in microreactor.

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