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Pauson–Khand Reactions in a Photochemical Flow Microreactor

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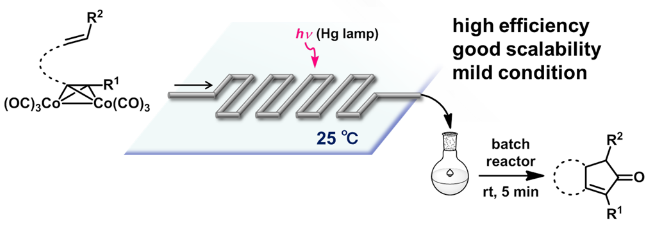
ABSTRACT

Photochemical Pauson–Khand Reaction



Pauson–Khand reactions were achieved at ambient temperature without any additive using a photochemical flow microreactor. The efficiency of the reaction was better than that in a conventional batch reactor, and the reaction could be operated continuously for 1 h.

The Pauson–Khand reaction is a powerful tool for the construction of cyclopentenone frameworks by [2 + 2 + 1] cocyclization between alkynes, alkenes, and CO.[1,2] The utility has been verified by many examples employing the reaction as a key step in natural product syntheses.[2] A plausible mechanism of this reaction was proposed by Magnus and Schore,[3] and it is widely recognized that the initial step is decarbonylation from an alkyne–cobalt complex to provide a vacant coordination site for an alkene.[4] Various protocols to promote this event have been studied. For example, the use of additives, such as

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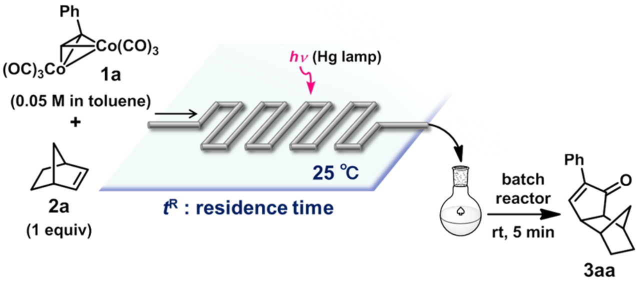
amine oxides,[5a−g] amines,[5h,i] phosphine oxides,[5j] phosphines,[5k] sulfoxides,[5c,l] sulfides,[5l,m] and other compounds,[5n,o] proved to have considerable advantages over the traditional thermal conditions. However, the use of an additive inherently leads to production of wastes derived from it. To circumvent the use of an additive, other methods for activation have also been investigated. However, such methods also suffer from some drawbacks. For example, the irradiation of microwaves should be classified as a harsh condition which is not suitable for the synthesis of complex molecules sensitive to heat.[6] Ultrasound needs to be used with additives to obtain a large accelerating effect.[5g,j] The dry state adsorption techniques were also shown to be efficient, but the synthesis on a solid surface is challenged in the process of scale-up.[7]

Meanwhile, light irradiation was found to be effective, and the photochemical method serves as a milder, greener approach for activation.[4a,8,9] However, photochemical reactions generally suffer from problems in efficiency and scale-up. Thus, we attempted to use a flow microreactor system[10,11] for the light-mediated Pauson−Khand reactions, because the short light path length and high surface-to-volume ratios of flow microreactors are generally beneficial for photochemical reactions from the viewpoints of efficiency and scalability.[12−14] Herein, we demonstrate that Pauson−Khand reactions could be effectively carried out in a photochemical flow microreactor in high efficiency and good productivity.

Table 1. Pauson−Khand Reaction of Phenylacetylene−Dicobalt Complex **1a** and Norbornene (**2a**) in a Photochemical Flow Microreactor[a]



entry	t^R (s)	conversion (%)[b]	yield (%)[b]
1	22	83	62
2	55	94	88
3[c]	55	71	71
4	110	99	90
5[d]	55	<1	<1

[a] For the microchannel: depth, 200 μm; width, 1000 μm; length, 916.04 mm; area, 916.83 mm^2. Flow rate: 0.1−0.5 mL/min. The light source: medium pressure mercury lamp. [b] Determined by ^{1}H NMR analysis of the crude products obtained by passing through a short silica gel pad to remove highly polar materials. [c] Run using the microreactor with 500 μm depth. [d] Run without light.

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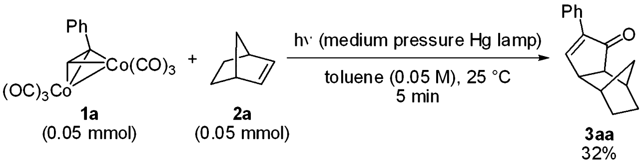
We initiated our investigations with the reaction of phenylacetylene–dicobalt complex **1a** and norbornene (**2a**) in a photochemical flow microreactor (YMC, KeyChem-Lumino 2) (Table 1). A solution of **1a** and **2a** in toluene was passed through the microchannel (depth, 200 μm; width, 1000 μm; length, 916 mm) covered with fused quartz glass, which was irradiated by a medium pressure Hg lamp (80 W) at a flow rate of 0.1–0.5 mL/min. The temperature (25 °C) was controlled by a Peltier cooling system. The collected solution was additionally stirred at ambient temperature for 5 min in the batch reactor.[15] The solution was concentrated under reduced pressure to obtain the crude product, which was purified by flash chromatography. Although the conversion of **1a** and the yield of cyclopentenone product **3aa** were not high with the residence times shorter than 55 s (entry 1), high conversions and yields were obtained with the residence time being longer than 55 s (entries 2–4). In addition, the use of a microreactor of a deeper channel (depth: 500 μm) was less effective (entry 3), indicating the importance of short light path length. It was also confirmed that the irradiation was essential for the process (entry 5).

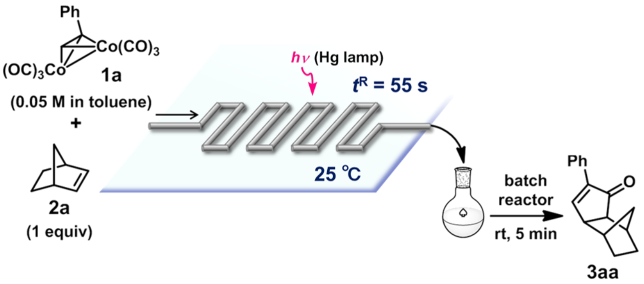
To demonstrate the advantage of the flow microreactor for the photochemical Pauson–Khand reactions, the reaction of **1a** with **2a** was examined using a conventional batch macroscale reactor as a control experiment (Scheme 1). The reaction was carried out in a 30 mL flask, which was placed 10 cm distant from the light source. The light source was the same one used for the reaction in a flow

Scheme 1. Photochemical Pauson–Khand Reaction of **1a** with **2a** in a Conventional Batch Reactor[a]



[a] Reaction was run in 30 mL flask, 10 cm distant from the light source.

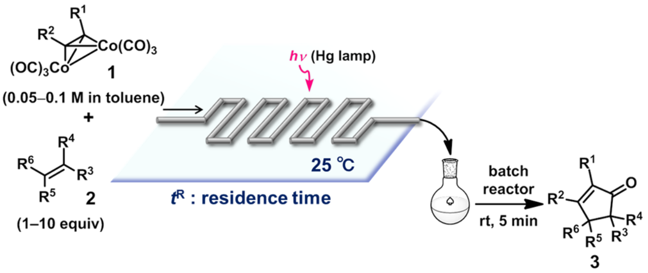
Scheme 2. Scalability of Pauson–Khand Reaction of **1a** with **2a** in a Photochemical Flow Microreactor[a]

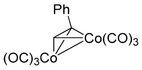
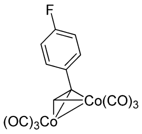
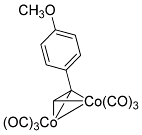
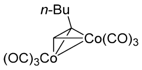
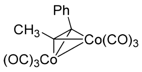
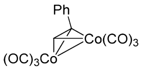
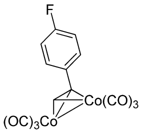
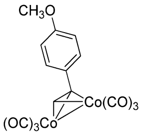
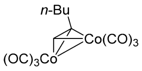
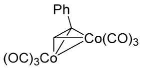
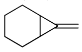


operation time[a] (reaction scale)	5 min (0.05 mmol)	1 h (0.6 mmol)
yield	88% (94% conv)	85% (85% conv)

[a] For the microchannel: depth, 200 μm; width, 1000 μm; length, 916.04 mm; area, 916.83 mm^2. The light source: medium pressure mercury lamp.

Table 2. Intermolecular Pauson–Khand Reactions in a Photochemical Flow Microreactor[a]



entry	1		2 (equiv)		3	t^R (s)	yield (%)[b]
1[c]		**1a**	 (1)	**2a**	**3aa**	55	88[f] (94)
2[c]		**1b**	 (1)	**2a**	**3ba**	55	90[f] (92)
3[c]		**1c**	 (1)	**2a**	**3ca**	55	75[f] (91)
4[c]		**1d**	 (1)	**2a**	**3da**	55	92[f] (95)
5[c]		**1e**	 (1)	**2a**	**3ea**	55 548[e]	4[f] (6) 5[f] (7)
6[d]		**1a**	 (10)	**2b**	**3ab**	548[e]	67 (77)
7[d]		**1b**	 (10)	**2b**	**3bb**	548[e]	73 (82)
8[d]		**1c**	 (10)	**2b**	**3cb**	548[e]	52 (65)
9[d]		**1d**	 (10)	**2b**	**3db**	548[e]	20 (45)
10[d]		**1a**	 (10)	**2c**	**3ac**	55	71[g] (88)

[a] For the microchannel: depth, 200 μm; width, 1000 μm; length, 916.04 mm; area, 916.83 mm^2. The light source: medium pressure mercury lamp. [b] Determined by ^1H NMR analysis of the crude products obtained by passing through a short silica gel pad to remove highly polar materials. Values in parentheses are the conversion of **1**. [c] Concentration of **1**: 0.05 M. [d] Concentration of **1**: 0.1 M. [e] Run using the microreactor with 500 μm depth. [f] The products were obtained as a single diastereomer. See Supporting Information (SI) for details. [g] The regioisomer ratio was 1.4:1.3:1. See SI for details.

microreactor, and the irradiation time was 5 min. The product was obtained only in 32% yield in batch, while the flow microreactor reaction afforded **3aa** in 88% yield (Table 1, entry 2; 0.05 mmol scale; flow rate, 0.2 mL/min; operation time, 5 min), indicating that the flow microreactor method is superior to the batch method.

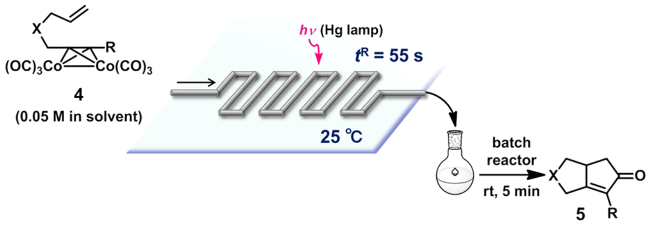
In addition, the scalability, another important feature of a photochemical flow microreactor system, was also verified (Scheme 2). The reaction of **1a** with **2a** in the flow microreactor system could be continuously operated for 1 h with high efficiency.

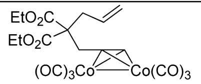
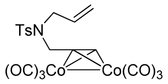
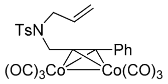
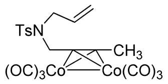
Under the optimized conditions (t^{R} = 55 s), the reactions of other alkyne–dicobalt complexes **1b**–**1e** with **2a** were investigated (Table 2, entries 2–5). Good yields were obtained with both electron-poor and -rich arylacetylene complexes (entries 2 and 3). A complex of an aliphatic alkyne also yielded the corresponding cyclopentenone product (entry 4). A disubstituted alkyne complex was unfortunately not applicable to the reaction (entry 5). Cyclopentene (**2b**) could also be used, although 10 equiv of **2b** and a much longer residence time (t^{R} = 548 s) were needed (entries 6–8). The reaction of **1d** and **2b**, however, gave rise to a modest yield of the product (entry 9). In addition, methylenecyclopropane **2c** could also be used to give the products as a mixture of regioisomers (1.4:1.3:1) in good yield (entry 10).[16]

Next, we examined intramolecular Pauson–Khand reactions using the photochemical flow microreactor (Table 3). The reaction of **4a** in toluene afforded the corresponding product only in 32% yield, although the starting material was consumed almost completely (entry 1). In this case, 1,2-dimethoxyethane (1,2-DME) was found to be a more efficient solvent, and the product was obtained in 76% yield (entry 3).[5o] Under the conditions (t^{R} = 55 s in 1,2-DME), nitrogen-bridged substrates could also be used (entries 4–6). It is noteworthy that intramolecular reactions of the complexes of disubstituted alkynes could be accomplished to obtain the corresponding products in high yield (entries 5 and 6).

In summary, we have demonstrated that a photochemical protocol using a flow microreactor system is effective for Pauson–Khand reactions. The method allowed for an effective activation of alkyne–cobalt complexes, thereby leading to the high efficiency of Pauson–Khand reactions at ambient temperature without any additive. Easy scale-up by elongating the operation time is beneficial for preparative purposes.

Table 3. Intramolecular Pauson–Khand Reactions in a Photochemical Flow Microreactor[a]



entry	4		5	solvent	yield (%)[b]
1		**4a**	**5a**	toluene	32 (95)
2				THF	60 (98)
3				1,2-DME[c]	76 (99)
4		**4b**	**5b**	1,2-DME[c]	65 (93)
5		**4c**	**5c**	1,2-DME[c]	80 (88)
6		**4d**	**5d**	1,2-DME[c]	78 (97)

[a] For the microchannel: depth, 200 μm; width, 1000 μm; length, 916.04 mm; area, 916.83 mm^2. The light source: medium pressure mercury lamp. [b] Determined by ^{1}H NMR analysis of the crude products obtained by passing through a short silica gel pad to remove highly polar materials. Values in parentheses are the conversion of **4**. [c] 1,2-DME = 1,2-dimethoxyethane.

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Supporting Information Available. Experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(15) The collected solution was additionally stirred in order to ensure that the reaction was complete.

(16) Unstrained alkenes failed to give the corresponding products in practical yields (< 20%).