The Catalytic Pauson-Khand Reaction Promoted by A Small Amount of 1,2-Dimethoxyethane or Water

Takumichi Sugihara† and Masahiko Yamaguchi

Faculty of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8514, Japan

Email: taku@ph.bunri-u.ac.jp

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Abstract: Various “hard” Lewis bases having less nucleophilic nature promoted the catalytic Pauson-Khand reaction. Among those Lewis bases, 1,2-dimethoxyethane seems to be the most promising promoter and a small amount of water, which is the cheapest reagent, also effectively promoted the cyclization.

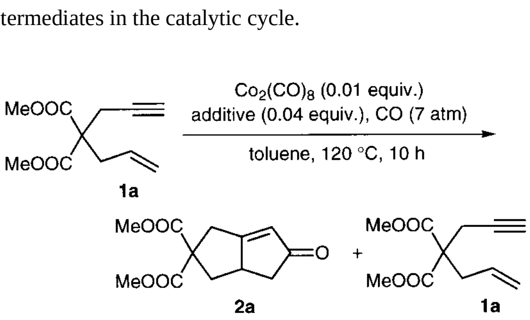
Since Pauson and Khand discovered a convenient and powerful method for constructing cyclopentenones by the coupling of an alkyne and an alkene mediated by dicobalt octacarbonyl,[1] it has been widely utilized in synthetic organic chemistry[2] including natural product synthesis.[3] The stoichiometric amount of cobalt complex was originally reported as a necessity. However, the catalytic version[4,5] has been recently developed for the intramolecular reaction by using the cobalt complex in the presence of either $P(OPh)_3$[4b] or ultraviolet light.[4c] In this communication, we report a new, cheap, and convenient method for the catalytic Pauson-Khand reaction promoted by a small amount of 1,2-dimethoxyethane or water.

It is known that ”hard” Lewis bases on low-valent organotransition metal complexes labilize the existing ligand.[6] This effect facilitates the ligand substitution reaction[7] and sometimes makes the coordinating ligands reactive. We recently demonstrated the labilizing effect of primary amines as for the promotion of the *stoichiometric* Pauson-Khand reaction.[8] When the same reaction was carried out in toluene, the desired cyclization also took place within a couple of minutes, and metalic cobalt was obtained as a coproduct. Since dicobalt octacarbonyl can be synthesized by reduction of Co^{2+} species under carbon monoxide atmosphere,[9] we felt that the complex might be regenerated *in situ* in toluene under a carbon monoxide atmosphere. To confirm this, the reactions of **1a** in the presence of a catalytic amount of dicobalt octacarbonyl (1 mol%)[10,11] and various Lewis bases (4 mol%) were investigated, and the results are summarized in Table 1 (Eq. 1). First, only low conversions and turnovers were observed when no ”hard” Lewis base was added (Entry 1). Addition of cyclohexylamine, which was the best promoter for the stoichiometric Pauson-Khand reaction,[8] was not effective at all (Entry 2). On the other hand, secondary and tertiary amines allowed catalytic cyclization, and diisopropylethylamine was the most effective among investigated amines (Entry 4). It is worth pointing out that the complex **4** gave **2b** in a low yield along with numerous byproducts in the presence of diisopropylethylamine, while its corresponding reaction with cyclohexylamine was fast and high yielding (Eq. 2).[8] The reaction course appeared to differ in the stoichiometric and catalytic Pauson-Khand reaction. Amines might not react with the alkyne-dicobalt hexacarbonyl complexes in the catalytic reaction, but react directly with the dicobalt octacarbonyl or some intermediates in the catalytic cycle.

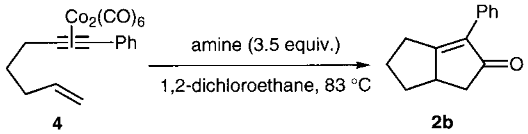
Table 1. The catalytic Pauson-Khand reaction in the presence of various ‘hard’ Lewis bases [a]

Entry	Additives	Yield (%)	
		2a	**1a**
1	none	12	82
2	cyclohexylamine	5	93
3	diisopropylamine	64	28
4	diisopropylethylamine	81	7
5	benzyl alcohol	73	21
6	2-methoxyethanol	27	71
7	ethylene glycol	–	97
8	1,4-dioxane	72	5
9	1,2-dimethoxyethane	91	–
10	in 1,2-dimethoxyethane[b]	9	78
11	1,2-dimethoxyethane[c]	5	83
12	1,2-dimethoxyethane[d]	82	6
13	1,2-dimethoxyethane[e]	93	–
14	H_2O[f]	63	33
15	H_2O[g]	21	65

[a] A mixture of enyne **1a**, 0.01 molar equivalent of $Co_2(CO)_8$, and 0.04 molar equivalents of additives in toluene (0.4 M solution) was stirred at 120 ℃ under 7 atm of CO atmosphere for 10 h. [b] The reaction was carried out in 1,2-dimethoxyethane instead of toluene. [c] The reaction was caried out under an ambient pressure of CO. [d] The reaction was caried out under 3 atm of CO. [e] The reaction was caried out under 20 atm of CO. [f] 20 molar equivalents of water was used. [g] The reaction was carried out in H_2O-toluene (1:2 v/v; 0.3 M solution)



(Eq. 1)



(Eq. 2)

	Time	Yield [%]
with $CyNH_2$	5 min	99
with $i\text{-}Pr_2NEt$	90 min	35

Besides amines, alcohols also promoted this catalytic cyclization (Entry 5), but those having chelatable substituents, such as 2-methoxyethanol and ethylene glycol, killed the catalytic process (Entries 6 and 7). Ethers were also effective and 1,2-dimethoxyethane turned out to be the best promoter (Entries 8 and 9). However, large excess of 1,2-dimethoxyethane was detrimental to catalysis (Entry 10).[12] Although 1,2-dimethoxyethane was used as conventional solvent in the catalytic Pauson-Khand reaction,[4b,c,d] it could have prevented the cyclization especially at higher reaction temperature.[13,14] It should be emphasized that a small amount of 1,2-dimethoxyethane could dramatically promote the catalytic Pauson-Khand reaction in toluene. The pressure of carbon monoxide had also an influence on the reaction, and **2b** was obtained in high yields under CO pressures greater than 3 atm (Entries 12 and 13). Finally, it was found that even a small amount of water also effectively promoted the catalytic cyclization (Entry 14). Again, its amount was critical, and the yield decreased in a biphasic system (Entry 15).[12] Since an excess amount of water did not promote the *stoichiometric* Pauson-

Khand reaction at all,[8] the reaction course was again shown to differ in the stoichiometric and catalytic Pauson-Khand reaction. Use of water as the promoter for the catalytic Pauson-Khand reaction is economical and convenient. It should be mentioned that water must be rigorously excluded from substrate and solvent to bring about reproducible results.[15] Overall, small amounts of less nucleophilic "hard" Lewis bases, especially 1,2-dimethoxyethane and water, turned out to be the most promising promoter in this catalytic cyclization.

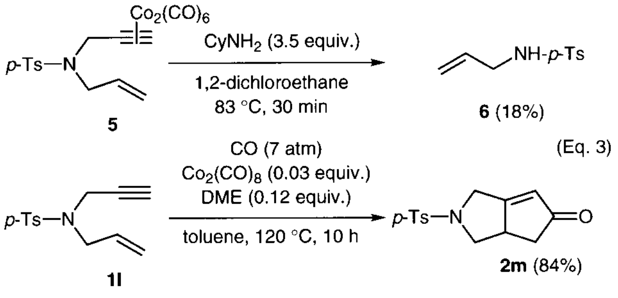
We then continued investigating the scope of this reaction using the best additives; 1,2-dimethoxyethane or water, use of which gave comparable results (Table 2). Intramolecular reactions, *e. g.* cyclization of **1a**, **1b**, and **1c**, gave the corresponding products in good yield (Entries 1-3). When the alkyne or the alkene had substituents (Entries 4-7), the reaction was slower and more catalyst was required to allow full conversion within reasonable reaction time (10 h). Formation of bicyclo[4.3.0]nonenone system like **2g** was also successful (Entry 7). In some cases, the catalytic reaction has advantage over the stoichiometric reaction. When **5** was treated with cyclohexylamine in 1,2-dichloroethane, the reaction gave a complex mixture: The major isolated product in this stoichiometric reaction was **6**. In contrast, the catalytic cyclization of **1l** gave the desired enone **2m** in good yield (Eq. 3). The observation again indicated that the mechanisms differ between the catalytic and stoichiometric Pauson-Khand reaction when the reaction was promoted by the "hard" Lewis bases. Interestingly, the catalytic cyclization of **1m** failed, while **1i** gave **2i** in a good yield (Entry 9). This might be due to the competition between the cyclization and the decomposition of the active catalyst by reaction with ethers. The intermolecular Pauson-Khand reaction can also be catalyzed under the same conditions for reactive olefins, such as norbornene (**3a**) and norbornadiene (**3b**) (Entries 10-12).

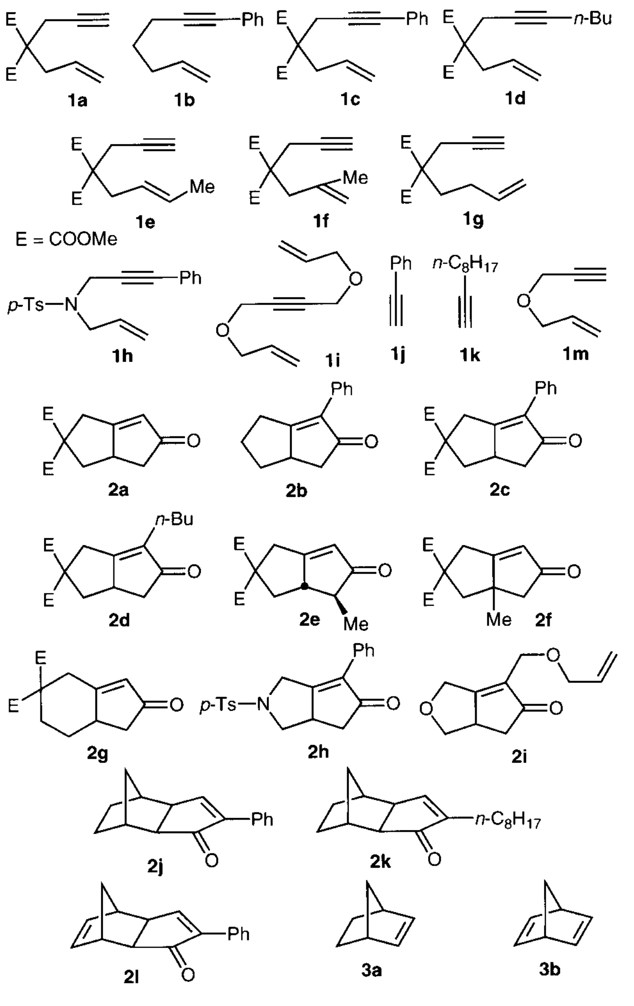
Table 2. The catalytic Pauson-Khand reaction of various substrate [a]

Entry	Substrate	Product	Yield (%) Conditions A[b]	Yield (%) Conditions B[c]
1	**1a**	**2a**	94	97
2	**1b**	**2b**	98	94
3	**1c**	**2c**	87	90
4	**1d**	**2d**	75[d]	72[d]
5	**1e**	**2e**	82[d]	85[d]
6	**1f**	**2f**	86	88
7	**1g**	**2g**	85[d]	87[d]
8	**1h**	**2h**	86	85
9	**1i**	**2i**	90	95
10	**1j+3a**[e]	**2j**	98	97
11	**1k+3a**[e]	**2k**	100	98
12	**1j+3b**[e]	**2l**	92	90

[a] A mixture of 1 mmol of the enyne, 0.02 mol of $Co_2(CO)_8$, and 0.08 mol of the additive in 2 mL of toluene was stirred at 120 °C under 7 atm of CO atmosphere for 10 h. $Co_2(CO)_8$ was used as a solution in toluene after sublimation. [b] 1,2-Dimethoxyethane was used as an additive for the reaction after distilation over $LiAlH_4$. [c] The reactions were carried out in two-fold scale with 4 mL of water. [d] 0.03 mmol of $Co_2(CO)_8$ and 0.12 mmol of additives were used for the reaction. [e] A 1.5 molar equivalents of norbornene (**3a**) or norbornadiene (**3b**) was used for the reaction

In conclusion, we have shown that various "hard" Lewis bases having less nucleophilic nature promoted the catalytic Pauson-Khand reaction. Among those Lewis bases, 1,2-dimethoxyethane seems to be the most promising promoter and a small amount of water, which is the cheapest reagent, also effectively promoted the cyclization.





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References and Notes

† Present address: Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan. Fax +81-886-55-3051; E-mail taku@ph.bunri-u.ac.jp

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(10) Dicobalt octacarbonyl was used as a freshly-prepared solution in toluene after sublimation. Since purity of dicobalt octacarbonyl largely influenced its catalytic activity, we recommend to use the complexes right after purification.

(11) The use of the old stock solution of the catalyst in toluene sometimes gave better results than that of the freshly prepared solution. Standing the solution for a while might permit contamination of water and/or air to afford more reactive catalyst in such cases.

(12) Since dicobalt octacarbonyl is known to react with ”hard” ligands to produce cationic and anionic complexes *via* redox process, an excess amount of additives having more nucleophilic nature might promote the decomposition of dicobalt octacarbonyl prior to mediate the cyclization. For instance, see; Heiber, W.; Sedlmeier, J.; Abeck, W. *Chem. Ber.* **1953**, *86*, 700.

(13) When **1a** was treated with 0.2 molar equivalent of dicobalt octacarbonyl in 1,2-dimethoxyethane at 25 °C under 7 atm of carbon monoxide, the alkyne-dicobalt hexacarbonyl complex of **1a** was produced in 90% yield based on the cobalt complex. At lower temperature, an excess amount of 1,2-dimethoxyethane did not decompose dicobalt octacarbonyl but promoted ligand exchange reaction on the cobalt.

(14) Recently, Livinghouse *et al.* reported the intramolecular Pauson-Khand reaction catalyzed by $Co_2(CO)_8$ in 1,2-dimethoxyethane at *limited range of temperature*. See: ref. (4d).

(15) Although Rautenstrauch *et al.* reported the catalytic Pauson-Khand reaction using alkyne-$Co_2(CO)_6$ complexes as a catalyst, it could not be reproduced by the authors. The contamination of water might be one of the reasons for the unreproducibility. See: ref. (4a).