Catalytic Pauson–Khand Reaction in Super Critical Fluids

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Cocyclization of alkynes with alkenes and carbon monoxide by cobalt leading to cyclopentenones (known as Pauson–Khand reaction) has been accepted as one of the most powerful tools in the synthesis of cyclopentenones.[1] Recent developments in Pauson–Khand reaction, especially in the 1990s, have been quite impressive. These include findings of promoters such as silica gel,[2] tertiary amine *N*-oxide,[3] and DMSO[4] for the stoichiometric reaction, enantioselective reactions,[5] and catalytic versions of the reaction.[6] Many variations employing other metals are also reported.[7] Despite the successful progress and potential implications as an industrial process of this reaction, the use of this remarkable reaction has been limited only to the laboratory application.

This limitation is mainly attributed to the rather low turnover number and turnover frequency of the catalytic reaction. More severe limitations are associated with the practical operational difficulties such as removal of the catalyst and solvents from the homogeneous reaction media after completion of the reaction. The reaction with water soluble ligand bound catalysts in organic/aqueous phase process[8] and with perfluorinated ligands bound catalysts in the conventional organic solvent and perfluorinated solvent system are devised for the operational simplicity.[9]

Meantime, the use of supercritical fluids (Scfs) as reaction media is becoming an alternative for the reactions in which the previously described options are not suitable. The projected advantages of the reactions in supercritical fluids are the increased reaction rates and selectivities resulting from the high solubility of reactant gases, rapid diffusion of solutes, weakening of the solvation around reacting species, and the local clustering of reactants or solvents.[10] It is also interesting to note, in a practical sense, that those fluids are easily recycled and allow the separation of dissolved compounds by a gradual release of pressure. Sequential and selective precipitations of the catalyst and product would be possible.

Several recent reports have shown that supercritical CO_2 (sc CO_2) can replace the conventional organic solvents in various transformations such as radical reactions,[11] Diels–Alder reaction,[12] polymerization,[13] homogeneous catalytic hydrocarboxylation,[14] and asymmetric hydrogenations.[15]

Herein, we would like to report our preliminary study of the first catalytic Pauson–Khand reaction in supercritical fluids. The catalytic process by dicobalt octacarbonyl had been well conceived since the discovery of the reaction, but it was in quite recent years before it was realized.[16] To our experiences in this field, the control of aggregation status of the catalytic active species played a critical role. We hoped that the catalytic metals should be well dispersed in Scfs and the chances of the aggregation of metals would be reduced substantially.

Our initial studies using dicobalt octacarbonyl as a catalyst were mainly focused in sc CO_2 since there was a report dealing with a hydroformylation of olefin with a catalytic amount of dicobalt octacarbonyl.[16]

Catalytic intramolecular Pauson–Khand reactions were performed first in sc CO_2 by charging a cylindrical stainless steel reactor (80 mL capacity) with a catalyst and enynes followed by pressurization properly with carbon monoxide and carbon dioxide. A red homogeneous supercritical phase was obtained upon warming the mixture to 40 °C, and the reaction mixture was further heated up to an appropriate temperature, and the reaction was allowed to proceed.

After much trial experimentations, the range of the required minimal amount of the catalyst and various parameters of the reaction were roughly defined. Table 1 lists the trials to optimize the reaction condition. The required amount of catalyst is about 2–5 mol %[6] but it has not been fully optimized. The reactions under rather low carbon monoxide pressure (1–5 atm) frequently led to incompletion of the reaction or low chemical

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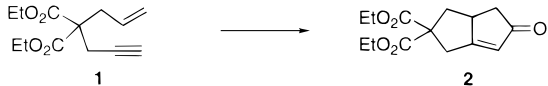(12) Ikushima, Y.; Saito, N.; Sato, O.; Ari, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1734. Ikushima, Y. *J. Phys. Chem.* **1992**, *96*, 2293. Paulatis, M. E.; Alexander, G. C. *Pure Appl. Chem.* **1987**, *59*, 61.
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Table 1. Trials To Optimize the PKR Condition in Supercritical CO_2

entry	$Co_2(CO)_8$ (mol %)	P_{CO} (atm)	P_{CO_2} (atm)	T (°C)	t (h)	final P (atm)	**1** (%)	**2** (%)
1	0.2	6	86 at 34 °C	48	70	96	77	0.5
2	1	15	100 at 36 °C	84	24	177	17	66
3	2.5	15	105 at 34 °C	69	62	180	0	85
4	2.5	1	86 at 34 °C	60	24	112	0	64
5	2.5	30	112 at 37 °C	90	24	198	0	82

Table 2. Intramolecular Catalytic PKR in Supercritical CO_2

Table 3. Intermolecular Catalytic PKR in Supercritical CO_2

also served as a good substrate albeit an eliminated product was obtained together with the desired one in the presence of a leaving group (entry 3, Table 2).[6]

Allyl propargyl ether also produced the corresponding product in excellent yield (entry 4, Table 2), but tosyl and cbz protected allyl propargyl amine, which were among the best substrates in the conventional catalytic reaction,[6b,c] remained unreacted under this condition since they are not reasonably soluble in sc CO_2 (entry 5, Table 2).

An intermolecular reaction also worked well under this condition. Phenyl acetylene can couple with norbonadiene (excess of) to give the bicyclic compound in 87% (entry 1, Table 3). Biscocyclization of diyne proceeded nicely to furnish the bis(bicyclicpentenone) in high yield (entry 2, Table 3).

These preliminary studies demonstrate the feasibility of conducting transition metal mediated transformations with high efficiency in Scfs. Especially reactions employing metal carbonyl under carbon monoxide pressure will be perfectly fit in this special phase due to their favorable solubility profiles. We are further optimizing the related reactions in SCFs to define the potential of these novel media and devise environmentally friendly processes.

yield (entries 1, 2, and 4, Table 1). Higher reaction temperature (90−100 °C) beyond critical temperature (31 °C at 72.9 atm) is necessary for the completion in a reasonable reaction time (<24 h). This reaction mixture requires higher carbon monoxide pressure (15−30 atm) to make the catalytic metal species as intact as possible. Otherwise, the metal catalyst was deactivated by that forming of an unidentified white precipitate.

The scope of the reaction in terms of the substrates was determined by employing a standard condition as follows: 2.5 mol % dicobalt octacarbonyl along with 30 atm of CO (at 23 °C) in CO_2 (final pressure is 110−120 atm at 36−9 °C) was heated at 90−95 °C for 24 h, and the results are summarized in Tables 2 and 3.

The reaction proceeded pretty well regardless of the substitution pattern of acetylene. Disubstituted acetylene gave a little better chemical yield (entry 2, Table 2). 1,1′-Disubstituted olefin