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Rh-Catalyzed Aqueous Pauson–Khand-Type Cycloaddition in Microwave-Irradiated Medium

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Abstract: Microwave-assisted Rh-catalyzed dual catalysis in aqueous medium is described. This tandem process transforms the enyne to cycloadduct by cascade decarbonylation of formate ester and subsequently carbonylation of enyne under microwave-irradiated conditions.

Keywords: aqueous, cycloaddition, catalysis, rhodium, microwave

Since the first reports on microwave-accelerated organic transformation by two independent groups of Gedye and Giguere/Majetich in 1986,¹ the application of microwave heating to microwave-assisted organic synthesis have attracted considerable amount of attention in recent years.² Particular advantages to microwave irradiation include minimization of thermal decomposition of reagents and/ or products by eliminating potential temperature gradients and localized overheating, which are common to conventional heating methods. Moreover, microwave heating significantly accelerates reaction rates and typically provides better yields along with fewer byproducts.³

In addition to the advancement of energy transfer by microwave irradiation, we speculated a prerequisite of an attractive protocol for a reaction should be operationally simple; especially the reaction can be carried out in less harmful solvents. Recently, tremendous attentions have been given to aqueous transition-metal-catalyzed reactions.⁴ However, no catalytic cascade systems that enable formate esters as the CO surrogate and the use of water as the solvent in carbonylative cyclization have been developed yet.⁵ In continuing our study on cycloadditions,⁶ we herein report the first aqueous Pauson-Khand-type reaction utilizing formate ester as the condensed CO source under microwave-assisted conditions (Scheme 1). This interesting methodology effectively accelerates the carbonylative reaction to provide the corresponding cycloadducts in a short period of time and can be achieved for asymmetric version with suitable choice of chiral phosphine ligands.

Initial screenings were triggered to accomplish the cascade decabonylation–carbonylation sequence in an aqueous medium in the presence of microwave energy. 1,3-Bis(diphenylphosphino)propane (dppp) showed the best

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Scheme 1 Microwave-assisted aqueous dual catalysis

result in both of the sequential processes. The Rh–dppp complex was applied to further examine the efficiency of the condensed CO source (Table 1). 4-Chlorobenzyl formate provided 60% isolated yield of the desired product (entry 6). The reaction temperature at 130 °C was required to drive the tandem reaction successfully (entries 2 vs. 4). In the absence of water solvent, only a trace amount of the product was obtained (entries 6 vs. 7).

 Table 1
 Initial Screening of Aqueous PKR with Formate Esters as

 CO Source^a
 PKR

	n Rhfor /==MN	-dppp mate N	Ph O H	
Entry	Formate	Solvent	Temp (°C)	Yield (%) ^b
1°	Bn	H_2O	130	33
2	Bn	H_2O	130	45
3 ^d	Bn	H_2O	130	30
4	Bn	H_2O	100	13
5	4-MeOBn	H_2O	130	35
6	4-ClBn	H_2O	130	60
7	4-ClBn	nil	130	Trace
8	4-CF ₃ Bn	H ₂ O	130	32

^a Reaction conditions: $[Rh(COD)Cl]_2$ (5 mol%), ligand (11 mol%), enyne (0.3 mmol), formate (1.5 mmol), and H₂O (1.0 mL) were placed in MW vials under nitrogen and the reactions were conducted at 130 °C for 50 min under microwave-conditions. ^b Isolated yield.

Demonstration (0.0 menus

^c Benzyl formate (0.9 mmol) was used.

^d Water (0.5 mL) was used.



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 Table 2
 Rh-Catalyzed Aqueous PKR with Formate Esters as CO

 Source^a (continued)
 Continued



X = O, NTs, C(COOEt)₂



^a Reaction conditions: $[Rh(COD)Cl]_2$ (5 mol%), ligand (11 mol%), enyne (0.3 mmol), 4-chlorobenzyl formate (1.5 mmol), and H₂O (1.0 mL) were placed in MW vials under nitrogen and the reactions were conducted at 130 °C for 50 min under microwave conditions. ^b Isolated yield.

To investigate effectiveness of the microwave-assisted aqueous dual catalysis, we surveyed various oxygen-tethered 1,6-envnes for the Pauson-Khand-type cycloaddition (Table 2). Substituted aromatic enynes were tolerable under these reaction conditions to furnish the corresponding cyclopentenones (Table 2, entries 1-7). Sterically congested 2-tolyl enyne afforded low yield of the product presumably the 2-methyl group hindered the coordination of yne moiety to the metal center (entry 8). It should be noted that we have successfully showed the transformation of thienyl-enyne to the desired product under aqueous microwave-assisted conditions (entry 9). In contrast, only a trace amount of desired product was obtained under conventional oil-bath heating, along with significant amount of substrate decomposition as judged by GC-MS analysis. Dienyne and 1,8-enyne were unsuccessful in this transformation and ca. 80% of starting material was recovered (entries 10 and 13). N- and C-tethered enynes were compatible in these reaction conditions (entries 11 and 12).

Apart from racemic tandem catalysis, we are attracted by the feasibility in achieving the first enantioselective version of the microwave-assissted aqueous cascade transformation. Commonly used chiral diphosphine ligands⁷ were examined in place of dppp (Table 3). The BINAP ligands provided good enantioselectivities, although poor yields were obtained (entries 1–3). BisbenzodioxanPhos⁸ (**4**, SYNPHOS)⁹ showed better yield and enantioselectivity than BINAP ligands (entry 4). Xylyl-P-Phos¹⁰ (**6**) gave

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^a Reaction conditions: $[Rh(COD)Cl]_2$ (5 mol%), L* (11 mol%), enyne (0.3 mmol), 4-chlorobenzyl formate (1.5 mmol), and H₂O (1.0 mL) were placed in MW vials under nitrogen and the reactions were conducted at 130 °C for 50 min under microwave conditions. ^b Isolated yield.

the highest yield of the cyclopentenone product (entry 6). The modified MeO-BIPHEP (8) furnished the product in excellent enantioselectivity of 98%, which is the highest ee achieved so far for the O-tethered aromatic enyne (entry 8). Chiral ferrocenyl ligands such as Walphos (9) and Taniaphos (10) were found to be inferior in these aqueous cascade processes (entries 9 and 10).

In summary, we have succeeded in showing the first aqueous dual catalysis in microwave-irradiated medium.¹¹ Various oxygen-, nitrogen-, and carbon-tethered enynes were successfully transformed to their corresponding cyclopentenones. Excellent product enantioselectivities (up to 98%) were obtained with axially chiral diphosphine ligands. Fine-tuning the chiral ligands to further increase both product and optical yield is currently under way.

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- (11) **Representative Procedures** [Rh(COD)Cl]₂ (7.4 mg, 15.0 μ mol) and dppp (13.6 mg, 33.0 μ mol) were charged into the reaction vial on bench-top at room temperature. The reaction vial was then transferred to the dry box for being evacuated and backfilled with nitrogen (3 cycles). Then, 4-chlorobenzyl formate (255 mg, 1.5 mmol, 5 equiv with respected to enyne) was added under

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nitrogen atmosphere and the reaction mixture was stirred for 1 h. Enynes (57 mg, 0.3 mmol) and H_2O (1.0 mL) were charged into the reaction vial. The vial was air-tightened by a special designed lid and transferred to the microwave oven. The reaction mixtures were heated to 130 °C by microwave irradiation with power of 500 W for 50 min. The vials were allowed to reach r.t. Diethyl ether or EtOAc (ca. 2 mL) was added. The crude reaction mixtures were directly purified by

column chromatography on silica gel using hexane–EtOAc as the eluent to afford chiral bicyclic cyclopentenones. For the asymmetric catalytic Pauson–Khand-type cyclization, the enantiomeric excesses of the products were determined by chiral HPLC analysis using Chiralcel[®] AD-H columns. All characterization data matched with the literature reports (ref. 6).

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