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Microwave-Assisted Rhodium-Complex-Catalyzed Cascade Decarbonylation and Asymmetric Pauson–Khand-Type Cyclizations

Hang Wai Lee,[a] Lai Na Lee,[a] Albert S. C. Chan,[a] and Fuk Yee Kwong*[a]

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Microwave-assisted Rh–diphosphane-complex-catalyzed dual catalysis is reported. This cooperative process provides [2+2+1] cycloadducts by sequential decarbonylation of aldehyde or formate and carbonylation of enynes within a short period of time. Various O-, N-, and C-tethered enynes were transformed into the corresponding products in good yields. The first enantioselective version of this microwave-accelerated cascade cyclization was realized. In the presence of chiral Rh-(*S*)-bisbenzodioxanPhos complex, the cyclopentenone products were achieved with *ee* values up to 90%.

Introduction

Microwave heating has penetrated many different areas of chemical research in the last decade and is set to revolutionize the foremost way that chemists will carry out transformations in the near future.[1] Since the pioneering reports on microwave-accelerated organic transformations by the groups of Gedye and Giguere/Majetich in 1986,[2] the application of microwave dielectric heating to microwave-assisted organic synthesis (MAOS) has attracted considerable amount of attention in recent years.[3] Advantages to microwave irradiation include minimization of thermal decomposition of reagents and products by eliminating potential temperature gradients and localized overheating, which are common to conventional heating methods. Moreover, microwave irradiation also greatly accelerates reaction rates and typically provides better yields with fewer byproducts.[4]

Inspired by the previous successful examples in MAOS,[5] we were intrigued to investigate whether the influence of microwave irradiation could reduce the prolonged reaction periods, as well as side-product formation, in catalytic Pauson–Khand-type processes. In fact, cobalt-mediated [2+2+1] carbonylative cyclization of an alkyne, alkene, and carbon monoxide (i.e., the Pauson–Khand reaction, PKR)[6] is a versatile protocol for the construction of various bicyclic cyclopentenones.[7] These valuable scaffolds are of particular interest in targeting a variety of synthetically useful and pharmaceutically attractive compounds.[8] Considerable advancements have been recently achieved from stoichiometric to catalytic Pauson–Khand-type reactions.[9] The reaction conditions for catalytic PKRs usually require elevated temperatures to carry out the reaction successfully. In view of the efficient heat-energy transfer, microwave irradiation would be an alternative energy source for this type of reaction. Nevertheless, microwave-promoted PKRs remain sporadically studied.[10] In continuing our cycloaddition study,[11] we herein report the first example of Rh-catalyzed a tandem decarbonylation–Pauson–Khand-type cyclization process under microwave conditions. This versatile protocol accelerates the carbonylative reaction to furnish the desired cycloadducts in minutes and can be rendered enantioselective with suitable choice of chiral diphosphane supporting ligands.

Results and Discussions

The feasibility of the Rh-catalyzed decarbonylation of aldehyde under microwave conditions was examined in our initial studies.[12] A stoichiometric amount of the $[Rh(COD)Cl]_2$/dppp complex and cinnamaldehyde were placed in the microwave reactor at 100 °C for 10 min. Styrene (>90% from GC–MS, by decarbonylation of cinnamaldehyde) and (carbonyl)(dppp)–rhodium(I) chloride were observed. These preliminary results showed the potential for catalytic decarbonylation under microwave-assisted reaction conditions.

We were not only focused on the decarbonylation reaction, but we also targeted the efficacy of dual catalysis (decarbonylation and subsequent carbonylative cyclization). Commercially available phosphane ligands were tested in the model reaction and oxygen-tethered enyne **1a** was chosen as the prototypical substrate (Table 1). Control experiments revealed that a phosphane ligand was necessary for the successful tandem transformation (Table 1, Entries 1–

[a] Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and the Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University,
Hong Kong, China
E-mail: bcfyk@inet.polyu.edu.hk
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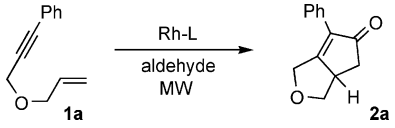
4). Diphosphane ligands (e.g. dppp) were found to be superior to monophosphane ligands (Table 1, Entries 3 and 5). It is interesting to show that the CO surrogates (aldehydes) were even better than gaseous CO as the CO source in these microwave-assisted carbonylative reactions (Table 1, Entries 6–10), and α,β-unsaturated aldehydes gave the best results (Table 1, Entry 3). Though the decarbonylation of aliphatic aldehyde was observed, the efficiency was inferior to that found in aromatic aldehydes (Table 1, Entry 10).

Table 1. Investigations on ligand and CO source effects in the microwave-assisted cascade PKR.[a]



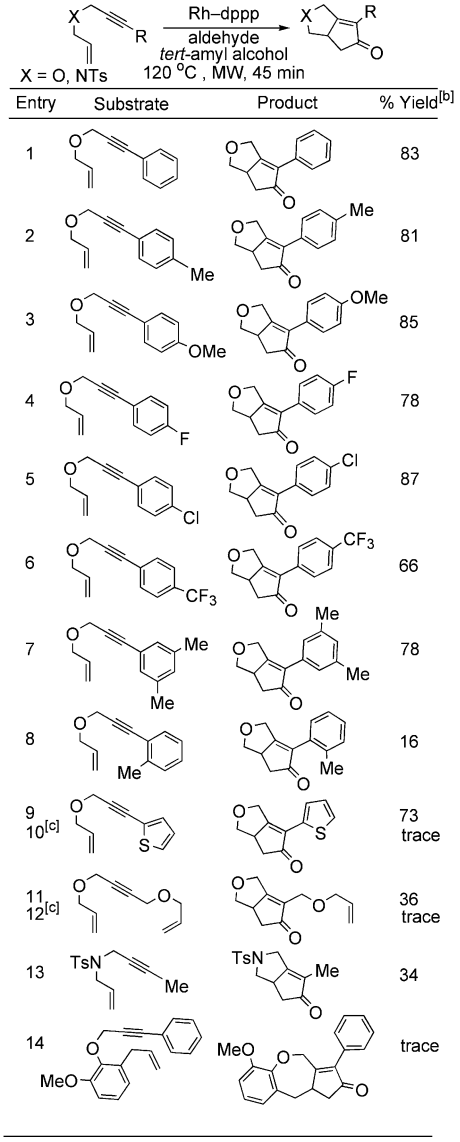
Entry	Ligand	CO source	% Yield[b]
1	no ligand	cinnamaldehyde	trace
2	dppe	cinnamaldehyde	22
3	dppp	cinnamaldehyde	75
4	dppf	cinnamaldehyde	12
5	Ph_3P	cinnamaldehyde	<5
6	dppp	CO gas[c]	15
7	dppp	*p*-ClC_6H_4CHO	44
8	dppp	C_6H_4CHO	55
9	dppp	*p*-$OMeC_6H_4CHO$	48
10	dppp	*n*-nonylaldehyde	36

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol-%), ligand (6 mol-%), enyne (0.3 mmol), aldehyde (0.45 mmol), and *tert*-amyl alcohol (1.0 mL) were placed in microwave-proof vials under an atmosphere of nitrogen, and the reaction mixture was heated at 120 °C for 45 min under microwave irradiation. [b] Isolated yield. [c] A CO pressure of 1 atm was applied.

To further probe the effectiveness of microwave-assisted dual catalysis, we examined various oxygen-tethered 1,6-enynes for the Pauson–Khand-type cyclization (Table 2). Electronically different aromatic enynes were found to be compatible under these reaction conditions to furnish the corresponding cyclopentenones (Table 2, Entries 1–7). Sterically hindered *ortho*-substituted aromatic enynes afforded low yields of the product; presumably, the *ortho*-methyl group hindered the coordination of the yne moiety to the Rh center (Table 2, Entry 8). Particularly noteworthy is that we firstly demonstrated the successful transformation of heterocyclic thienyl–enyne to the desired product under microwave-assisted conditions (Table 2, Entry 9). In contrast, only trace amounts of the product were obtained under conventional oil-bath heating (Table 2, Entry 10); moreover, a significant amount of substrate decomposition was observed by GC–MS analysis. The 1,8-enyne substrate was unsuccessful in this transformation, and ca. 80% of the starting material was recovered (Table 2, Entry 14).

Apart from achiral tandem catalysis, we were attracted by the possibility to achieve the first enantioselective version of microwave-assisted cascade transformation. Commonly used chiral diphosphane ligands were examined in place of dppp. (*S*)-BisbenzodioxanPhos provided the best results in terms of product yield and enantioselectivity.[13] Various substrates including O-, N-, and C-tethered enynes

Table 2. Microwave-assisted Rh-catalyzed cascade Pauson–Khand-type reaction.[a]

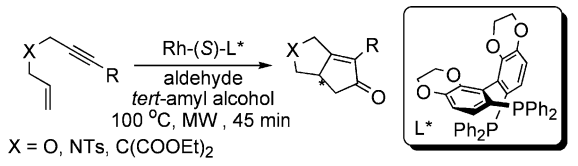


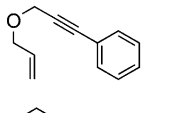
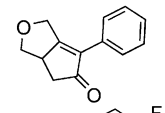
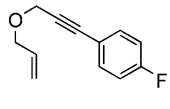
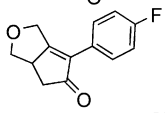
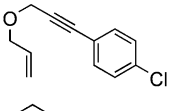
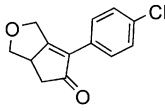
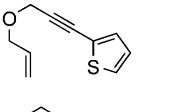
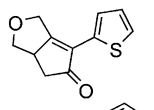
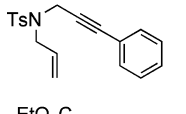
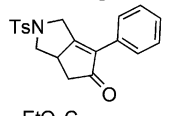
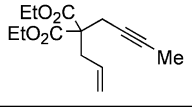
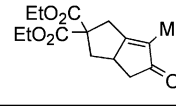
[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol-%), ligand (6.6 mol-%), enyne (0.3 mmol), cinnamaldehyde (0.45 mmol), and *tert*-amyl alcohol (1.0 mL) were placed in microwave-proof vials under an atmosphere of nitrogen, and the reaction mixture was heated at 120 °C for 45 min under microwave irradiation. [b] Isolated yields. [c] Reactions were performed under conventional heating at 120 °C for 36 h.

were successfully transformed into the corresponding cyclopentenones with better enantioselectivities (up to 90% *ee*; Table 3).

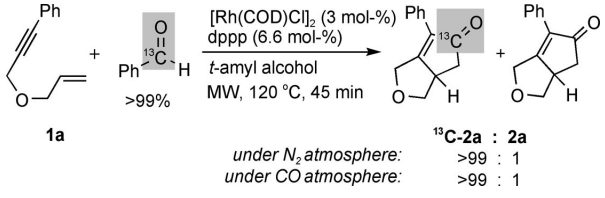
In order to determine the origin of carbonyl group in the microwave-promoted CO transfer process, we used ^{13}C-labeled benzaldehyde for the decarbonylation–carbonylation sequence (Scheme 1).[12f] When the reactions were placed under either a nitrogen or CO atmosphere, over 99% of the corresponding ^{13}C-cyclopentenone was obtained, as judged by MS and NMR spectroscopy. These informative results indicate that the CO moiety for carbonylative coupling is mainly provided by the decarbonylation of aldehyde.

Table 3. Microwave-assisted asymmetric Rh-catalyzed cascade Pauson–Khand-type reaction.[a]



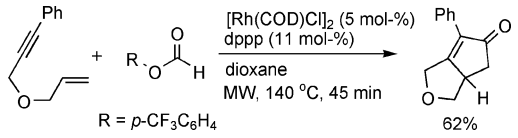
Entry	Substrate	Product	% Yield[b]	%ee[c]
1			73	89 85[d]
2			52	87
3			73	82 49[d]
4			58	90
5			53	80 65[d]
6			40	89 77[d]

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol-%), ligand (6.6 mol-%), enyne (0.3 mmol), cinnamaldehyde (0.45 mmol), and *tert*-amyl alcohol (1.0 mL) were placed in microwave-proof vials under an atmosphere of nitrogen, and the reaction was heated at 100 °C for 45 min under microwave irradiation. [b] Isolated yields. [c] Average of two runs from chiral HPLC analysis by using Daicel Chiracel AS-H and AD-H columns (0.46 cm × 25 cm). [d] Reactions were performed under conventional heating at 100 °C for 36 h.



Scheme 1. Labeling experiment for microwave-assisted sequential CO-transfer process.

There has been considerable interest in recent years in the chemistry of formate esters.[14] Particularly, the conversion of methyl formate into methanol and carbon monoxide is desirable in the generation of an easily handled "CO" moiety. Nevertheless, drastic reaction conditions are usually employed (e.g. >180 °C and/or >1 atm pressure).[15] It seemed conceivable to us that the decarbonylation of formates could be attained under mild reaction conditions with the suitable choice of mixed-metal complexes.[16] Attempts to study the first microwave-accelerated CO-transfer process by using formate ester as the CO surrogate was thus carried out (Scheme 2). The reaction was successful, and the advantages of our newly developed reaction conditions, including a shortened reaction time (3 d vs. 45 min), resulted in better product yield (43% vs. 62%) (Scheme 2).



Scheme 2. Microwave-assisted cascade decarbonylation–Pauson–Khand-type reaction with the use of formate as a CO surrogate; under conventional oil-bath heating, 3 d were required for completion of the reaction with 43% isolated yield.

Conclusions

We reported the first successful microwave-assisted cooperative process. The microwave energy considerably increase the rate of reaction in both decarbonylation and carbonylative cyclization. Substrates such as thienyl enyne significantly showed better yields under microwave conditions. Notably, the reaction conditions in this sequential process can be rendered enantioselective. Higher enantioselectivities were observed than conventional heating with product *ee* values up to 90%. In addition to aldehyde as the CO surrogate, we succeeded in showing that formate ester can be used as the condensed CO source in microwave-accelerated CO-transfer processes.

Experimental Section

General: Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. All air-sensitive reactions were performed in Rotaflo (England) resealable screw-cap Schlenk flasks (approx. 10-mL volume) or Teflon-lined screw cap vials (approx. 2-mL volume) in the presence of Teflon-coated magnetic stirrer bar (3 mm × 10 mm). Toluene and tetrahydrofuran (THF) were distilled from sodium and sodium benzophenone ketyl under an atmosphere of nitrogen, respectively. Allylamine and triethylamine were distilled from CaH_2 prior to use. Formate esters (liquid form at room temp.) were distilled under reduced pressure and stored in screw-capped vials. NaH (60% in mineral oil) was washed with dry hexane prior to use (*Caution*: This procedure should be performed under a relatively dry atmosphere with adequate shielding). Shiny-orange $[Rh(COD)Cl]_2$ crystalline solid and (*S*)-SYNPHOS (BisbenzodioxanPhos) were purchased from Strem Chemicals. Thin-layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates. Silica gel (Merck or MN, 230–400 mesh) was used for flash-column chromatography. Melting points were recorded with a Büchi Melting Point B-545 instrument and are uncorrected. ^1H NMR spectra were recorded with a Varian (500 MHz) spectrometer. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ = 7.26 ppm) or with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. Commercially available $CDCl_3$ was stored under anhydrous K_2CO_3 granules with 4-Å molecular sieves in desiccators. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. ^{13}C NMR spectra were recorded with a Varian 500 spectrometer and referenced to $CDCl_3$ (δ = 77.0 ppm).

Coupling constants (*J*) were reported in Hertz (Hz). Mass spectra (EI and FAB) were recorded with an HP 5989B Mass Spectrometer. High-resolution mass spectra (HRMS) were obtained with a Bruker APEX 47e FT-ICR mass spectrometer (ESI). HPLC analyses were performed with an HP-1100 system by using Chiralcel AS-H, AD-H, and OD-H (0.46 cm × 25 cm) columns. Racemic bicyclic cyclopentenone products (for chiral HPLC analysis calibration) were obtained from the same PKR representative procedure except dppp ligand was used. GC–MS analysis was conducted with an HP 6890 system with an HP 5973N mass-selective detector by using an HP5MS column (30 m 0.25 mm). Microwave-assisted reactions were performed with a Milestone MicroSynth Combichem microwave reactor.

General Procedures for Microwave-Assisted Catalytic Pauson–Khand Cyclization: $[Rh(COD)Cl]_2$ (4.4 mg, 9.0 μmol) and dppp (7.4 mg, 19.8 μmol) were charged into the reaction vial on a bench top at room temperature. The reaction vial was then transferred into the dry box before being evacuated and backfilled with nitrogen (3 cycles). *tert*-Amyl alcohol (0.2 mL), cinnamaldehyde (59 mg, 0.45 mmol, 1.5 equiv. with respected to enyne) and enynes (57 mg, 0.3 mmol) 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 120 °C by microwave irradiation with power of 500 watts for 45 min. The vials were allowed to reach room temperature. Diethyl ether or ethyl acetate (ca. 2 mL) was added. The crude reaction mixtures were directly purified by column chromatography on silica gel (hexane/ethyl acetate) to afford bicyclic cyclopentenones. Note: for the asymmetric Pauson–Khand-type cyclization, the enantiomeric excess values of the products were determined by chiral HPLC analysis by using Chiralcel columns.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, preparation of enyne substrates, initial screening results, compound characterization data and copies of ^1H and ^{13}C NMR spectra and chiral HPLC chromatograms.

Acknowledgments

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[13] Reaction conditions same as Table 1. (*S*)-BINAP (30% yield, 85% *ee*); (*S*)-tol-BINAP (12% yield, 90% *ee*); Et-Duphos (trace, n. d.).
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